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/2022/129*

organised by SKUP at the request of

Roche Diagnostics in Denmark and Norway

*This evaluation is a follow-up of a previous evaluation

SKUP in Denmark, DEKS, Rigshospitalet-Glostrup, DK-2600 Glostrup, Phone +45 38634406, www.skup.org
SKUP in Norway, Noklus, Box 6165, NO-5892 Bergen, Phone +47 404 72 92, www.skup.org
SKUP in Sweden, Equalis, Box 977, SE-751 09 Uppsala, Phone: +46 18 490 31 44, www.skup.org

SKUP secretariat
Elisabet Eriksson Boija
+46 18 490 31 44
elisabet.eriksson.boija@equalis.se

SKUP in Denmark
Dår Kristian Kur
Gitte M. Henriksen
DEKS
Rigshospitalet – Glostrup
Valdemar Hansens vej 1-23
DK-2600 Glostrup
+45 38 63 44 06
daar.kur@deks.dk
gitte.henriksen@deks.dk

SKUP in Norway
Christine Morken
Hege Alvheim
Joakim Hekland
Mette Christophersen Tollånes
Sverre Sandberg
Noklus
Boks 6165
NO-5892 Bergen
+47 404 72 928
christine.morken@noklus.no
hege.alvheim@noklus.no
joakim.hekland@noklus.no
mette.tollanes@noklus.no
sverre.sandberg@noklus.no

SKUP in Sweden
Elisabet Eriksson Boija
Mathias Karlsson
Gunnar Nordin
Equalis AB
P.O. Box 977
SE-751 09 Uppsala
+46 18 490 31 44
elisabet.eriksson.boija@equalis.se
mathias.karlsson@equalis.se
gunnar.nordin@equalis.se

www.SKUP.org

SKUP would like to acknowledge with thanks those who contributed to the practical work with this evaluation including Ingvild Garnes and Grete Teigland Olsnes in Øyrane primary health care centre, Eirin Gjermundnes, May Bente Espeland and Anita Kokai in Varden primary health care centre, Berit Storvik Brendehaug and Solveig Simmenes in department of Medical Biochemistry and Pharmacology at Haukeland University Hospital, and Anne Marit Fjeldstad at Haraldsplass Deaconess Hospital.

Table of contents

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
7. Raw data, internal analytical quality control results, **cobas b** 101 HbA1c, intended users
8. Raw data, **cobas b** 101 HbA1c results, intended users

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

1. Summary of an evaluation provided by SKUP | cobas b 101 for measurement of HbA1c

Manufacturer	Roche Diagnostics GmbH
Supplier	Roche Diagnostics Norge AS in Norway* Roche Diagnostics A/S in Denmark*
Launched in Scandinavia	April 2013

SKUP
www.skup.org
SKUP/2022/129

Aim

The aim of the evaluation was to assess the analytical quality and user-friendliness of **cobas b** 101 HbA1c, when used under real-life conditions by intended users in primary health care centres (PHCCs). Assessment under optimal and real-life conditions was performed under a former evaluation (SKUP/2020/117). The quality goal for repeatability was fulfilled under optimal conditions (CV 1,4-3,4%), while the quality goal for accuracy was not (83%).

Evaluated parameters	Quality goals	Conclusions and results
Repeatability	CV ≤3,0 %	**Fulfilled under real-life conditions** (CV 1,4-2,6 %)
Accuracy	≥95 % of the results should be within ±3,0 mmol/mol from the results of the comparison method at HbA1c concentration <35,3 mmol/mol and within ±8,5 % at HbA1c concentration ≥35,3 mmol/mol	**Not fulfilled under real-life conditions** (83 %)
User-friendliness	A total rating of "Satisfactory"	**Not fulfilled** (Fulfilled under real-life conditions in SKUP/2020/117)

Background

Measurement system	In vitro diagnostic device for measurement of C-reactive protein (CRP), Haemoglobin A1c (HbA1c) and a Lipid Panel
Intended users	Health care professionals
Sample material	Capillary whole blood, or venous ethylenediaminetetraacetic acid (EDTA) or lithium-heparinised venous whole blood. Capillary whole blood was evaluated.

Material and methods

Participants	106 patients in PHCC's
Comparison method	A high performance liquid chromatography (HPLC) method implemented on D-100 HbA1c System (Bio-Rad Laboratories, Inc.)
Analytical procedure	The PHCC's received a demonstration of **cobas b** 101 HbA1c by Roche Diagnostics Norway. Analysis of fresh capillary whole blood samples from each participant on **cobas b** 101 HbA1c. The measurements were performed in duplicate, i.e. two separate finger sticks. Three lots of test discs were used. Analysis of venous samples (K_2-EDTA sample tubes) from the same individuals were measured in duplicate on the comparison method. The evaluation was carried out from June to December 2021.
User-friendliness	Assessed using a questionnaire with three given ratings; satisfactory, intermediate and unsatisfactory

Additional findings

Bias	≈+2 mmol/mol between **cobas b** 101 HbA1c and the comparison method
Technical errors	None

Roche Diagnostics has accepted the report without further comments

* Requesting company

This summary is also published in Danish, Norwegian and Swedish at www.skup.org.

