cobas b 101

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

An evaluation of the measurement of Lipid Panel
Total cholesterol, HDL-cholesterol, LDL-cholesterol, Triglycerides

Report from the evaluation SKUP/2020/118

organised by SKUP at the request of

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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 Lipid Panel measurements can be capillary whole blood, as well as venous ethylenediaminetetraacetic acid (EDTA) and lithium heparin anticoagulated whole blood and plasma. The system is produced by Roche Diagnostics GmbH and was launched into the Scandinavian market April 2013. The SKUP evaluation was carried out in spring/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 Lipid Panel, both when used under optimal conditions by experienced laboratory personnel and when used under real-life conditions by intended users in primary health care.

Materials and methods
Capillary whole blood samples from 111 patients were measured on **cobas b** 101 Lipid Panel under optimal conditions. Under real-life conditions in two primary health care centres (PHCC1 and PHCC4), fresh capillary whole blood samples from 48 and 40 patients, respectively, were measured on **cobas b** 101 Lipid Panel. Venous plasma samples from the same patients were analysed on a comparison method **cobas** 8000, Roche Diagnostics. The analytical results and user-friendliness were assessed according to pre-set quality goals. The quality goal for precision was a repeatability (CV) for cholesterol ≤3,0 %, for HDL- and LDL-cholesterol ≤4,0 % and for triglycerides ≤5,0 %. The quality goal for accuracy was that ≥95 % of the results should be within the deviation limits of ±9,0 % for cholesterol, ±13,0 % for HDL- and LDL-cholesterol and ±16,0 % for triglycerides in relation to the comparison method.
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
Cholesterol: The CV achieved under optimal conditions was between 1,3 and 2,0 % depending on the concentration level and the PHCCs achieved a CV between 0,8 and 2,4 %.
Under optimal conditions 98 % of the results were within the allowable deviation limits for accuracy and in the PHCCs 95 % of the results were within the allowable deviations limits.
A small but statistical significant bias was seen at medium and high levels under optimal condition (+0,03 – +0,11 mmol/L) and in the PHCCs (+0,13 – +0,23 mmol/L).
HDL-cholesterol: The CV achieved under optimal conditions was between 0,8 and 0,9 % depending on the concentration level and the PHCCs achieved a CV between 1,0 and 2,2 %.
Under optimal condition 99 % of the results were within the allowable deviation limits for accuracy and in the PHCCs 98 % of the results were within the allowable deviation limits.
Under optimal condition a small but statistically significant bias was seen at the low level (-0,04 mmol/L). No statistically significant bias was seen at the medium and high levels.
For PHCC1 a small but statistically significant bias was seen at the low level (-0,04 mmol/L). No statistically significant bias was seen at the medium and high levels.
In PHCC4 no statistically significant bias was seen.

Triglycerides: The CV achieved under optimal conditions was between 4,0 and 8,0 % depending on the concentration level. The PHCCs achieved a CV between 1,4 and 8,5 %.
Under optimal conditions 50 % of the results were within the allowable deviation limits for accuracy and in the PHCCs 54 % of the results were within the allowable deviation limits.
Both under optimal condition and in PHCCs a statistically significant bias was seen at all three levels (+0,22 – +0,40 mmol/L).
LDL-cholesterol: The CV achieved under optimal conditions was between 1,9 and 10,3 % depending on the concentration level. The PHCCs achieved a CV between 1,9 and 5,1 %. Under optimal conditions 91 % of the results were within the allowable deviation limits for accuracy and in the PHCCs 91 % of the results were within the limits.
Under optimal condition a negative bias was seen (-0,10 and -0,07 mmol/L). The bias was statistically significant at the low and high level. For the PHCCs no statistically significant bias was seen. The user-friendliness for the instrument was rated as satisfactory.

Conclusion
***Cholesterol*:** The quality goals for repeatability and accuracy were fulfilled both under optimal conditions and when the measurements were performed by intended users.
***HDL-cholesterol**:* The quality goals for repeatability and accuracy were fulfilled both under optimal conditions and when the measurements were performed by intended users.
Triglycerides: The quality goals for repeatability and accuracy were not fulfilled neither under optimal conditions nor by intended users.
LDL-cholesterol: The quality goals for repeatability and accuracy were not fulfilled neither under optimal conditions nor by intended users.

The quality goal for user-friendliness was fulfilled.

