cobas b 101

A system for measurement of CRP, HbA1c and Lipid Panel manufactured by Roche Diagnostics GmbH

An evaluation of the measurement of HbA1c

Report from the evaluation SKUP/2020/117

organised by SKUP at the request of

Roche Diagnostics in Denmark and Norway

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ATTACHMENTS

Attachments with data are included only in the copy to Roche Diagnostics Denmark and Roche Diagnostics Norway.

1. Summary

Background
The **cobas b** 101 system is an in vitro diagnostic device for quantitative measurement of Haemoglobin A1c (HbA1c), C-reactive protein (CRP) and lipids. The product is intended for professional use. The sample material for HbA1c measurements can be capillary whole blood, venous ethylenediaminetetraacetic acid (EDTA) or lithium-heparinised venous whole blood. The system is produced by Roche Diagnostics GmbH and was launched into the Scandinavian market April 2013. The SKUP evaluation was carried out in summer 2019 at the request of Roche Diagnostics Denmark and Roche Diagnostics Norway.

The aim of the evaluation
The aim of the evaluation was to assess the analytical quality and user-friendliness of **cobas b** 101 HbA1c, when used both under optimal conditions by experienced laboratory personnel and under real-life conditions by intended users in primary health care.

Materials and methods
Fresh capillary whole blood samples from 111 patients were measured on **cobas b** 101 HbA1c under optimal conditions in a hospital laboratory. Under real-life conditions in two primary health care centres (PHCC1 and PHCC2), fresh capillary whole blood samples from 50 and 40 patients, respectively, were measured on **cobas b** 101 HbA1c. Venous whole blood samples from the same patients were analysed with a comparison method in one of two hospital laboratories (capillary electrophoresis in free solution, Capillarys 3, Sebia and high performance liquid chromatography, TOSOH G8, TOSOH Bioscience, Inc). The analytical quality and user-friendliness were assessed according to pre-set quality goals. The quality goal for precision was a repeatability CV (coefficient of variation) ≤3,0 %. The quality goal for accuracy was that ≥95 % of the results should be within ±8,5 % in relation to the results of the comparison method. The results and limits for the quality goals are presented in mmol/mol. The user-friendliness was assessed using a questionnaire with three given ratings; satisfactory, intermediate and unsatisfactory, and with the quality goal of a total rating of "satisfactory".

Results
The CV achieved under optimal conditions was between 1,4 and 3,4 % depending on the concentration level. The CV achieved under real-life conditions for PHCC1 was between 2,4 and 4,0 %. The calculated CVs achieved under optimal conditions and by PHCC1 include instrument-to-instrument variation and was therefore carried out under "intermediate precision conditions", hence the repeatability from these evaluation sites have not been assessed. The CV for PHCC2 was between 1,3 and 1,7 and was obtained under repeatability conditions.
Under optimal conditions 83 % of the results were within the allowable deviation limits for accuracy and when handled by intended users 57 % of the results were within the limits. In the clinically relevant HbA1c interval ≥38 mmol/mol 85 % and 61 %, respectively, were within the limits. A statistical significant positive bias was seen between **cobas b** 101 and the comparison method both under optimal conditions and under real-life conditions by the intended users.
The user-friendliness was rated as satisfactory.

Conclusion
Based on an assessment of the measurements performed by the intended users in PHCC2, the quality goal for repeatability was fulfilled. The quality goal for accuracy was not fulfilled neither under optimal conditions nor by intended users. The quality goal for user-friendliness was fulfilled.

Comments from Roche Diagnostics
A letter with comment from Roche Diagnostics is attached to the report.

2. Abbreviations and Acronyms

BLS	Biomedical Laboratory Scientist
C-NPU	Committee on Nomenclature, Properties and Units
CI	Confidence Interval
CRP	C-reactive protein
CV	Coefficient of Variation
DCCT	The Diabetes Control and Complications Trial
DEKS	Danish Institute of External Quality Assurance for Laboratories in Health Care
DSKB	The Danish Society of Clinical Chemistry
EDTA	Ethylenediaminetetraacetic acid
EQA	External Quality Assessment
Equalis	External quality assessment in laboratory medicine in Sweden
HbA1c	Haemoglobin A1c
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
KB-AaUH	Clinical Biochemistry, Aalborg University Hospital
KBF-OUH	Clinical Biochemistry and Pharmacology, Odense University Hospital
MCA	Multiple Compound Analyse
NGSP	National Glycohaemoglobin Standardization Program
Noklus	Norwegian Organization for Quality Improvement of Laboratory Examinations
PHCC	Primary health care centre
QC	Quality control
SD	Standard deviation
SKUP	Scandinavian evaluation of laboratory equipment for point of care testing
SLS	Sodium lauryl sulphate

3. Introduction

The purpose of Scandinavian evaluation of laboratory equipment for point of care testing (SKUP) is to improve the quality of near patient testing in Scandinavia by providing objective information about analytical quality and user-friendliness of laboratory equipment. This information is generated by organising SKUP evaluations in point of care settings.

3.1. The concept of SKUP evaluations

SKUP evaluations follow common guidelines and the results from various evaluations are comparable[1]. The evaluation set-up and details are described in an evaluation protocol and agreed upon in advance. The analytical results and user-friendliness are assessed according to pre-set quality goals. To fully demonstrate the quality of a product, the end-users should be involved in the evaluation. If possible, SKUP evaluations are carried out using three lot numbers of test discs from separate and time-spread productions. Some evaluation codes are followed by an asterisk (*), indicating an evaluation with a more specific objective. The asterisk is explained on the front page of these protocols and reports.

3.2. Background for the evaluation

The **cobas b** 101 system is an in vitro diagnostic device for the quantitative measurement of C-reactive protein (CRP), Haemoglobin A1c (HbA1c) and a Lipid Panel. The product is intended for professional use. The system is produced by Roche Diagnostics GmbH and was launched into the Scandinavian market April 2013. The SKUP evaluation was carried out in May to August 2019 at the request of Roche Diagnostics Denmark and Roche Diagnostics Norway. This report describes the evaluation of **cobas b** 101 HbA1c. Evaluation of **cobas b** 101 CRP and **cobas b** 101 Lipid Panel are described in the reports SKUP/2019/116 and SKUP/2020/118, respectively.

3.3. The aim of the evaluation

The aim of the evaluation was to assess the analytical quality and user-friendliness of **cobas b** 101 HbA1c, both when used under optimal conditions by experienced laboratory personnel and when used under real-life conditions by intended users in primary health care.

3.4. The model for the evaluation of cobas b 101 HbA1c

SKUP evaluations for quantitative methods are based upon the fundamental guidelines in a book concerning evaluations of laboratory equipment in primary health care [1]. This evaluation consisted of two parts (figure 1). One part of the evaluation was carried out under optimal conditions by experienced laboratory personnel. This part documents the quality of the system under conditions as favourable as possible for achieving good analytical quality. The other part of the evaluation was carried out by intended users in two primary health care centres (PHCCs). This part documents the quality of the system under real-life conditions.

The evaluation included:

- Examination of the analytical quality (precision and accuracy) under optimal conditions
- Examination of the analytical quality (precision and accuracy) in the hands of intended users
- Evaluation of the user-friendliness of **cobas b** 101 and its manual

[1]SKUP evaluations are under continuous development. In some cases, it may be difficult to compare earlier protocols, results and reports with more recent ones.