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 the Health Sector
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
HPLC	High performance liquid chromatography
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
LC/MS	Liquid Chromatography / Mass Spectrometry
MBF	Medical Biochemistry and Pharmacology
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
VUK	Videnskabeligt Udvalg for Kvalitetssikring (The Danish Scientific Committee for Quality Assurance)

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 sample material is fresh capillary whole blood or venous ethylenediaminetetraacetic acid (EDTA) whole blood. The system is produced by Roche Diagnostics GmbH and was launched into the Scandinavian market April 2013. The **cobas b** 101 HbA1c system was evaluated by SKUP in 2020 (SKUP/2020/117) and the current evaluation was a follow-up of that evaluation. The SKUP evaluation of **cobas b** 101 HbA1c was carried out in June to December 2021 at the request of Roche Diagnostics Denmark and Roche Diagnostics Norway.

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, 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 was carried out by intended users in two primary health care centres (PHCCs) (figure 1), and it documents the quality of the system under real-life conditions.

[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.

The evaluation of **cobas b** 101 for measurement of HbA1c in fresh capillary whole blood samples include:

- Examination of the analytical quality (precision and accuracy) in the hands of intended users
- Evaluation of the user-friendliness of the **cobas b** 101 HbA1c and its manual

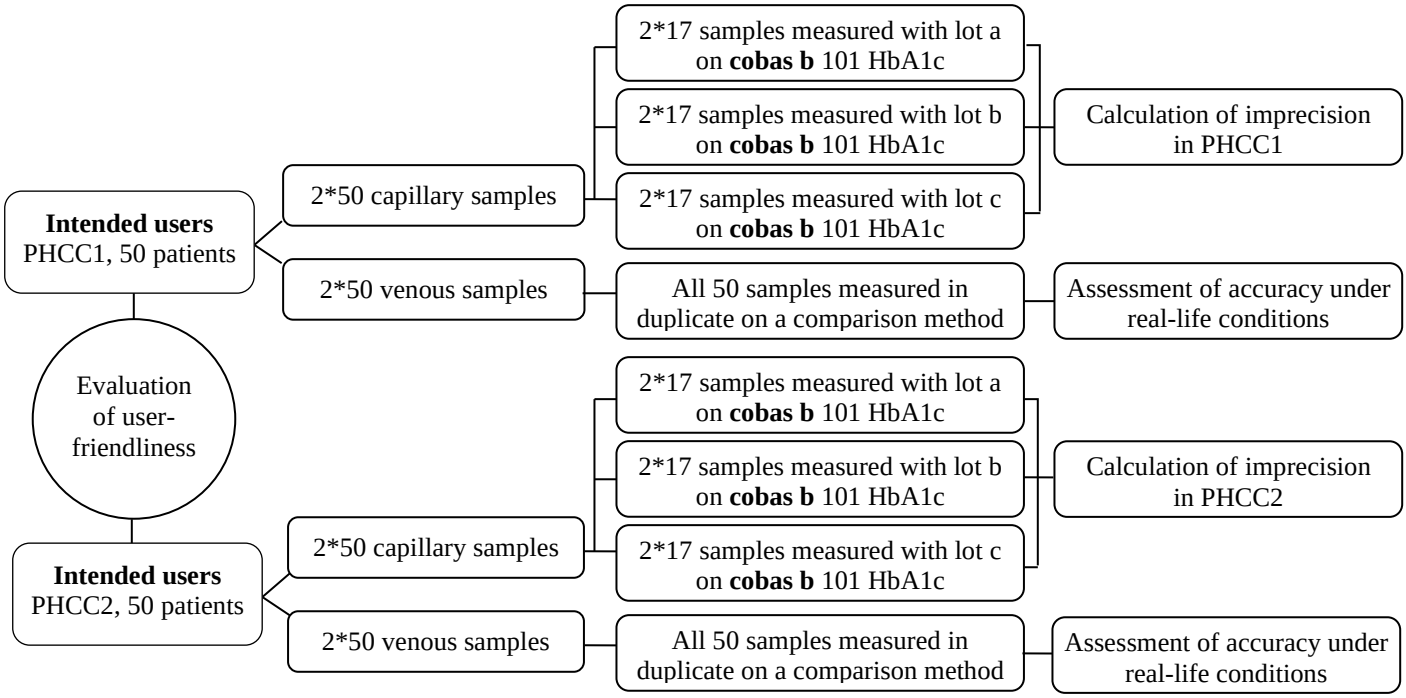

Figure 1. Flowchart illustrating the model for the evaluation of **cobas b** 101 HbA1c.