This summary will also be 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
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CRM	Certified reference material
CRP	C-reactive protein
CV	Coefficient of Variation
DEKS	Danish Institute of External Quality Assurance for Laboratories in Health Care
DS/EN ISO	Danish Standard/European Norm International Organization for Standardization
EAS	European Atherosclerosis Society
EDTA	Ethylenediaminetetraacetic acid
EFLM	European Federation of Clinical Chemistry and Laboratory Medicine
EQA	External Quality Assessment
Equalis	External quality assessment in laboratory medicine in Sweden
ESC	European Society of Cardiology
HbA1c	Haemoglobin A1c
HDL	High-density lipoprotein
ID/MS	Isotope Dilution/ Mass Spectrometry
KB-AaUH	Clinical Biochemistry, Aalborg University Hospital
KBF-OUH	Clinical Biochemistry and Pharmacology, Odense University Hospital
LDL	Low-density lipoprotein
LNE	National Testing Laboratory
NAD	Nicotinamide adenine dinucleotide (oxidized form NAD+, reduced form NADH)
NCEP	National Cholesterol Education Program
Noklus	Norwegian Organization for Quality Improvement of Laboratory Examinations
PHCC	Primary health care centre
QC	Quality control
SKUP	Scandinavian evaluation of laboratory equipment for point of care testing

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 Lipid Panel. Evaluation of **cobas b** 101 CRP and **cobas b** 101 HbA1c are described in the reports SKUP/2019/116 and SKUP/2020/117, 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 Lipid Panel, 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 Lipid Panel

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.

[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 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 Lipid Panel and its manual