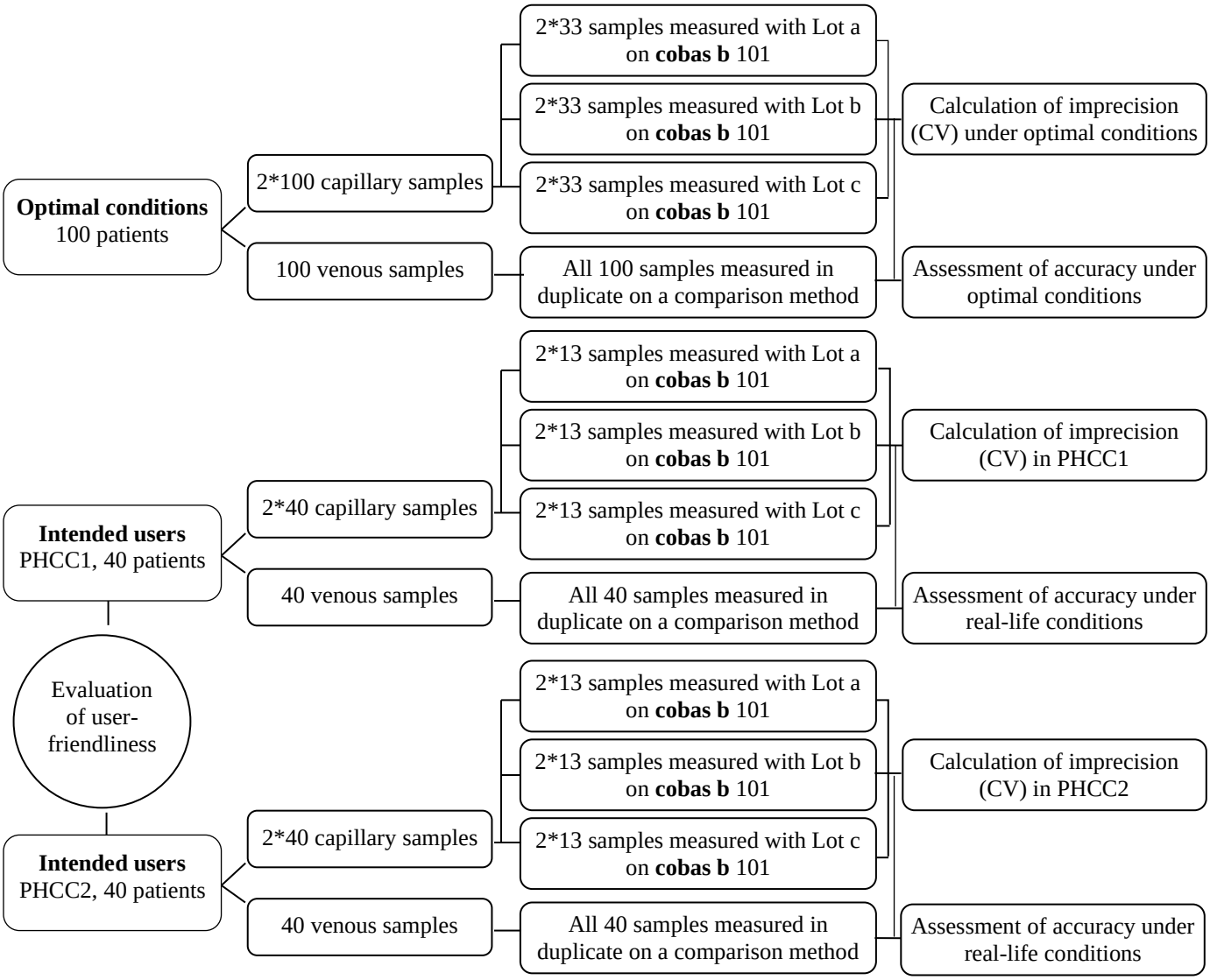

Figure 1. Flowchart illustrating the model for the evaluation of **cobas b** 101 HbA1c.

4. Quality goals

4.1. Analytical quality

The quality goals in this evaluation are based on HbA1c results expressed in mmol/mol (IFCC units; International Federation of Clinical Chemistry and Laboratory Medicine). Quality goals specified for HbA1c results in mmol/mol must be recalculated to quality goals for results expressed in National Glycohaemoglobin Standardization Program (NGSP) units. Weycamp *et al.* [2] have explained why the analytical goals for HbA1c measurement in mmol/mol and the Diabetes Control and Complications Trial (DCCT) % are different.

The Danish Society of Clinical Chemistry (DSKB) has a scientific committee for quality assurance, the Scientific committee for quality assurance in Denmark. In 2011, the committee specified the following quality goals for HbA1c mmol/mol when used for diagnosis and monitoring of diabetes in Denmark [3]:
Maximum allowable imprecision CV (coefficient of variation): 2,8 %
Maximum allowable bias at HbA1c level 48 mmol/mol: ±2,8 %
Maximum allowable deviation at HbA1c level 48 mmol/mol: ±7,3 % (requirement for deviation from true target)

In 2012, the Norwegian Directorate of Health specified quality goals for diagnostic use of HbA1c [4]. The HbA1c method must be traceable to the IFCC reference method, and a deviation $\leq$±10 % from reference target at a level of 48 mmol/mol and a CV <3 % must be documented.
In November 2019 the quality goal for the deviation from reference target were changed to $\leq$±7,4 % [5].

In Sweden, the national analytical quality goals are set up by External quality assessment in laboratory medicine in Sweden's (Equalis) advisory group for protein analysis and were approved by the Swedish Association for Clinical Chemistry in 2010 [6].
Maximum bias: ±1,5 mmol/mol
Between-laboratories-variation (CV): 2,5 %
Allowable deviation: bias + 1,65 × standard deviation (SD) ~ bias + 1,65 × 0,025 × HbA1c level.

Based on the national practices, imprecision and bias of 3 % each are used to calculate the limit for allowable deviation in this evaluation. When the imprecision of the comparison method is taken into account this allows for a deviation of an individual result within ±8,5 %. SKUP's quality goals for HbA1c in this evaluation are as presented in section 4.4.

4.2. User-friendliness

The evaluation of user-friendliness will be carried out by asking the evaluating persons to fill in a questionnaire, see section 6.5.

Technical errors
SKUP recommends that the fraction of tests wasted due to technical errors should not exceed 2 %.

4.3. Principles for the assessments

To qualify for an overall good assessment in a SKUP evaluation, the measuring system must show satisfactory analytical quality as well as satisfactory user-friendliness.

4.3.1. Assessment of the analytical quality

The analytical results were assessed according to pre-set quality goals.

Precision

The decision whether the achieved CV fulfils the quality goal or not, is made on a 5 % significance level (one-tailed test). The distinction between the ratings, and the assessment of precision according to the quality goal, are shown in table 1. Based on the results from each evaluation site, an overall conclusion will be drawn in the summary of the report

Table 1. The rating of precision

Distinction between the ratings	Assessment according to the quality goal
The CV is lower than the quality goal (statistically significant)	The quality goal is fulfilled
The CV is lower than the quality goal (not statistically significant)	Most likely the quality goal is fulfilled
The CV is higher than the quality goal (not statistically significant)	Most likely the quality goal is not fulfilled
The CV is higher than the quality goal (statistically significant)	The quality goal is not fulfilled

Bias

SKUP does not set separate quality goals for bias. The confidence interval (CI) of the measured bias is used for deciding if a difference between the evaluated method and the comparison method is statistically significant (two-tailed test, 5 % significance level). The bias will also be discussed in connection with the accuracy. Proven systematic deviation of the results achieved by intended users will be discussed in relation to the bias found under optimal conditions.

Bias with three lots of test discs

Separate lot calculations are not performed. The results achieved with the three lots are included in the assessment of accuracy in the difference plots for the results achieved under optimal conditions. If distinct differences between the lots appear, this will be pointed out and discussed.

Accuracy

The accuracy is illustrated in a difference plot with limits for the allowable deviation according to the quality goal. The fraction of results within the limits is counted. The accuracy is assessed as either fulfilling the quality goal or not fulfilling the quality goal.

4.3.2. Assessment of the user-friendliness

The user-friendliness is assessed according to the answers and comments given in the questionnaire. For each question, the evaluator can choose between three given ratings; satisfactory, intermediate and unsatisfactory. The responses from the evaluators are reviewed and summed up. To achieve the overall rating "satisfactory", the tested equipment must reach a total rating of "satisfactory" in all four subareas of characteristics described in section 6.5.

Technical errors

The evaluating persons register error codes, technical errors and failed measurements during the evaluation. The fraction of tests wasted due to technical errors is calculated and taken into account in connection with the assessment of the user-friendliness.

4.4. SKUP's quality goals in this evaluation

As agreed upon when the protocol was drawn up, the results from the evaluation of **cobas b** 101 HbA1c are assessed against the following quality goals:

Repeatability (CV)..... ≤3,0 %

Allowable deviation
of the individual result from the comparison method result..... ≤±8,5 %

Required percentage of individual results
within the allowable deviations..... ≥95 %

User-friendliness, overall rating..... Satisfactory

The results in this evaluation will only be presented in mmol/mol.
Results can be recalculated between the two units with the following equations:
HbA1c (IFCC, mmol/mol) = 10,93 × HbA1c (NGSP, %) – 23,54
HbA1c (NGSP, %) = 0,0915 × HbA1c (IFCC, mmol/mol) + 2,153

5. Materials and methods

5.1. Definition of the measurand

The measurement system intends to measure the substance fraction of glycated haemoglobin per mol haemoglobin in whole blood. For the evaluated system, the sample material in this evaluation was fresh capillary whole blood and for the comparison method, the sample material was venous K_2-ethylenediaminetetraacetic acid (EDTA) blood. The results are traceable to the IFCC Reference method and are expressed in the unit mmol/mol. The Committee on Nomenclature, Properties and Units (C-NPU) systematically describes clinical laboratory measurands in a database [7]. The NPU-code related to the measurand in this evaluation is NPU27300. Some parts of the world only accept HbA1c results in NGSP unit, which is specified in NPU03835. In this protocol, the term HbA1c is used for the measurand.

5.2. The evaluated measurement system cobas b 101 HbA1c

The information in this section derives from the company's information material.

The **cobas b** 101® system (figure 2) is intended for professional use in clinical laboratory settings or point of care locations. **cobas b** 101 CRP, HbA1c and Lipid Panel test kits are available.
The **cobas b** 101 HbA1c system includes:

- **cobas b** 101 instrument
- **cobas b** 101 HbA1c test discs
- **cobas** HbA1c quality control (QC) info disc
- **cobas** HbA1c internal analytical quality control kit
- Optical check disc

Figure 2. cobas b 101 instrument and three different test discs.

cobas b 101 HbA1c is an in vitro diagnostic test system designed to quantitatively determine HbA1c in human capillary whole blood, lithium-heparinised and K_2/K_3-EDTA venous whole blood. The measurement principle of **cobas b** 101 is immunoturbidimetry.

The blood sample is diluted and mixed with buffer to release haemoglobin from the erythrocytes. A fraction of the sample is conveyed into a reaction chamber where it is mixed with sodium lauryl sulfate (SLS). SLS is used to form SLS-haemoglobin complex. The concentration of total haemoglobin is calculated by measuring SLS-haemoglobin complex with a wavelength of 525 nm. HbA1c in another fraction of the sample is first denatured by potassium ferricyanide and sucrose laurate. The denatured HbA1c bonds with an HbA1c antibody on the latex particle. Latex agglutination inhibition then occurs by reacting with the agglutinator that has a synthetic antigen which can bond with the HbA1c antibody. The concentration of HbA1c is calculated by measuring the latex agglutination inhibitory reaction with a wavelength of 625 nm.