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 Diabetes Control and Complications Trial (DCCT) % are different.

The Danish Society of Clinical Chemistry (DSKB) has a scientific committee for quality assurance Videnskabeligt Udvalg for Kvalitetssikring (VUK). 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).

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 <±7,4 % (in IFCC units) from reference target at a level of 48 mmol/mol and a CV <3 % must be documented [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
Thus, the allowable deviation at 48 mmol/mol is <±3,5 mmol/mol.

SKUP has chosen to use a quality goal of 3,0 CV % for repeatability. To fulfil the accuracy goal at least 95 % of the individual HbA1c results shall fall within ±3,0 mmol/mol of the average measured values of the comparison method at HbA1c concentrations <35,3 mmol/mol, or within ±8,5 % at HbA1c concentrations ≥35,3 mmol/mol. The quality goals are based on SKUPs own estimations and the national recommendations from Denmark, Norway and Sweden [7]. 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 was carried out by asking the evaluating persons to fill in a questionnaire, see section 6.4.

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 equal to or lower than the quality goal (statistically significant)	The quality goal is fulfilled
The CV is equal to or 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.

Bias with three lots of test discs

Separate lot calculations were not performed. The results achieved with the three lots are included in the assessment of accuracy in a difference plot. 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 6.4.

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. User errors are not included in the calculation.

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

for HbA1c concentrations <35,3 mmol/mol ..... ≤±3,0 mmol/mol

and for HbA1c concentrations ≥35,3 mmol/mol ..... ≤±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 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 [8]. 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 b** 101 HbA1c test disc are traceable to the IFCC reference method.

Every **cobas b** 101 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** 101 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

Technical details for cobas b 101 HbA1c	
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
Electrical power supply	100 – 240 V

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 in this evaluation was a high performance liquid chromatography (HPLC) method implemented on D-100 HbA1c System (Bio-Rad Laboratories, Inc.), hereafter called "the comparison method", in Medical Biochemistry and Pharmacology (MBF), Haukeland University Hospital, Norway. The method is accredited according to NS-EN ISO/IEC 15189:2012 (Norsk Standard_Europeisk Norm International Organization for Standardization). The instrument reports the results with one decimal.

Method:	HPLC
Principle:	Ion-Exchange chromatography
Traceability:	Traceable to NGSP and IFCC [5,6]
Reagent:	D-100 HbA1c Elution Buffer A and B, and D-100 Wash Solution
Calibrators:	D-100 HbA1c Analytical Cartridge/Calibrator Pack
Reportable range:	15 – 195 mmol/mol

Internal analytical quality control

Internal analytical quality control samples, two levels (Lyphochek Diabetes Control, Bio-Rad) and one level of pooled blood (MBF in-house production) were measured each evaluation day on the comparison method.

External analytical quality control
The clinical laboratory participates in Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus) external quality assessment (EQA) scheme for HbA1c with two levels in four rounds per year. The materials are fresh-pooled K_2-EDTA blood from Norwegian donors with assigned HbA1c values from the IFCC reference method of INSTAND, Germany [9].

5.3.2. 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 document the trueness of the comparison method, fresh frozen venous K_2-EDTA patient samples with certified values assigned from the IFCC liquid chromatography / mass spectrometry (LC/MS) reference measurement procedure at INSTAND, Germany, were used [10]. The samples consist of four patient samples with HbA1c concentrations at different levels with given uncertainties. The target values are given with an expanded uncertainty of <2 % (k=2). If necessary, the comparison method's results are adjusted according to the certified INSTAND targets. The adjustment is carried out by means of inverse calibration [11,12]. The trueness of the comparison method was also verified with EQA results for a period circumventing the evaluation period.

5.4. The evaluation

5.4.1. Planning of the evaluation

Inquiry about an evaluation
Roche Diagnostics via Medical Affairs Manager Liv-Janne Øvrebust, applied to SKUP during spring 2021 for a follow-up evaluation of **cobas b** 101.

Protocol, arrangements and contract
In August 2021, the protocol for the evaluation was approved, and Roche Diagnostics and SKUP signed a contract for the evaluation. Two primary health care centres, Legehuset Varden and Øyrane Legekontor in Bergen, Vestland county agreed to represent the intended users in this evaluation.

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

5.4.2. Evaluation sites and persons involved

The practical work in the PHCCs was carried out from June 2021, ending in December 2021.

Biomedical laboratory scientists (BLSs) in MBF, Haukeland University Hospital, Norway, were responsible for the measurements on the comparison method.

Three health secretaries in PHCC1 and two in PHCC2 were involved in the practical work for sampling and for measurements on **cobas b** 101 HbA1c. The PHCCs have three and four physicians employed, respectively. They use fresh capillary or venous whole blood samples in their routine method for measurement of HbA1c.