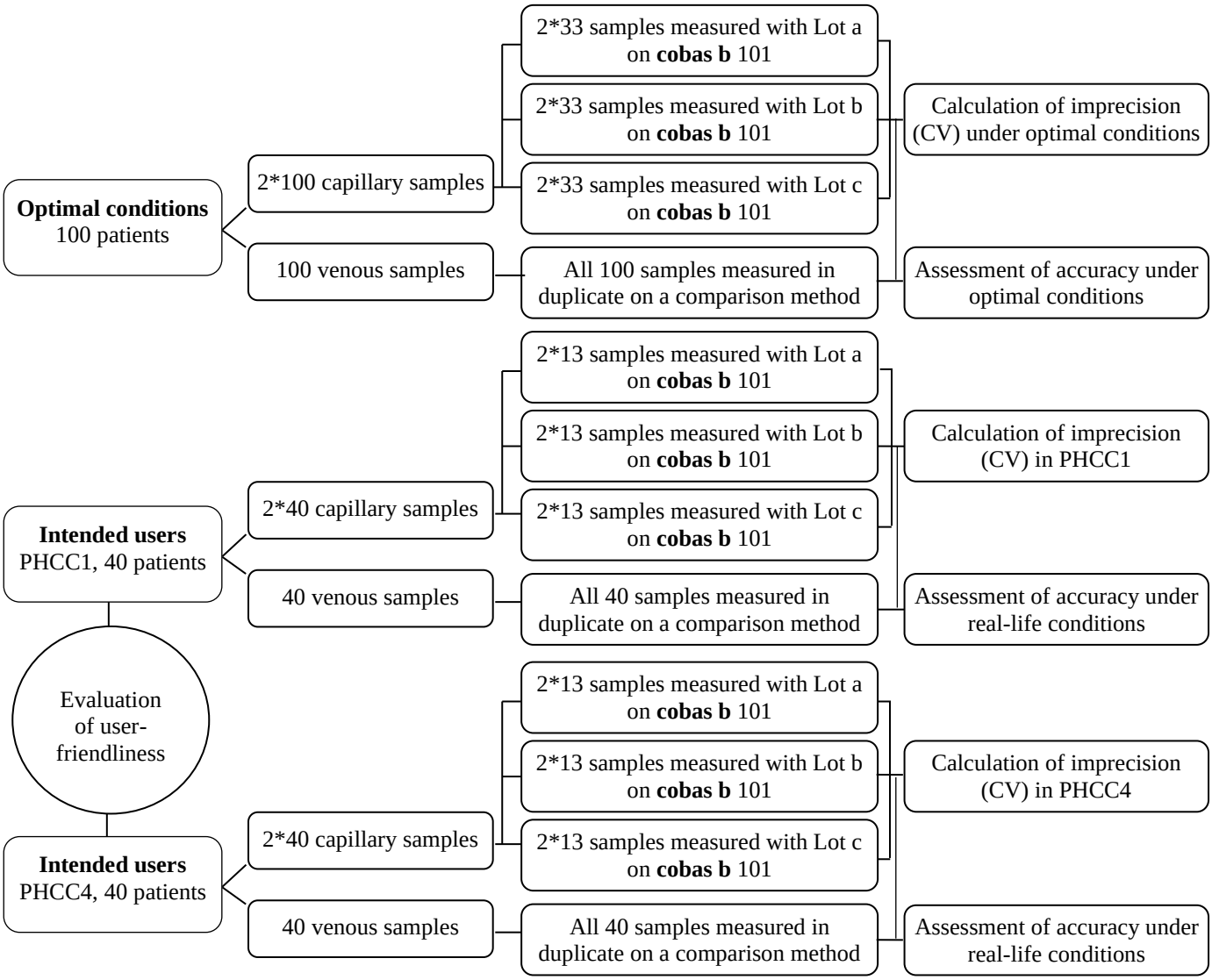

Figure 1. Flowchart illustrating the model for the evaluation of **cobas b** 101 Lipid Panel.

4. Quality goals

4.1. Analytical quality

Total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol have a central role in the definition of the cardiovascular risk. Clearly defined decision limits are established for each of the measurands in the European Society of Cardiology (ESC)/the European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias [2] and in the National Cholesterol Education Program (NCEP) guidelines for cholesterol management in the United States [3]. The guidelines also emphasise on triglycerides as an independent risk factor for coronary heart disease. According to the consensus statement from the 1st strategic conference of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) analytical quality specifications for these measurands should be based on clinical outcome studies [4,5].

The medical decision points in the NCEP guidelines are derived from national population studies in which the cholesterol assays were standardised to the Abell-Kendall reference method at the Centers for Disease Control and Prevention (CDC). From these outcome studies the NCEP laboratory standardisation panel gave the following recommendations stated in terms of total error* which reflects both bias from the true value (reference method) and imprecision as measured by coefficient of variation (CV) [6,7].

Cholesterol:	Total error ≤8,9 %, bias ≤±3,0 % and CV ≤3,0 %
HDL-cholesterol:	Total error ≤13 %, bias ≤±5,0 % and CV ≤4,0 % (at level ≥1,09 mmol/L)
LDL-cholesterol:	Total error ≤12 %, bias ≤±4,0 % and CV ≤4,0 %
Triglycerides:	Total error ≤15 %, bias ≤±5,0 % and CV ≤5,0 %

*Calculations of total error with z-value = 1,96

The NCEP recommendations differ slightly from CDC's certification criteria for manufacturers as CDC consider bias and imprecision separately. New clinical decision points are being developed using mass spectrometry-based reference methods [7].

In the external quality assessment (EQA) scheme for serum cholesterol in primary health care offered by the Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus), the participants achieve the assessment "very good" if the deviation from the control target value is less than approximately ±3 %, and the assessment "acceptable" if the deviation is less than approximately ±8 %, depending on the cholesterol concentration in the control samples. The control material is fresh pooled human serum samples with assigned values from the Abell-Kendall reference method (Lipid Reference Lab, Erasmus MC, Rotterdam).

The acceptable limits used by the External quality assessment in laboratory medicine in Sweden (Equalis) in the EQA scheme for hospital laboratories are that the maximum deviation for a single result measured in pooled serum should be less then ±5 % for cholesterol, ±10 % for HDL-cholesterol, ±12 % for LDL-cholesterol and ±15 % for triglycerides when compared to the consensus value from all participants, except for LDL-cholesterol where it is the consensus value within the output group.

Most Danish hospital laboratories participate in the Labquality EQA scheme for general chemistry. Labquality's acceptable limits for the lipid measurements correspond the acceptable

limits of Equalis, except for LDL-cholesterol where the maximum deviation should be less than ±10 %.

Based on recommendations from professionals and results in Noklus and Equalis EQA schemes, SKUP's quality goals for the lipids 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 in the PHCCs to fill in a questionnaire, see section 11.

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-cartridges
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 11.1.