The **cobas b** 101 instrument automatically reads in the lot-specific calibration data from the barcode information printed on the disc, eliminating the need for calibration by the user. Results from each lot of the **cobas** HbA1c test disc are traceable to the IFCC reference method.

Every **cobas b** HbA1c control kit contains a lot-specific QC information disc for the liquid quality control samples. The QC info disc contains the target values and ranges for the **cobas b** HbA1c test.

For technical details about the **cobas b** 101 HbA1c, see table 2. For more information about the **cobas b** 101 system, and name of the manufacturer and the suppliers in the Scandinavian countries, see attachment 2 and 3. For product specifications in this evaluation, see attachment 4.

Table 2. Technical details for **cobas b** 101 HbA1c from the manufacturer

Sample volume	2 µL
Measuring time	5 minutes and 20 seconds
Measuring range	20 – 130 mmol/mol (IFCC) or 4 – 14 % (DCCT/NGSP)
Haematocrit range	30 % – 55 %
Storage capacity	5000 patient test results, 500 control test results, 500 sets of patient information, 50 sets of operator information, including 5 for administrators

5.3. The selected comparison method

A selected comparison method is a fully specified method which, in the absence of a Reference method, serves as a common basis for the comparison of the evaluated method.

5.3.1. The selected comparison method in this evaluation

The selected comparison method for samples taken under optimal conditions was a capillary electrophoresis in free solution method implemented on Capillarys 3, Sebia in the Clinical Biochemistry laboratory at Aalborg University Hospital (KB-AaUH). The method uses reagents from Sebia. The instrument reports the results in whole numbers without decimals. The method is traceable to the IFCC method and reference materials developed by IFCC Working group on Standardization of HbA1c.

The selected comparison method for samples taken in the PHCCs was a high performance liquid chromatography method implemented on TOSOH G8 in the Clinical Biochemistry and Pharmacology laboratory at Odense University hospital (KBF-OUH). The method uses reagents from TOSOH Bioscience, Inc. The instrument reports the results with one decimal. The method is traceable to the IFCC method and reference materials developed by IFCC Working group on Standardization of HbA1c.

Internal analytical quality control
Internal analytical quality control samples were measured daily on the comparison method
KB-AaUH: Sebia Multi-system HbA1c capillary controls in two levels
KBF-OUH: BIO-RAD Lyphochek Diabetes Control in two levels

External analytical quality control
Both hospital laboratories participate in the external quality assessment (EQA) scheme for HbA1c organised by Labquality with two levels in six rounds per year. The EQA control materials are produced by Labquality and are fresh whole blood (genuine human material). The assigned value for HbA1c is traceable to the IFCC reference method.

5.4. Verification of the analytical quality of the comparison method

Precision
The repeatability (CV) of the comparison methods was calculated from duplicate measurements of the venous samples from the patients participating in the evaluation.

Trueness
To demonstrate the trueness of the two comparison methods, HbA1c calibrators with certified values (three levels) from Multiple Compound Analyse (MCA) Laboratory were analysed on both comparison methods. In addition, 35 patient samples in different concentration levels were analysed on both comparison methods, to verify the agreement between the methods.

5.5. The evaluation

5.5.1. Planning of the evaluation

Inquiry about an evaluation
Roche Diagnostics via Medical Affairs Manager Liv-Janne Øvrebust, applied to SKUP in September 2018 for an evaluation of **cobas b** 101.

Protocol, arrangements and contract
In March 2019, the protocol for the evaluation was approved, and Roche Diagnostics and SKUP signed a contract for the evaluation. Biomedical laboratory scientists (BLSs) at the Farsø department of the laboratory in Aalborg were assigned to do the practical work with **cobas b** 101 in the evaluation under optimal conditions. Two primary health care centres from Region Southern Denmark agreed to represent the intended users in this evaluation.

Training
Roche Diagnostics Denmark demonstrated **cobas b** 101 HbA1c for all the evaluation sites. The training in the PHCCs reflected the training usually given to the end-users. Roche was not allowed to contact or supervise the evaluators during the evaluation period.

5.5.2. Evaluation sites and persons involved

The practical work with the evaluation of **cobas b** 101 HbA1c was carried out during 12 weeks under optimal conditions in the Farsø department of the laboratory in Aalborg, and eight weeks in the PHCCs, ending in August 2019.

Two BLSs at the Department of Clinical Biochemistry, Aalborg University Hospital Aalborg-department and two BLSs at the Department of Clinical Biochemistry and Pharmacology in Odense University Hospital were responsible for analysing the samples on the comparison methods.

In the Farsø department of the laboratory in Aalborg, three BLSs were involved in the practical work for sampling and measurements on **cobas b** 101.

Two BLSs in PHCC1 and three nurses in PHCC2 were involved in the practical work for sampling and measurements. Both PHCCs are large centres with four and five physicians, respectively. None of the PHCCs have a routine method for HbA1c measurement.

5.5.3. The evaluation procedure

Internal analytical quality control

Internal analytical quality control samples for **cobas b** 101 HbA1c, two levels (**cobas** HbA1c internal analytical quality control kit, Roche Diagnostics GmbH), were measured each evaluation day on **cobas b** 101 HbA1c. The reproducibility (CV) as achieved with the quality control material was calculated.

Recruitment of patients

Patients 18 years or older, coming into the laboratory or PHCC for HbA1c measurements, were asked if they were willing to donate two capillary and one venous blood sample for the evaluation. Participation was voluntary and verbal informed consent was considered sufficient. Patients with known hemoglobinopathies were not included.

Handling of the samples and measurements

Fresh capillary whole blood samples were used for measurement with the **cobas b** 101 HbA1c system. All measurements were performed in duplicate, i.e. two separate finger sticks.
Under optimal conditions and in PHCC1, the duplicate measurements were performed using two **cobas b** 101 instruments because these evaluation sites also contributed to the evaluation of **cobas b** 101 Lipid Panel.

The participants washed and dried their hands, and the puncture site was disinfected with alcohol pads and the area dried completely before sampling. Disposable lancing devices with depth settings 2,3 mm were used. The first drop of blood was wiped off with a swab. The second drop of blood was applied to a test disc in accordance with the instructions from the manufacturer. The test discs were measured immediately (within 60 seconds). The complete sampling and measurement procedures were repeated for the second measurement on **cobas b** 101 HbA1c. For patients where both HbA1c and lipids were requested, the dual-test mode was used as described in the **cobas b** 101 manual, i.e. the second drop of blood was applied to the lipid disc and the third drop of blood was applied to the HbA1c disc. In case of error codes, the test was repeated if possible until a result was obtained. Three lot numbers of test discs were used in the evaluation.

The venous samples for the comparison method were obtained from venous puncture and collected into Vacutainer tubes with K_2-EDTA. The tubes were inverted ten times to ensure thorough mixing and kept in room temperature until transported to KB-AaUH (samples from optimal conditions) or KBF-OUH (samples from the PHCCs) the same day. The venous samples were measured in duplicate for HbA1c on the comparison method within 24 hours after sampling. All samples were treated according to the internal procedures of the hospital laboratory regarding potential interfering substances.

6. Results and discussion

Statistical expressions and calculations used by SKUP are shown in attachment 5.

6.1. Number of samples

Scheduled number of samples in this evaluation was 100 patient samples measured in duplicate under optimal conditions and 80 patient samples measured in duplicate by users in the PHCCs.

At the end of the evaluation a total of 201 patients were enrolled. Under optimal conditions, 111 patients were recruited (SKUP ID 1 – 100 and F101 – F111). PHCC1 recruited 50 patients (SKUP ID 101 – 144 and 146 – 151) and PHCC2 recruited 40 patients (SKUP ID 201 – 240). The results from the comparison methods covered a HbA1c interval from 27 – 122 mmol/mol of which 57 % of the samples were in the clinically relevant HbA1c interval ≥38 mmol/mol.
An account of the number of samples not included in the calculations, is given below.

Missing results

- From PHCC1 internal analytical quality control results for one evaluation day were missing. The results from the patient samples this day were still included in the calculations.
- From optimal conditions the internal analytical quality control result for Level 1 for one of the instruments on one evaluation day was missing. The results from the patient samples this day were still included in the calculations.
- ID 105; only single measurement from **cobas b** 101. The results were included in the calculation of bias and the assessment of accuracy but not included in the calculation of repeatability.
- ID 38, 91, 92, 141 and 142; only single measurements from the comparison method were reported. The single values from the comparison method were still included in the calculations of bias and in the assessment of accuracy.
- ID 20, 21 and F103; no measurements were reported from the comparison method. The results from **cobas b** 101 were included in the calculations of repeatability.

Omitted results

- ID 6, 7, 8, 26, 34, 35, 36, 39, 40, 68, 69, 70, 83 were analysed with the comparison method >24 hours after sampling. The results from **cobas b** 101 were included in the calculations of repeatability.

Excluded results (statistical outliers)

Statistical outliers according to Burnett [8]:

- ID 4 and 236; the results from **cobas b** 101 were classified as outliers according to Burnett's model in the calculation of repeatability and therefore not included in the calculation of bias but in the assessment of accuracy (the first of the duplicate measurements).
- ID F110 and 118; the results from **cobas b** 101 were classified as outliers according to Burnett's model in the calculation of bias. The results were included in the calculation of repeatability and the assessment of accuracy (the first of the duplicate measurements).
- ID 135 and 224; the results from the comparison method were classified as outliers according to Burnett's model in the calculation of repeatability. The results were not included in the calculation of bias and the assessment of accuracy, but the results from **cobas b** 101 were included in the calculation of repeatability.