5.4.3. 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 16 years or older, coming into the PHCCs for HbA1c measurements, were asked if they were willing to donate two capillary and two venous blood samples for the evaluation. Participation was voluntary and verbal informed consent was considered sufficient. Patients with known hemoglobinopathies were not included. An ethical approval was not necessary because the evaluation was considered as a quality assurance project.

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.

The patients 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 1,8 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. 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 one venous puncture and collected into two Vacutainer tubes with K_2-EDTA. The tubes were inverted ten times to ensure thorough mixing and kept in room temperature until transported to MBF the same day. Both Vacutainer tubes were analysed within 72 hours after sampling. Each of the two venous samples was measured once on the comparison method, resulting in duplicate results. 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 by the intended users in the PHCCs.

At the end of the evaluation a total of 107 patients were enrolled. PHCC1 recruited 70 patients (SKUP ID 101 – 174, except SKUP ID 108, 109, 118 and 124) and PHCC2 recruited 37 patients (SKUP ID 201 – 237). The results from the comparison methods covered an HbA1c interval from 26 – 92 mmol/mol of which 94 % of the samples were in the clinically relevant HbA1c interval ≥39 mmol/mol. An account of the number of samples not included in the calculations, is given below.

Missing results

- From PHCC1 and PHCC2; internal analytical quality control results for one evaluation day at each site were missing. The results from the patient samples these days were still included in the calculations.
- ID 108, ID 109, ID 118 and ID 124; SKUP ID's not used.
- ID 160; 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 207, ID 208, ID 217 and ID 220; only single measurement from **cobas b** 101 due to error code E-216. The results were included in the calculation of bias and the assessment of accuracy but not included in the calculation of repeatability.
- ID 225; no results from the comparison method, and only one result from **cobas b** 101. The result was not included in any calculations.

Omitted results

- ID 104; measured on comparison method >72 hours after sampling. The results from **cobas b** 101 were included in the calculations of repeatability for **cobas b** 101 but not included in the calculation of bias and the assessment of accuracy.
- ID 122 and ID 123; the results from **cobas b** 101 were omitted due to suspected mix-up between patients. The results from these patients were only included in the calculation of repeatability for the comparison method.

Excluded results (statistical outliers)

Statistical outliers according to Burnett [10]:

– ID 230; 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 repeatability and bias but were included in the assessment of accuracy (the first of the duplicate measurements).

Recorded error codes, technical errors and failed measurements
Error code E-216 (“Shock during measurement”) was reported related to measurement of HbA1c in PHCC2 four times. Since this might have been caused by construction work outside of the evaluation site these errors will not be included in technical errors. No other error codes were reported. The SKUP recommendation of a fraction of ≤2 % tests wasted due to technical errors was achieved.

6.2. Analytical quality of the selected comparison method

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

6.2.2. The precision of the comparison method
Duplicate measurements of venous samples from the patients participating were performed on the comparison method. The results were checked visually to meet the imposed condition for using formula 1 in attachment 5. There was no systematic difference between the paired measurements (data not shown).

The precision is presented as repeatability (CV). The CV with a 90 % CI is shown in table 3. 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.

Table 3. Repeatability (CV) of the comparison method D-100 (Bio-Rad) for HbA1c measured in venous whole blood samples.

Level	n*	Excluded results (statistical outliers)	Mean HbA1c value, mmol/mol	CV (90 % CI), %
1	7	0	33,8	2,0 (1,4 - 3,9)**
2	85	0	50,1	1,5 (1,3 - 1,7)
3	13	0	67,0	1,0 (0,7 - 1,4)

*An account of the number of samples is given in section 6.1.
**Due to the low number of results, the CV is less certain för level 1, which can be seen by the higher CI at this level.

Discussion
The CV for the comparison method was between 1,0 and 2,0 %.

6.2.3. The trueness of the comparison method

In order to demonstrate the trueness of the comparison method, four levels of venous fresh frozen K_2-EDTA patient samples with assigned values from a reference method at INSTAND were analysed. The analyses were performed in triplicate once, and with ten replicates on three occasions during the evaluation period. The agreement between the comparison method and the samples with assigned reference values is shown in table 4.

Table 4. Samples with assigned reference values measured on the comparison method.

Material	Date	Assigned HbA1c values INSTAND (k=2) mmol/mol	n	Mean D-100 (Bio-Rad)	Deviation from target value, %
Level 1	2021-06-24	**29,1** (28,7 – 29,5)	3	29,8	+2,4
	2021-07-05		10	30,1	+3,5
	2021-09-21		10	30,0	+3,2
	2021-12-06		10	29,9	+2,6
	Total		**33**	**30,0**	**+2,9**
Level 2	2021-06-24	**48,4** (47,7 – 49,1)	3	49,0	+1,3
	2021-07-05		10	50,1	+3,5
	2021-09-21		10	49,8	+2,8
	2021-12-06		10	50,5	+4,3
	Total		**33**	**49,9**	**+3,0**
Level 3	2021-06-24	**57,2** (56,3 – 58,1)	3	58,7	+2,6
	2021-07-05		10	59,5	+4,1
	2021-09-21		10	58,8	+2,7
	2021-12-06		10	59,6	+4,2
	Total		**33**	**59,2**	**+3,4**
Level 4	2021-06-24	**79,6** (78,4 – 80,8)	3	83,1	+4,4
	2021-07-05		10	84,1	+5,6
	2021-09-21		10	82,4	+3,6
	2021-12-06		10	84,6	+6,3
	Total		**33**	**83,6**	**+5,0**