Recorded error codes, technical errors and failed measurements
No error codes were reported related to measurement of HbA1c.
The SKUP recommendation of a fraction of ≤2 % tests wasted due to technical errors was achieved.

6.2. Analytical quality of the selected comparison methods

6.2.1. Internal analytical quality control

All results from the internal analytical quality control for both comparison methods were within the allowable control limits (data not shown).

6.2.2. The precision of the comparison methods

Duplicate measurements of venous samples from the patients participating under optimal conditions and in the PHCCs were performed on the comparison methods. The results were checked to meet the imposed condition for using formula 1 in attachment 5. There was no systematic difference between the paired measurements (data not shown) in neither of the methods.

The precision is presented as repeatability (CV). The CV with a 90 % CI is shown in table 3a and 3b. The results were sorted and divided into three levels according to the mean of the results. Raw data is attached for the requesting company only, see attachment 6 and 7.

Table 3a. Repeatability (CV) of the comparison method Capillarys 3, Sebia for HbA1c measured in venous whole blood samples.

Level	HbA1c interval, mmol/mol	n	Excluded results (statistical outliers)	Mean HbA1c value, mmol/mol	CV (90% CI), %
Low	29,0 – 37,9	37	0	34,4	1,6 (1,3 – 2,0)
Medium	38,4 – 50,6	29	0	43,0	1,4 (1,2 – 1,8)
High	51,1 – 120,8	26	0	69,0	1,4 (1,2 – 1,9)

An account of the number of samples is given in section 6.1.

Table 3b. Repeatability (CV) of the comparison method TOSOH G8 for HbA1c measured in venous whole blood samples.

Level	HbA1c interval, mmol/mol	n*	Excluded results (statistical outliers)	Mean HbA1c value, mmol/mol	CV (90% CI), %
Low	30,8 – 37,7	30	1**	35,1	0,6 (0,5 – 0,8)
Medium	38,0 – 50,8	39	1**	42,6	0,9 (0,8 – 1,2)
High	51,0 – 91,0	19	0	58,1	0,5 (0,4 – 0,7)

*The given number of results (n) were counted before the exclusion of statistical outliers. Mean and CV were calculated after the exclusion of statistical outliers. An account of the number of samples is given in section 6.1.
**ID 135 and 224 were statistical outliers according to Burnett's model [8] in the calculation of repeatability and therefore excluded.

Discussion
The CV for the comparison method Capillarys 3, Sebia was between 1,4 and 1,6 %. The CV for the comparison method TOSOH G8 was between 0,5 and 0,9 %.

6.2.3. The trueness of the comparison methods

To demonstrate the trueness of the two comparison methods, HbA1c calibrators (three levels) from MCA Laboratory (table 4a, 4b) and EQA HbA1c controls from Labquality (two levels, round 2 2019, table 4c) were analysed on both methods (specified in section 5.3.1).

Table 4a. HbA1c calibrators from MCA Laboratory measured on the comparison method Capillarys 3, Sebia.

Date: 22.05.2019 and 20.06.2019		Site: KB-AaUH		
Level	Certified values k=2, mmol/mol	n	KB-AaUH Capillary 3, Sebia mean, mmol/mol	Deviation from target value, mmol/mol
Low	38,0 (0,7)	9	36,6	-1,4
Medium	49,1 (0,9)	9	48,1	-1,0
High	59,6 (1,0)	9	58,6	-1,0

Table 4b. HbA1c calibrators from MCA Laboratory measured on the comparison method TOSOH G8.

Date: 22.05.2019 and 20.06.2019		Site: KBF-OUH		
Level	Certified values k=2, mmol/mol	n	KBF-OUH TOSOH G8 mean, mmol/mol	Deviation from target value, mmol/mol
Low	38,0 (0,7)	10	38,7	0,7
Medium	49,1 (0,9)	10	50,0	0,9
High	59,6 (1,0)	10	61,0	1,4

Table 4c. EQA HbA1c control material from Labquality measured on the comparison methods.

April 2019 Sample	Reference value* HbA1c (±8 % acceptance limits)	KB-AaUH Capillarys 3, Sebia		KBF-OUH TOSOH G8	
	mmol/mol	n	mmol/mol	n	mmol/mol
S001	34,9 (32,1 – 37,7)	1	33	1	33,8
S002	50,1 (46,1 – 54,1)	1	48	1	49,2

*Determined by the European Reference Laboratory for Glycohemoglobin

Discussion
Table 4a and 4b show that the results obtained with the HbA1c calibrators in KB-AaUH were just below the certified values and outside the uncertainty limits except for the high level. The results obtained in KBF-OUH were just above the certified values but within the uncertainty limits except for the high level. 35 patient samples were also measured in duplicate on both comparison

methods to verify the agreement between the methods. The same deviation was seen on the patient samples (attachment 8). Thus, it was decided to adjust all results from the two comparison methods. The adjustment was carried out by means of invers calibration [9].
All results from the comparison method in KB-AaUH were adjusted according to the certified values on the HbA1c calibrators using the following regression equation: y = 0,981x + 2,0452. All results from the comparison method in KBF-OUH were then adjusted using the 35 patient samples (attachment 8) with transferred MCA values from KB-AaUH with the following regression equation: y = 0,956x + 1,2740. Further on in this report, whenever results from the comparison methods are presented, they have been adjusted according to this. Both comparison methods were within the acceptance limits (±8 %) of the assigned values in the EQA program for HbA1c, se table 4c.

6.3. Analytical quality of cobas b 101 HbA1c under optimal conditions

The results below reflect the analytical quality of **cobas b** 101 HbA1c under optimal conditions. Duplicate measurements were performed using two **cobas b** 101 instruments.
The results document the quality of the system under conditions as favourable as possible for achieving good analytical quality.

6.3.1. Internal analytical quality control

All results from the internal analytical quality control (**cobas** HbA1c Control), two levels, were within the allowable control limits (data not shown). The reproducibility (CV) achieved with the internal analytical quality control samples were 4,7 % for level 1 (n=87) and 1,9 % for level 2 (n=88). Raw data is attached for the requesting company only, see attachment 9.

6.3.2. The precision of cobas b 101 HbA1c

The samples from each patient were measured in duplicate using two **cobas b** 101 instruments. The results were checked to meet the imposed condition for using formula 1 in attachment 5. There were no systematic differences pointed out between the paired measurements (data not shown).
The precision is presented as repeatability (CV), but includes instrument-to-instrument variation. The CV with a 90 % CI is shown in table 5. The results were sorted and divided into three concentration levels according to the mean of the results of the **cobas b** 101 HbA1c method. Raw data is attached for the requesting company only, see attachment 10.

Table 5. Repeatability (CV) of **cobas b** 101 for HbA1c measured in capillary whole blood samples. Results achieved under optimal conditions.

Level	HbA1c interval, mmol/mol	n*	Excluded results (statistical outliers)	Mean HbA1c value, mmol/mol	CV (90% CI), %
Low	30,5 – 38,0	37	0	35,3	3,4 (2,9 – 4,3)
Medium	38,5 – 48,0	40	0	43,2	1,9 (1,6 – 2,3)
High	51,5 – 92,5	34	1**	67,7	1,4 (1,2 – 1,7)

*The given number of results (n) were counted before the exclusion of statistical outliers. Mean and CV were calculated after the exclusion of statistical outliers. An account of the number of samples is given in section 6.1
**ID 4 was a statistical outlier according to Burnett's model [8] in the calculation of repeatability and therefore excluded.

Discussion
The CV for the low level was higher than the quality goal (≤3 %), but not statistically significant higher. The CV for the medium and high levels were statistically significantly lower than the quality goal. However, as two instruments were used for duplicate measurements any between-instrument difference is included in the CV's given in table 5.

Conclusion
Since the calculated CVs include instrument-to instrument variation, the results have not been assessed according to the present quality goal for repeatability

6.3.3. The bias of cobas b 101

The mean deviation (bias) of **cobas b** 101 results from the comparison method was calculated. The bias is presented with a 95 % CI in table 6.
The results were sorted and divided into three concentration levels according to the mean results of the comparison method. Raw data is attached for the requesting company only, see attachment 6 and 10.

Table 6. Bias of **cobas b** 101 for HbA1c measured in capillary whole blood samples. Results achieved under optimal conditions.

Level	HbA1c interval comparison method, mmol/mol	n*	Excluded results (statistical outliers)	Mean HbA1c value comparison method, mmol/mol	Mean HbA1c value, mmol/mol	Bias (95 % CI), mmol/mol	Bias, %
Low	29,0 – 37,9	39	0	34,3	36,0	1,77 (1,21 – 2,33)	5,2
Medium	38,4 – 50,6	30	0	42,9	44,6	1,66 (1,08 – 2,24)	3,9
High	51,1 – 99,7	25	1**	67,0	68,8	1,75 (0,79 – 2,70)	2,6

*The given number of results (n) were counted before the exclusion of statistical outliers. Mean and bias were calculated after the exclusion of statistical outliers. An account of the number of samples is given in section 6.1.
**ID F110 was a statistical outlier according to Burnett's model [8] in the calculation of bias and therefore excluded.

Discussion
For all three levels there was a statistically significant bias between **cobas b** 101 HbA1c and the comparison method. The results from **cobas b** 101 were systematically higher than the results from the comparison method.

6.3.4. The accuracy of cobas b 101 HbA1c

To evaluate the accuracy of HbA1c results on **cobas b** 101, the agreement between **cobas b** 101 HbA1c and the comparison method is illustrated in a difference plot (figure 3). The limits for the allowable deviation according to the quality goal are shown with stippled lines. The samples were measured in parallel on the two **cobas b** 101 instruments used in the hospital laboratory. For odd patient numbers results from instrument Q66111787 were regarded as the first result, and for even patient numbers results from instrument Q66111686 were regarded as the first result. If the result from one instrument was missing the result from the other instrument was used. The plots illustrate both random and systematic errors, reflecting the total measuring error in the **cobas b** 101 results. Raw data is attached for the requesting company only, see attachment 6 and 10.

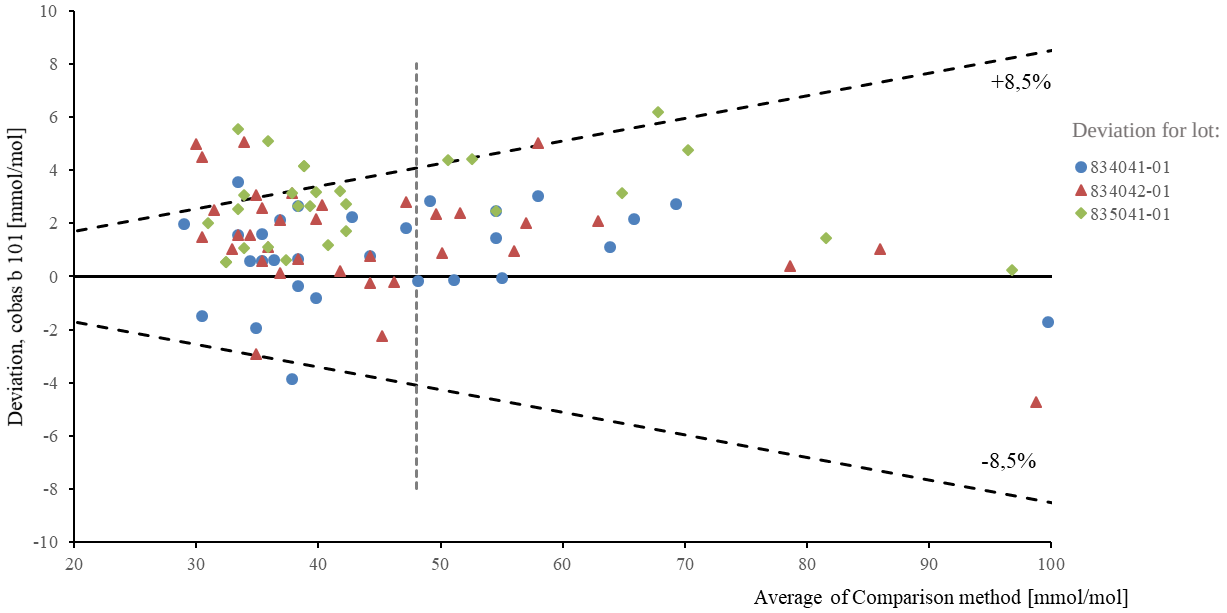

Figure 3. Accuracy of HbA1c results on **cobas b** 101 under optimal conditions. The x-axis represents the mean HbA1c result of the comparison method. The y-axis represents the HbA1c deviation in mmol/mol of capillary whole blood measurement on **cobas b** 101 from the mean result of the corresponding sample of the comparison method. The vertical line at 48 mmol/mol HbA1c illustrates the diagnostic threshold value for diabetes. The different lots of test discs are illustrated with the symbols ● (Lot 834041-01), ▲ (lot 834042-01) and ♦ (lot 835041-01). Stippled lines represent the allowable deviation limits of ±8,5 %. Number of results (n) = 95. An account of the number of samples is given in section 6.1.

Discussion

As shown in figure 3, the **cobas b** 101 HbA1c results are higher than the results from the comparison method. This is in consistence with the calculated bias in table 6. Of the 95 results 16 results were outside the limits for allowable deviation (±8,5 %) and 79 results were within the limits, amounting to 83 % within the limits. However, most of the results that are outside the limits are in the lower level. For results >38 mmol/mol (n = 55), 85 % were within the limits. The quality goal for individual results within the limits is ≥95 %.

Conclusion

Under optimal conditions the quality goal for accuracy was not fulfilled.

6.4. Analytical quality of cobas b 101 HbA1c achieved by intended users

The results below reflect the analytical quality of **cobas b** 101 HbA1c under real-life conditions in the hands of intended users in PHCCs. In PHCC1 duplicate measurements were performed using two **cobas b** 101 instruments and in PHCC2 duplicate measurements were performed using one **cobas b** 101 instrument. The results may deviate from the results achieved under optimal conditions.

6.4.1. Internal analytical quality control

All results from the internal analytical quality control (**cobas** HbA1c Control), two levels, were within the allowable control limits (data not shown). The reproducibility (CV) achieved with the internal analytical quality control samples were 7,0 % for level 1 (n=37) and 2,8 % for level 2 (n=37). Raw data is attached for the requesting company only, attachment 11.

6.4.2. The precision of cobas b 101

The samples from each patient in PHCC1 were measured in duplicate using two **cobas b** 101 instruments, and in PHCC2 the samples from each patient were measured in duplicate using one **cobas b** 101 instrument.
The results were checked to meet the imposed condition for using formula 1 in attachment 5.
The paired measurements from PHCC1 show systematic difference at low level (data not shown), which may be due to a difference between the two **cobas b** 101 instruments used
The precision is presented as repeatability (CV), but includes instrument-to-instrument variation. The CV with a 90 % CI is shown in table 7. The results were sorted and divided into three concentration levels according to the mean of the results of **cobas b** 101 HbA1c system. Raw data is attached for the requesting company only, see attachment 12.

Table 7. Repeatability (CV) of **cobas b** 101 for HbA1c measured in capillary whole blood samples. Resuls achieved by intended users.

Place	Level	HbA1c interval, mmol/mol	n*	Excluded results (statistical outliers)	Mean HbA1c value, mmol/mol	CV (90% CI), %
PHCC 1	Low	32,5 – 38,0	10	0	36,3	3,3 (2,4 – 5,5)
	Medium	38,5 – 48,0	27	0	42,7	2,4 (2,0 – 3,2)
	High	51,5 – 92,5	12	0	63,5	4,0 (3,0 – 6,1)
PHCC 2	Low	32,5 – 37,5	6***			
	Medium	39,0 – 51,0	20	1**	43,5	1,3 (1,1 – 1,9)
	High	51,5 – 65,5	14	0	55,9	1,7 (1,3 – 2,5)

*The given number of results (n) were counted before the exclusion of statistical outliers. Mean and CV were calculated after the exclusion of statistical outliers. An account of the number of samples is given in section 6.1.
**ID 236 was a statistical outlier according to Burnett's model [8] in the calculation of repeatability and therefore excluded.
*** n<8; CV not reported due to high degree of uncertainty in the estimated CV

Discussion

For PHCC1 only the medium level was below the quality goal but not statistically significant lower. However, as two instruments were used for duplicate measurements this can cause a higher CV. For PHCC2 the number of samples were lower than 8 and the CV was not estimated.

For the medium and high level the CV was 1,3 % and 1,7 %, respectively and both were statistically significant lower than the quality goal.

Conclusion
Since two instruments were used for duplicate measurements in PHCC1 only results from PHCC2 are included in this conclusion. When measurements were performed by the intended users in PHCC2 the quality goal for repeatability (CV ≤3 %) was fulfilled for medium and high level.

6.4.3. The bias of cobas b 101 HbA1c

The mean deviation (bias) of **cobas b** 101 HbA1c results from the comparison method was calculated. The bias is presented with a 95 % CI in table 8. The results were sorted and divided into three concentration levels according to the mean results of the comparison method. Raw data is attached for the requesting company only, see attachment 7 and 12.

Table 8. Bias of **cobas b** 101 for HbA1c measured in capillary whole blood samples. Results achieved by intended users.

Place	Level	HbA1c interval comparison method, mmol/mol	n*	Excluded results statistical outliers)	Mean HbA1c value comparison method, mmol/mol	Mean HbA1c value PHCCs, mmol/mol	Bias (95 % CI), mmol/mol	Bias, %
	Low	30,8 – 37,6	17	0	34,6	38,1	3,53 (2,98 – 4,07)	10,2
PHCC 1	Medium	38,1 – 50,8	23	1**	41,8	45,2	3,43 (2,83 – 4,02)	8,2
	High	53,7 – 91,0	9	0	62,8	66,7	3,94 (2,08 – 5,79)	6,3
	Low	33,3 – 37,7	12	0	35,8	37,4	1,60 (0,60 – 2,61)	4,5
PHCC 2	Medium	38,0 – 50,4	15	0	43,9	46,7	2,81 (1,92 – 3,70)	6,4
	High	51,0 – 61,8	11	0	54,4	57,0	2,55 (1,78 – 3,33)	4,7

*The given number of results (n) were counted before the exclusion of statistical outliers. Mean and CV were calculated after the exclusion of statistical outliers. An account of the number of samples is given in section 6.1.
**ID 118 was a statistical outlier according to Burnett's model [8] in the calculation of bias and therefore excluded.

Discussion
For all three levels there was a statistically significant bias between **cobas b** 101 HbA1c and the comparison method. The results from **cobas b** 101 were systematically higher than the results from the comparison method for both PHCCs at all three levels.