Discussion

Table 4 shows that the HbA1c results for the reference samples were above the upper uncertainty limit for all levels. All results from the comparison method were therefore adjusted according to the assigned values from INSTAND. Since the collection of patient samples were divided into two periods (summer and autumn/winter) the adjustment was carried out by means of inverse calibration [11, 12] by one of the following regression equations: **y = 0,9352x + 1,3929** (reference samples analysed 2021-06-24 and 2021-07-05) or **y = 0,9405x + 1,1917** (reference samples analysed 2021-09-21 and 2021-12-06). Further on in the report, whenever a result from the comparison method is presented, the result has already been adjusted according to this.
The comparison method was within the acceptance limits of the target values in the EQA program for HbA1c, se table 5.

Table 5. Trueness of the comparison method.

Control	Date	Target value* HbA1c, (acceptance limits) mmol/mol	n	Reported value HbA1c, mmol/mol	Adjusted with the regression equation value HbA1c, mmol/mol
SPLHBA2021.01_1	2021-01-25	34,0 (31,3-36,8)	2	34,0	33,2
SPLHBA2021.01_2	2021-01-25	52,9 (49,2-56,7)	2	54,2	52,1
SPLHBA2021.02_1	2021-05-03	41,7 (38,6-44,9)	2	41,8	40,5
SPLHBA2021.02_2	2021-05-03	50,6 (47,0-54,3)	2	50,4	48,5
SPLHBA2021.03_1	2021-08-23	31,2 (28,0-34,5)	2	31,2	30,5
SPLHBA2021.03_2	2021-08-23	42,6 (38,6-46,8)	2	43,8	42,4
SPLHBA2022.01_1	2022-01-17	35,5 (32,0-39,2)	2	37,2	36,2
SPLHBA2022.01_2	2022-01-17	47,5 (43,1-52,0)	2	50,5	48,7

*Determined by INSTAND with exception for SPLHBA2021.02, where target values were consensus values from participants using the same method (n=8).

6.3. 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.

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 8,4 % for level 1 (n=58) and 4,3 % for level 2 (n=63). Raw data is attached for the requesting company only, attachment 7.

6.3.2. The precision of cobas b 101

Duplicate measurements of fresh capillary whole blood from each patient were performed on the **cobas b** 101 HbA1c system. The results were checked visually 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). The CV with a 90 % CI is shown in table 6. The results were sorted and divided into three concentration levels according to the mean of the results on the **cobas b** 101 HbA1c system. Raw data is attached for the requesting company only, see attachment 8.

Table 6. Repeatability (CV) of **cobas b** 101 for HbA1c measured in capillary whole blood samples. Resuls achieved by intended users.

Place	Level	n*	Excluded results (statistical outliers)	Mean value HbA1c, mmol/mol	CV (90 % CI), %
	1	5**			
PHCC1	2	50	0	49,7	2,6 (2,2 - 3,1)
	3	12	0	66,4	1,9 (1,5 - 3,0)
	1	2**			
PHCC2	2	28	1***	50,2	1,4 (1,1 - 1,8)
	3	2**			

*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.
**n<8; CV not reported due to high degree of uncertainty.
***ID 230 was statistical outliers according to Burnett's model [10] in the calculation of repeatability and therefore excluded.

Discussion
The CV achieved by intended users varied between 1,4 and 2,6 % depending on the concentration level. A statistically significant difference in the CVs between the two PHCCs was shown for level 2. In PHCC2 the CV for this level was statistically significant below the quality goal

Conclusion
When measurements were performed by the intended users the quality goal for repeatability (CV ≤3 %) was most likely fulfilled in PHCC1 and fulfilled in PHCC2.

6.3.3. 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 7. 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 8.

Table 7. Bias of **cobas b** 101 for HbA1c measured in capillary whole blood samples. Results achieved by intended users.

Place	Level	n	Excluded results (statistical outliers)	Mean HbA1c value comparison method, mmol/mol	Mean HbA1c value cobas b 101, mmol/mol	Bias (95 % CI), mmol/mol	Bias, %
	1	7	0	34,9	37,1	2,19 (-0,09 – 4,47)	6,3
PHCC 1	2	51	0	49,0	50,6	1,63 (1,03 – 2,23)	3,3
	3	9	0	65,3	67,9	2,60 (0,96 – 4,24)	4,0
	1	2	0	31,6	36,0	4,41 (-18,88 – 27,69)	13,9
PHCC 2	2	30	0	47,7	50,4	2,61 (1,81 – 3,41)	5,5
	3	3	0	63,4	63,5	0,14 (-3,51 – 3,79)	0,2

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

Discussion
There was a statistically significant bias between **cobas b** 101 HbA1c and the comparison method for level 2 for both PHCC's, and for level 3 for PHCC1. The results from **cobas b** 101 were systematically higher than the results from the comparison method. The results with few samples should be interpreted with caution.

6.3.4. The accuracy of cobas b 101 HbA1c

To evaluate the accuracy of HbA1c results on the **cobas b** 101, the agreement between the **cobas b** 101 and the comparison method is illustrated in a difference plot (figure 3a and 3b). The limits for the allowable deviation according to the quality goal (within ±3,0 mmol/mol of the results of the comparison method for HbA1c concentrations <35,3 mmol/mol and within ±8,5 % for HbA1c concentrations ≥35,3 mmol/mol), are shown with stippled lines. All the first measurements from the **cobas b** 101 are included in the plot. The plot illustrates 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 8.

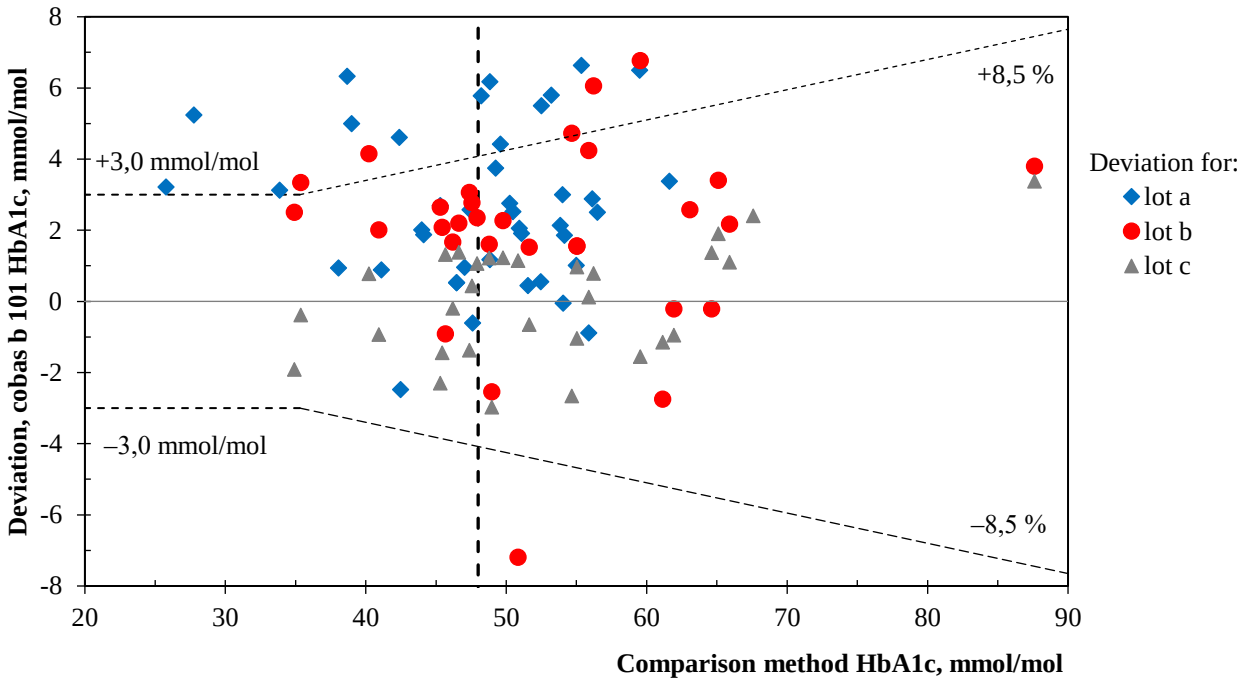

Figure 3a. Accuracy of HbA1c results on **cobas b** 101 achieved by intended users presented per lot number. The x-axis represents the mean HbA1c result of the comparison method. The y-axis represents the HbA1c deviation of the first capillary measurement on **cobas b** 101 from the mean result of the corresponding sample of the comparison method. The vertical line at 48 mmol/mol HbA1c illustrates the diagnostic threshold value for diabetes. The different lot numbers are illustrated with the symbols ♦ (Lot a), ● (Lot b), and ▲ (Lot c). Stippled lines represent the allowable deviation limits of the quality goal (within ±3,0 mmol/mol of the results of the comparison method for HbA1c concentrations <35,3 mmol/mol and within ±8,5 % for HbA1c concentrations ≥35,3 mmol/mol). Number of results (n) = 103. An account of the number of samples is given in section 6.1.