6.4.4. The accuracy of cobas b 101 HbA1c

To evaluate the accuracy of HbA1c results on **cobas b** 101, the agreement between **cobas b** 101 HbA1c and the comparison method is illustrated in a difference plot (figure 4). The limits for the allowable deviation according to the quality goal (±8,5 %) are shown with stippled lines. In PHCC1 the samples were measured in parallel on the two **cobas b** 101 instruments. For odd patient numbers results from instrument Q66111787 were regarded as the first result, and for even patient numbers results from instrument Q66111686 were regarded as the first result. If the result from one instrument was missing the result from the other instrument was used.
In PHCC2 the samples were measured on the same **cobas b** 101 instrument. The plots illustrate both random and systematic errors, reflecting the total measuring error in the **cobas b** 101 results.
Raw data is attached for the requesting company only, see attachment 6 and 10.

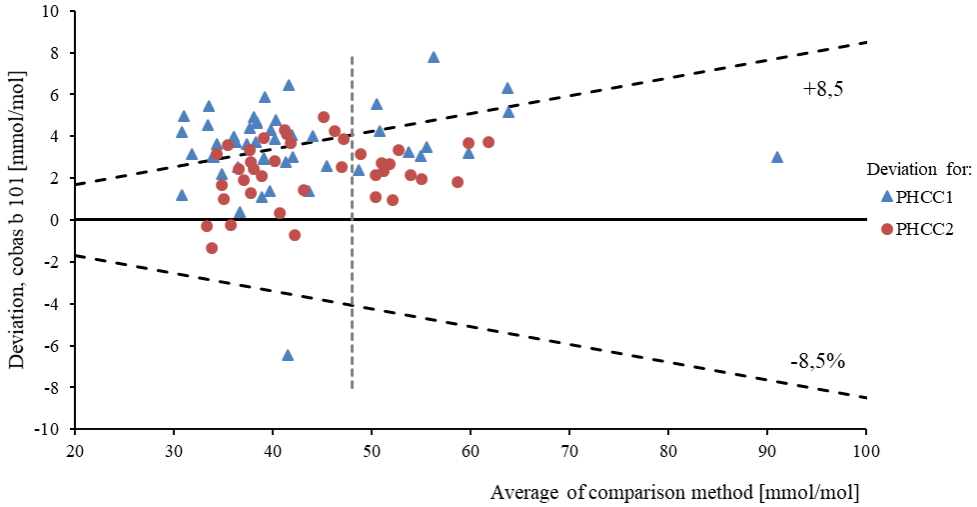

Figure 4. Accuracy of HbA1c results on **cobas b** 101 achieved by intended users. The x-axis represents the mean HbA1c result of the comparison method. The y-axis represents the HbA1c deviation in mmol/mol of the first capillary whole blood sample measurement on **cobas b** 101 HbA1c from the mean result of the corresponding sample of the comparison method.
The vertical line at 48 mmol/mol HbA1c illustrates, the diagnostic threshold value for diabetes.
The different PHCCs are illustrated with the symbols ▲ (PHCC1) and ● (PHCC2). Stippled lines represent the allowable deviation limits of ±8,5 %. Number of results (n) = 90.
An account of the number of samples is given in section 6.1.

Discussion

As shown in figure 4, the **cobas b** 101 HbA1c results are higher than the results from the comparison method, this is especially seen for the results from PHCC1 and this is in consistence with the calculated bias. Of the 90 results 39 results were outside the limits for allowable deviation of ±8,5 % and 51 results were within the limits, amounting to 57 % within the limits. The quality goal for individual results within the limits is ≥95 %.
For results >38 mmol/mol (n=59) 61 % were within the limits.

Conclusion

When measurements were performed by the intended users the quality goal for accuracy was not fulfilled.

6.5. Evaluation of user-friendliness

6.5.1. Questionnaire to the evaluators

The most important response regarding user-friendliness comes from the intended users themselves. The end-users often emphasise other aspects than those pointed out by more extensively trained laboratory personnel.
At the end of the evaluation period, the evaluating persons filled in a questionnaire about the user-friendliness of the measurement system. SKUP has prepared detailed instructions for this.

The questionnaire is divided into four sub-areas:

Table A) Rating of operation facilities. Is the system easy to handle?
Table B) Rating of the information in the manual / insert / quick guide
Table C) Rating of time factors for the preparation and the measurement
Table D) Rating of performing internal and external analytical quality control

The evaluating persons filled in table A and B. SKUP filled in table C and D and in addition, ratings marked with grey background in table A and B.

In the tables, the first column shows the topic for consideration. The second column in table A and B shows the rating by the users at the evaluation sites. The rest of the columns show the rating options. The overall ratings from all the evaluating sites are marked in coloured and bold text. The total rating is an overall assessment by SKUP of the described topics, and not necessarily the arithmetic mean of the rating in the rows. Consequently, a single poor rating can justify an overall poor rating, if this topic seriously influences on the user-friendliness of the system.

Unsatisfactory and intermediate ratings are marked with a number and explained below the tables. The intermediate category covers neutral ratings assessed as neither good nor bad.

An assessment of the user-friendliness is subjective, and the topics in the questionnaire may be emphasised differently by different users. The assessment can therefore vary between different persons and between the countries. This will be discussed and taken into account in the overall assessment of the user-friendliness.

Comment
In this evaluation, the user-friendliness was assessed by:
PHCC1 (evaluation of HbA1c and Lipid Panel in parallel), the opinion of two BLSs.
PHCC2 (evaluation of HbA1c), the opinion of three nurses.

Table A. Rating of operation facilities

Topic	Rating	Rating	Rating	Rating	Option
To prepare the test / instrument	**S, I[1]**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
To prepare the sample	**S, S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
Application of specimen	**S, I[2]**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Specimen volume	**N, S**	**Satisfactory**	Intermediate	Unsatisfactory	**No opinion**
Number of procedure step	**I[3], S**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Instrument / test design	**I[4], S**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Reading of the test result	**S, S**	**Easy**	Intermediate	Difficult	No opinion
Sources of errors	**I[5], S**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Cleaning / Maintenance	**S, S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
Hygiene, when using the test	**S, S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
Size and weight of package	**S, S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
Storage conditions for tests, unopened package	**S**	**+2 to +30°C**	+2 to +8°C	–20°C	
Storage conditions for tests, opened package	**S**	**+15 to +30°C max. 20 min.**	+2 to +8°C	–20°C	
Environmental aspects: waste handling	**S**	**No precautions**	Sorted waste	Special precautions	
Intended users	**S**	**Health care personnel** or patients	Laboratory experience	Biomedical laboratory scientists	
Total rating by SKUP		**Satisfactory**			

[1)] Daily three control tests had to be made (the optical test and two quality controls).
[2)] The time/ time pressure from the preparation to start of analysis.
[3)] Comment from SKUP: This PHCC evaluated both HbA1c and Lipid Panel, which might explain this PHCC's rating on procedure steps.
[4)] No comment from the PHCC.
[5)] One of the instruments had "some" error reports.
Comment from SKUP: The PHCC had two instruments, SKUP has no further information about the error reports.

Additional negative comments:
- Noise from the instrument.

Additional comments:
- As with everything new, it takes practice in the beginning.
- Compared to other instruments in the clinic it is more demanding to use.

Table B. Rating of the information in the manual and quick guide

Topic	Rating	Rating	Rating	Rating	Option
Table of contents/Index	**S, N[1]**	**Satisfactory**	Intermediate	Unsatisfactory	**No opinion**
Preparations/Pre-analytic procedure	**N[1], N[1]**	Satisfactory	Intermediate	Unsatisfactory	**No opinion**
Specimen collection	**N[1], N[1]**	Satisfactory	Intermediate	Unsatisfactory	**No opinion**
Measurement procedure	**N[1], N[1]**	Satisfactory	Intermediate	Unsatisfactory	**No opinion**
Reading of result	**N[1], N[1]**	Satisfactory	Intermediate	Unsatisfactory	**No opinion**
Description of the sources of error	**U[2], S**	**Satisfactory**	Intermediate	**Unsatisfactory**	No opinion
Help for troubleshooting	**U[2], S**	**Satisfactory**	Intermediate	**Unsatisfactory**	No opinion
Readability / Clarity of presentation	**S, N[1]**	**Satisfactory**	Intermediate	Unsatisfactory	**No opinion**
General impression	**I[2], N[1]**	Satisfactory	**Intermediate**	Unsatisfactory	**No opinion**
Measurement principle		**Satisfactory**	Intermediate	Unsatisfactory	
Available insert in Danish, Norwegian, Swedish		**Satisfactory**	Intermediate	Unsatisfactory	
Total rating by SKUP		**Satisfactory**			

[1)]We did not use the user manual as it was not necessary. We received a very thorough instruction before using the instrument.
[2)]We only used the manual for troubleshooting and our experience was that we did not find out what was wrong.

Table C. Rating of time factors (filled in by SKUP)

Topic	Rating	Rating	Rating
Required training time	**<2 hours**	2 to 8 hours	>8 hours
Durations of preparations / Pre-analytical time	**<6 min.**	6 to 10 min.	>10 min.
Duration of analysis	**<10 min.**	10 to 20 min.	>20 min.
Stability of test, unopened package	**>5 months**	3 to 5 months	<3 months
Stability of test, opened package	>30 day or **disposable***	14 to 30 days	<14 days
Stability of quality control material, unopened	**>5 months**	3 to 5 months	<3 months
Stability of quality control material, opened	**>6 days or disposable**	2 to 6 days	≤1 day
Total rating by SKUP	**Satisfactory**		

*The test discs should be used within 20 minutes after the pouch is opened.