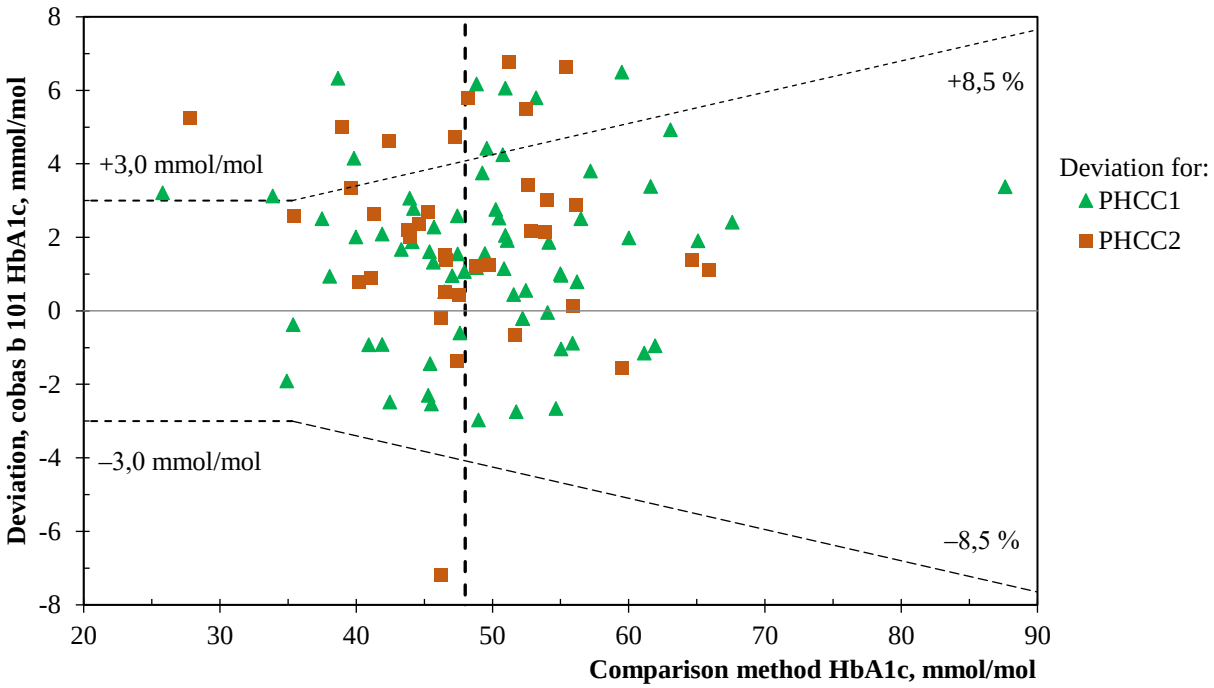

Figure 3b. Accuracy of HbA1c results on **cobas b** 101 achieved by intended users presented per centre. The x-axis represents the mean HbA1c result of the comparison method. The y-axis represents the HbA1c deviation in mmol/mol of the first capillary whole blood sample measurement on **cobas b** 101 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 the quality goal (within ±3,0 mmol/mol of the results of the comparison method for HbA1c concentrations <35,3 mmol/mol and within ±8,5 % for HbA1c concentrations ≥35,3 mmol/mol). Number of results (n) = 103. An account of the number of samples is given in section 6.1.

Discussion

As shown in figure 3a and 3b, the **cobas b** 101 HbA1c results are higher than the results from the comparison method for both PHCCs, which is in consistence with the calculated bias. The difference is more apparent for two of the three lot numbers (lot a and b). Of the 103 results, 85 results were inside the limits for allowable deviation of ±3,0 mmol/mol of the results of the comparison method for HbA1c concentrations <35,3 mmol/mol and within ±8,5 % for HbA1c concentrations ≥35,3 mmol/mol, corresponding to 83 % within the limits. One of the lot numbers (lot c) corresponds better than the other lot numbers with the comparison method, as the deviations are distributed evenly around the zero-line. For this lot, all results were within the limits of accuracy.

Conclusion

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

6.4. Evaluation of user-friendliness

6.4.1. Questionnaire to the evaluators

The most important response regarding user-friendliness comes from the intended users themselves. The end-users often emphasize other aspects than those pointed out by more extensively trained laboratory personnel.
At the end of the evaluation period, the intended users 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 intended users 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 emphasized 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, the opinion of three health secretaries.
PHCC2, the opinion of two health secretaries.

Table A. Rating of operation facilities

Topic	Rating	Rating	Rating	Rating	Option
To prepare the test / instrument	**S, S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
To prepare the sample	**S, S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
Application of specimen	**U[1], U[1]**	Satisfactory	Intermediate	**Unsatisfactory**	No opinion
Specimen volume	**S, S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
Number of procedure step	**S, S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
Instrument / test design	**I[1,2], I[1]**	Satisfactory	**Intermediate**	Unsatisfactory	No opinion
Reading of the test result	**S, S**	**Easy**	Intermediate	Difficult	No opinion
Sources of errors	**S, U[4]**	**Satisfactory**	Intermediate	**Unsatisfactory**	No opinion
Cleaning / Maintenance	**I[3], I[3]**	Satisfactory	**Intermediate**	Unsatisfactory	No opinion
Hygiene, when using the test	**S, I[3]**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Size and weight of package	**I[2], 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			**Intermediate**		

[1)] Application of the sample into the sampling unit of the disc could be "tricky", one had to be very precise. Sometimes hard to "close" the disc.
[2)] The instrument together with the printer, barcode reader, cables and reagent were a bit space consuming.
[3)] Excess blood was thrown into the instrument during centrifuging
[4)] One PHCC experienced error E-216 several times: "Shock during measurements". There was construction work outside the site, and they suggested that it may have contributed to shaking of the instrument. Comment from SKUP: These errors have not been included in the conclusion of the user-friendliness and not in the calculation of technical errors.

Additional positive comments: Messages from the instrument were easy to understand

Additional negative comments: Many steps and hard to navigate in the menu of the screen in the beginning but got used to it eventually. Noise from the instrument.

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

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

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**		

6.4.2. Assessment of the user-friendliness

Assessment of the operation facilities (table A)
The operation facilities were in total assessed as intermediate. The motivations for the lower ratings mainly concerned the handling of the test discs.

Assessment of the information in the manual (table B)
The manual and the quick guide were assessed as satisfactory.

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

Assessment of analytical quality control possibilities (table D)
The imprecision achieved with the internal analytical quality control material was above the repeatability of the patient samples, i.e., less possibilities to discover errors in the analytical system. In all, the analytical quality control possibilities were assessed as satisfactory.

Conclusion
The user-friendliness of **cobas b** 101 HbA1c was rated as intermediate. The quality goal for user-friendliness was not fulfilled.

7. References

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

2. Weykamp CW. *et al*. The analytical goals for hemoglobin A1c measurement in IFCC units and national glycohemoglobin standardization program units are different. Clin Chem 2011; 57: 1204 – 1206.

3. DSKB. Rapport fra VUK om HbA1c. Analysekvalitetskrav til HbA1c ved brug til diagnostik og monitorering af diabetes (2011). https://dskb.dk/wp-content/uploads/2020/11/VUK-HbA1c.pdf (accessed 2021-12-17)

4. The Norwegian Directorate of Health. https://www.helsedirektoratet.no/tema/diabetes#diagnostiske-kriterier-for-diabetessterk-anbefaling (accessed 2021-12-17)

5. Noklus. https://www.noklus.no/media/lexh2sbo/innsnevring-av-kvalitetskrav-for-hba1c_2019.pdf (accessed 2021-12-17)

6. Equalis. https://www.equalis.se/sv/produkter-tjanster/kunskapsstod/rekommendationer/kvalitetsmal-for-hba1c-metoder-vid-diagnostik-av-typ-2-diabetes-s006/ (accessed 2021-12-17)

7. DSKB-nyt 2/2021. Analysekrav til HbA1c på POCT-udstyr ved SKUP-afprøvning. https://dskb.dk/wp-content/uploads/2021/06/202102_DSKBnyt_web.pdf (accessed 2021-09-22)

8. The IFCC – UPAC terminology for properties and units. http://www.ifcc.org/ifcc-scientific-division/sd-committees/c-npu/npusearch/ (accessed 2021-12-17)

9. Kaiser P. *et al.* Modified HPLC-electrospray ionization/mass spectrometry method for HbA1c based on IFCC reference measurement procedure. Clin Chem 2008; 54 (6): 1018 – 1022.

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

11. Krutchkoff RG. Classical and inverse regression methods of calibration. Technometrics 1967; 9 (3): 425 – 439.

12. 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
7. Raw data, internal analytical quality control results, **cobas b** 101 HbA1c, intended users
8. Raw data, **cobas b** 101 HbA1c results, intended users

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 DEKS[1] in Denmark, Noklus[2] in Norway 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.

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

[2] Noklus (Norwegian Organization for Quality Improvement of Laboratory Examinations) is a national not for profit organisation 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.

[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
SN-Q60081177	PHCC1
SN-Q60081179	PHCC2

cobas b *101 HbA1c test discs*

Lot no	Alias	Expiry date	Used by
029043-01	Lot a	2022-02-28	Both evaluation sites
018042-01	Lot b	2022-03-31	Both evaluation sites
030042-01	Lot c	2022-03-31	Both evaluation sites

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

Control	Lot no	Expiry date	Used by
Level 1	004223	2022-04-30	Both evaluation sites
Level 2			

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 (formula 1)
n = number of differences

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.

Data, HbA1c results from the comparison method

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

Raw data, internal analytical quality control results, cobas b 101 HbA1c, intended users

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

Raw data, cobas b 101 HbA1c results, intended users

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