Table D. Rating of analytical quality control (filled in by SKUP)

Topic	Rating	Rating	Rating
Reading of the internal quality control	**Satisfactory**	Intermediate	Unsatisfactory
Usefulness of the internal quality control	**Satisfactory**	Intermediate	Unsatisfactory
External quality control	**Satisfactory**	Intermediate	Unsatisfactory
Total rating by SKUP	**Satisfactory**		

6.5.2. Assessment of the user-friendliness

Assessment of the operation facilities (table A)

The operation facilities were in total assessed as satisfactory. Both PHCCs had intermediate ratings but PHCC1, who evaluated HbA1c and Lipid Panel in parallel, rated more of the topics as intermediate. Thus, it seems that the users were more satisfied when analysing only one component, hence the final assessment was interpreted as satisfactory for **cobas 101** b HbA1c.

Assessment of the information in the manual (table B)

The manual was assessed as satisfactory, but there were one intermediate and two unsatisfactory ratings. The motivation for the lower ratings was mainly that the PHCC could not find guidance in the troubleshooting part of the manual.

Assessment of time factors (table C)
The time factors were assessed as satisfactory.

Assessment of analytical quality control possibilities (table D)
The analytical quality control possibilities were assessed as satisfactory.

Conclusion
In all, the user-friendliness of **cobas b** 101 HbA1c and its manual was rated as satisfactory. The quality goal for user-friendliness was fulfilled.

7. References

1. Christensen NG., Monsen G. & Sandberg S. Utprøving av analyseinstrumenter, 1997. Alma Mater Forlag ISBN 82-419-0230-1.

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8. Burnett RW. Accurate estimation of standard deviations for quantitative methods used in clinical chemistry. Clin Chem 1975; **21** (13): 1935 **–** 1938.

9. Tellinghuisen J. Inverse vs. classical calibration for small data sets. *Fresenius J. Anal. Chem.* 2000; **368** (6): 585 – 588.

Attachments

1. The organisation of SKUP
2. Facts about **cobas b** 101 HbA1c
3. Information about manufacturer, retailers and marketing
4. Product specifications for this evaluation, **cobas b** 101 HbA1c
5. Statistical expressions and calculations
6. Data, HbA1c results from the comparison method – KB-AaUH
7. Data, HbA1c results from the comparison method – KBF-OUH
8. Data, HbA1c results from samples for trueness of the comparison methods
9. Data, internal analytical quality control results, **cobas b** 101 HbA1c, optimal conditions
10. Data, **cobas b** 101 HbA1c results, optimal conditions
11. Data, internal analytical quality control results, **cobas b** 101 HbA1c, intended users
12. Data, **cobas b** 101 HbA1c results, intended users
13. List of previous SKUP evaluations
14. Comments from Roche Diagnostics A/S

Attachments with data are included only in the copy to Roche Diagnostics Denmark and Roche Diagnostics Norway.

The organisation of SKUP

Scandinavian evaluation of laboratory equipment for point of care testing, SKUP, is a co-operative commitment of Noklus[1] in Norway, DEKS[2] in Denmark, and Equalis[3] in Sweden. SKUP was established in 1997 at the initiative of laboratory medicine professionals in the three countries. SKUP is led by a Scandinavian *steering committee* and the secretariat is located at Noklus in Bergen, Norway.

The purpose of SKUP is to improve the quality of near patient testing in Scandinavia by providing objective and supplier-independent information about analytical quality and user-friendliness of laboratory equipment. This information is generated by organising SKUP *evaluations*.

SKUP offers manufacturers and suppliers evaluations of laboratory equipment for point of care testing. Provided the equipment is not launched onto the Scandinavian market, it is possible to have a confidential pre-marketing evaluation. The company requesting the evaluation pays the actual testing costs and receives in return an impartial evaluation.

There are *general guidelines* for all SKUP evaluations and for each evaluation a specific *SKUP protocol* is worked out in co-operation with the manufacturer or their representatives. SKUP signs *contracts* with the requesting company and the evaluating laboratories. The analytical results are assessed according to *pre-set quality goals*. To fully demonstrate the quality of a product, the *end-users* should be involved in the evaluations.

Each evaluation is presented in a *SKUP report* to which a unique *report code* is assigned. The code is composed of the acronym SKUP, the year the report was completed and a serial number. A report code, followed by an asterisk (*), indicates an evaluation with a more specific objective. The asterisk is explained on the front page of these protocols and reports.

SKUP reports are published at www.skup.org.

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[1] Noklus (Norwegian Organization for Quality Improvement of Laboratory Examinations) is a national not for profit organisation offering activities for quality improvement to all medical laboratory services in Norway. Noklus was established in 1992 and is governed by a management committee consisting of representatives from the Norwegian Government, the Norwegian Medical Association and the Norwegian Society of Medical Biochemistry, with the Norwegian Association of Local and Regional Authorities (KS) as observer.

[2] DEKS (Danish Institute for External Quality Assurance for Laboratories in Health Care) is a non-profit organisation owned by the Capital Region of Denmark on behalf of all other Regions in Denmark.

[3] Equalis AB (External quality assessment in laboratory medicine in Sweden) is a limited company in Uppsala, Sweden, owned by “Sveriges Kommuner och Regioner” (Swedish Association of Local Authorities and Regions), “Svenska Läkaresällskapet” (Swedish Society of Medicine) and IBL (Swedish Institute of Biomedical Laboratory Science).

Fact about cobas b 101 HbA1c

This form is filled in by Roche Diagnostics.

Table 1. Basic facts.

Name of the measurement system	**cobas b** 101
Dimensions and weight	Width: 135 mm Depth: 234 mm Height: 184 mm Weight: 2,0 kg (without power adapter + cable)
Components of the measurement system	• **cobas b** 101 system • Power adapter • Power cable • HbA1c Test
Measurand	HbA1c
Sample material	Fresh capillary blood, lithium‑heparinised or K2‑ or K3‑EDTA venous blood
Sample volume	2 µL
Measuring principle	Immunturbidimetric method
Traceability	This method has been standardized against the IFCC reference method for the measurement of HbA1c in human blood and can be transferred to results traceable to DCCT/NGSP by calculation. Each disc lot of the **cobas** HbA1c Test is traceable to IFCC
Calibration	The instrument automatically reads in the lot-specific calibration data from the barcode information printed on the disc, eliminating the need for calibration by the user
Measuring range	20 – 130 mmol/mol (IFCC) or 4 – 14 % (DCCT/NGSP)
Haematocrit range	30 % – 55 %
Measurement time	5 minutes and 20 seconds
Operating conditions	+15 ºC to +32 ºC
Electrical power supply	Yes
Recommended regular maintenance	No
Package contents	• **cobas b** 101 system • Power adapter • Power cable • Optical check disc
Necessary equipment not included in the package	No

Table 2. Post analytical traceability.

Is input of patient identification possible?	Yes
Is input of operator identification possible?	Yes
Can the instrument be connected to a bar-code reader?	Yes
Can the instrument be connected to a printer?	Yes
What can be printed?	Patient ID Patient date of birth Operator name Test name Date and time when result was generated Results Comment Date and time when result was printed Facility information Patient name Operator ID Disc lot number
Can the instrument be connected to a PC?	Yes
Can the instrument communicate with LIS (Laboratory Information System)? If yes, is the communication bidirectional?	Yes and yes
What is the storage capacity of the instrument and what is stored in the instrument?	5.000 patient test results 500 control test results 500 sets of patient information 50 sets of operator information, including 5 for administrators
Is it possible to trace/search for measurement results?	Yes

Table 3. Facts about the reagent/test strips/test cassettes.

Name of the reagent/test strips/test cassettes	**cobas b** 101 HbA1c Test
Stability in unopened sealed vial	Stored at 2 – 30 ºC, until the expiration date printed on the pouch
Stability in opened vial	20 minutes
Package contents	10 tests

Table 4. Quality control.

Electronic self check	Yes, Use Optical check disc every day
Recommended control materials and volume	**cobas** HbA1c Control Level 1, 2 bottles 1 mL each, normal range Level 2, 2 bottles 1 mL each, pathologic range
Stability in unopened sealed vial	Up to the stated expiration date at 2 – 8 °C
Stability in opened vial	7 days at 20 – 25 °C or 30 days at 2 – 8 °C
Package contents	▪ 2 x 1 mL Control Level 1 (normal range) ▪ 2 x 1 mL Control Level 2 (pathologic range) ▪ 1 x QC info disc ▪ 2 x 2 droppers, color coded

Information about manufacturer, retailers and marketing

This form is filled in by Roche Diagnostics.

Table 1. Marketing information.

Manufacturer	Roche Diagnostics GmbH
Retailers in Scandinavia	Denmark: Abena A/S, OneMed A/S and Mediq Danmark A/S Norway: Norengros AS Sweden: Not launched
In which countries is the system marketed	Globally ☒ Scandinavia ☒ Europe ☒
Date for start of marketing the system in Scandinavia	April 2013
Date for CE-marking	17.12.2012 and 20.07.2016
In which Scandinavian languages is the manual available	Danish, Norwegian and Swedish

Product specifications for this evaluation, cobas b 101 HbA1c

cobas b *101 HbA1c instrument serial numbers*

Serial no	Used by
Q66111686	Optimal conditions
Q66111787	Optimal conditions
Q66111675	PHCC1
Q66111789	PHCC1
Q66111770	PHCC2

cobas b *101 HbA1c test discs*

Lot no	Expiry date	Used by
834041-01	2020-01-31	All evaluation sites
834042-01	2020-01-31	All evaluation sites
835041-01	2020-02-29	All evaluation sites

cobas b *101 HbA1c internal analytical quality control kit liquid controls*

Control	Lot no	Expiry date	Used by
Level 1	004173	2019-10-31	All evaluation sites
Level 2	004173		

Statistical expressions and calculations

This chapter with standardised text deals with the statistical expressions and calculations used by SKUP. The statistical calculations will change according to the type of evaluation. The descriptions in this document are valid for evaluations of quantitative methods with results on the ratio scale.

Statistical terms and expressions

The definitions in this section come from the International Vocabulary of Metrology - Basic and general concepts and associated terms; VIM [a].

Precision

Definition: Precision is the closeness of agreement between measured quantity values obtained by replicate measurements on the same or similar objects under stated specified conditions.

Precision is measured as *imprecision*. Precision is descriptive in general terms (good, poor e.g.), whereas the imprecision is expressed by means of the standard deviation (SD) or coefficient of variation (CV). SD is reported in the same unit as the analytical result. CV is usually reported in percent.

To be able to interpret an assessment of precision, the precision conditions must be defined.
Repeatability is the precision of consecutive measurements of the same component carried out under identical measuring conditions (within the measuring series).
Reproducibility is the precision of discontinuous measurements of the same component carried out under changing measuring conditions over time.

Trueness

Definition: Trueness is the closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value.

Trueness is inversely related to systematic measurement error. Trueness is measured as *bias*. Trueness is descriptive in general terms (good, poor e.g.), whereas the bias is reported in the same unit as the analytical result or in percent.

Accuracy

Definition: Accuracy is the closeness of agreement between a measured quantity value and the true quantity value of a measurand.

Accuracy is not a quantity and cannot be expressed numerically. Accuracy is descriptive in general terms (good, poor e.g.). A measurement is said to be more accurate when it offers a smaller measurement error. Accuracy can be illustrated in a difference plot.

a. International vocabulary of metrology – Basic and general concepts and associated terms, VIM, 3rd edition, JCGM 200;2012. www.bipm.org

Statistical calculations

Statistical outliers

The criterion promoted by Burnett [b] is used for the detection of outliers. The model takes into consideration the number of observations together with the statistical significance level for the test. The significance level is set to 5 %. The segregation of outliers is made with repeated truncations, and all results are checked. Where the results are classified according to different concentration levels, the outlier-testing is carried out at each level separately. Statistical outliers are excluded from the calculations.

Calculation of imprecision

The precision of the evaluated method is assessed by use of paired measurements of genuine patient sample material. The results are usually divided into three concentration levels, and the estimate of imprecision is calculated for each level separately, using the following formula [c,d,e]:

$$SD = \sqrt{\frac{\sum d^2}{2n}}$$

d = difference between two paired measurements
n = number of differences

(formula 1)

This formula is used when the standard deviation can be assumed reasonable constant across the concentration interval. If the coefficient of variation is more constant across the concentration interval, the following formula is preferred:

$$CV = \sqrt{\frac{\sum (d/m)^2}{2n}}$$

m = mean of paired measurements

(formula 2)

The two formulas are based on the differences between paired measurements. The calculated standard deviation or CV is still a measure of the imprecision of single values. The imposed condition for using the formulas is that there is no systematic difference between the 1st and the 2nd measurement of the pairs. The CV is given with a 90 % confidence interval.

Calculation of bias

The mean deviation (bias) at different concentration levels is calculated. A paired t-test is used with the mean values of the duplicate results on the comparison method and the mean values of the duplicate results on the evaluated method. The mean difference is shown with a 95 % confidence interval.

Assessment of accuracy

The agreement between the evaluated method and the comparison method is illustrated in a difference plot. The x-axis represents the mean value of the duplicate results on the comparison method. The y-axis shows the difference between the first measurement on the evaluated method and the mean value of the duplicate results on the comparison method. The number of results within the quality goal limits is counted and assessed.

b. Burnett RW. Accurate estimation of standard deviations for quantitative methods used in clinical chemistry. *Clin Chem* 1975; **21** (13): 1935 – 1938.
c. Dahlberg G. Statistical methods for medical and biological students, 1940. Chapter 12, Errors of estimation. George Allen & Unwin Ltd.
d. Saunders E. Tietz textbook of clinical chemistry and molecular diagnostics, 2006. Chapter 14, Linnet K., Boyd J. Selection and analytical evaluation of methods – with statistical techniques. Elsevier Saunders ISBN 0-7216-0189-8.
e. Fraser C.G. Biological variation: From principles to practice, 2006. Chapter 1, The Nature of Biological Variation. AACC Press ISBN 1-890883-49-2.

List of previous SKUP evaluations

The 30 latest SKUP evaluations

Evaluation no.	Component	Instrument/test kit	Producer
SKUP/2020/117	HbA1c	**cobas b** 101	Roche Diagnostics GmbH
SKUP/2020/122	Glucose[1]	*Confidential*	
SKUP/2019/116	CRP	**cobas b** 101	Roche Diagnostics GmbH
SKUP/2018/114	Strep A	DIAQUICK Strep A Blue Dipstick	DIALAB GmbH
SKUP/2018/115*	PT (INR)	*Confidential*	
SKUP/2017/113	Glucose[1]	Accu-Chek Instant	Roche Diabetes Care GmbH
SKUP/2017/111	Glucose[1]	*Confidential*	
SKUP/2017/112	Glucose[1]	Accu-Chek Guide	Roche Diabetes Care GmbH
SKUP/2016/110	PT (INR)	Xprecia Stride Coagulation system	Siemens Healthcare Diagnostics INC
SKUP/2015/107	Strep A	QuickVue Dipstick Strep A Test	Quidel Corporation
SKUP/2015/109	PT (INR)	microINR portable coagulometer	iLine Microsystems S.L.
SKUP/2015/108	HbA1c	*Confidential*	
SKUP/2015/102	HbA1c	*Confidential*	
SKUP/2015/106*	Strep A	QuikRead go	Orion Diagnostica Oy
SKUP/2014/101	HbA1c	InnovaStar analyzer	DiaSys Diagnostic Systems GmbH
SKUP/2014/104	PT (INR)	ProTime InRythm	ITC International Technidyne Corporation
SKUP/2014/105	Glucose[1]	Accu-Chek Aviva	Roche Diagnostics GmbH
SKUP/2014/103	PT (INR)	*Confidential*	
SKUP/2013/87	Glucose[1]	Wella Calla Light	Med Trust Handelsges.m.b.H.
SKUP/2013/100	Glucose[1]	Mylife Unio	Bionime Corporation
SKUP/2013/97	NT-proBNP	Cobas h 232 POC system	Roche Diagnostics GmbH
SKUP/2013/92	CRP	Eurolyser smart 700/340	Eurolyser Diagnostica GmbH
SKUP/2013/99*	Glucose	Accu-Chek Mobile	Roche Diagnostics
SKUP/2013/98*	Glucose	Accu-Chek Aviva	Roche Diagnostics
SKUP/2013/85	Glucose, β-Ketone	Nova StatStrip	Nova Biomedical Corporation, USA
SKUP/2013/96	Hemoglobin	DiaSpect Hemoglobin T	DiaSpect Medical GmbH
SKUP/2013/68	Allergens	ImmunoCap Rapid	Phadia AB Marknadsbolag Sverige
SKUP/2012/95	Glucose[1]	Mendor Discreet	Mendor Oy
SKUP/2012/94	Glucose[1]	Contour XT	Bayer Healthcare
SKUP/2012/91	HbA1c	Quo-Test A1c	Quoient Diagnostics Ltd

*Some evaluation codes are followed by an asterisk (*), indicating an evaluation with a more specific objective. The asterisk is explained on the front page of these protocols and reports.
[1]Including a user-evaluation among diabetes patients

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13 October 2020

Comments for report on testing of cobas b 101 HbA1c; SKUP/2019/117

Roche is pleased to see the excellent results obtained in the evaluation of the user-friendliness of the **cobas** HbA1c Test on the **cobas b** 101 system. The user-friendliness, the information in the manual, time factors and analytical quality controls all received the best possible rating and confirms the market feedback we received for the **cobas b** 101 system. We would like to thank SKUP for the comprehensive evaluation.

In addition we also would like to thank SKUP for the excellent collaboration. In the review process of the initial results, SKUP and Roche identified several items in the evaluation protocol which need optimization (see below). Therefore we concluded that the analytical performance shall be reassessed in an additional study. Roche acknowledges the possibility of a reevaluation of the analytical performance.

Among the various deficiencies in the protocol the following main issues were identified:

Assessment of imprecision:
The usage of more than one **cobas b** 101 instrument in one site was identified as an additional source of variation. Therefore a final assessment against the defined quality goal for precision is not possible.

Accuracy and bias:
In recent years the general performance requirements for HbA1c have become stricter. For example the criteria for obtaining certificate of traceability to NGSP was updated several times. We acknowledge that SKUP is following this trend by using very stringent criteria for analytical performance in the evaluation. However, the comparison of the **cobas** HbA1c Test with the stringent criteria used in this evaluation, and competitor devices evaluated earlier with less stringent criteria, is not feasible.

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In addition we learned that even small inaccuracies from the chosen reference system during the performance evaluation might have a great impact on the results. Roche thinks that the current protocol must be improved regarding the control and selection of the reference systems in order to provide best possible traceability of reference values to primary reference materials (IFCC). We are convinced that the setup used in this performance evaluation does not fully recover the excellent accuracy of the **cobas** HbA1c Test.

We are looking forward to reassess the analytical performance of the **cobas** HbA1c Test with an improved protocol.

Kind regards,

Roche Diagnostics A/S

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