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 Lipid Panel are assessed against the following quality goals:

	Cholesterol	**HDL-cholesterol**	**LDL-cholesterol**	**Triglycerides**
Repeatability (CV):	CV ≤3,0 %	CV ≤4,0 %	CV ≤4,0 %	CV ≤5,0 %
Allowable deviation of the individual result from the comparison method result:	≤±9,0 %	≤±13,0 %	≤±13,0 %	≤±16,0 %
Required percentage of individual results within the allowable deviations:	≥95 %			
User-friendliness, overall rating:	Satisfactory			

5. Materials and methods

5.1. Definition of the measurand

The measurement systems intend to measure the substrate concentration of cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides in plasma. For the evaluated system the sample material in this evaluation was fresh whole blood capillary samples, and for the comparison method the sample material was lithium heparin plasma. All results are expressed in the unit mmol/L. The Committee on Nomenclature, Properties and Units (C-NPU) systematically describes clinical laboratory measurands in a database [8]. The NPU codes related to the measurands in this evaluation are shown in table 2. In this protocol the trivial names are used for the measurands.

Table 2. NPU-specifications

NPU code	Name of test according to NPU	Unit	Trivial name
NPU01566	P—Cholesterol+ester; subst.c.	mmol/L	Cholesterol
NPU01567	P—Cholesterol+ester, in HDL; subst.c	mmol/L	HDL-cholesterol
NPU01568	P—Cholesterol+ester, in LDL; subst.c.	mmol/L	LDL-cholesterol
NPU04094	P—Triglyceride; subst.c.	mmol/L	Triglycerides

5.2. The evaluated measurement system cobas b 101 Lipid Panel

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 a clinical laboratory setting or point of care locations. **cobas b** 101 CRP, HbA1c and Lipid Panel test kits are available.

The **cobas b** 101® Lipid Panel system includes:

- **cobas b** 101 instrument
- **cobas b** 101 Lipid Panel test discs
- **cobas b** 101 Lipid quality control (QC) info disc
- **cobas** Lipid Panel internal analytical quality control kit

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

The **cobas b** 101 Lipid Panel is an in vitro diagnostic test system designed to quantitatively determine cholesterol, HDL-cholesterol and triglycerides in fresh human capillary whole blood samples, or lithium-heparinised or K_2- or K_3-Ethylenediaminetetraacetic acid (EDTA) venous whole blood or plasma. The system provides calculated values for LDL-cholesterol, non-HDL-cholesterol and the cholesterol/HDL-cholesterol ratio.

The measurement principle of **cobas b** 101 is photometric transmission measurement, and the **cobas b** 101 system determines cholesterol, HDL-cholesterol and triglycerides by enzymatic principles. Initially, the erythrocytes of a capillary or venous blood sample are separated from the plasma by centrifugation. In the next step, the plasma sample is diluted with phosphate buffer, and then each of the parameters (cholesterol, HDL-cholesterol and triglycerides) are measured in separate measurement chambers.

The HDL-cholesterol test uses a precipitation method with Mg^{2+} and phosphotungstic acid as precipitant reagent. The measurands, except for HDL-cholesterol, are precipitated and removed. Cholesterol esters in the sample are hydrolysed to cholesterol and fatty acids. Cholesterol and oxidised nicotinamide adenine dinucleotide (NAD+) generate cholestenone and reduced NAD (NADH) in the presence of cholesterol dehydrogenase. A chromogenic indicator for NADH (WST-8) is reduced to formazan dye by diaphorase and NADH through an oxidation-reduction reaction. The colour intensity of formazan is measured at wavelength 460 nm and is directly proportional to the concentration of cholesterol and HDL-cholesterol in the sample.

Triglycerides in the sample are hydrolysed to glycerol and fatty acids by lipoprotein lipase. Glycerol and NAD+ generate dihydroxyacetone and NADH in the presence of glycerol dehydrogenase. The chromogenic indicator is reduced to formazan and the colour intensity of the formazan measured at 460 nm is proportional to the triglyceride concentration.

When the concentration of triglycerides is <4,52 mmol/L, the LDL-cholesterol is calculated using the Friedewald formula. LDL-cholesterol = cholesterol – HDL-cholesterol – triglycerides × 0,45 (measured in mmol/L). Where the concentration of triglycerides is ≥4,52 mmol/L, LDL-cholesterol is not reported. The formula is also not valid for non-fasting patients and patients with Type III hyperlipoproteinemia (dysbetalipoproteinemia).

The **cobas b** 101 instrument calculates the cholesterol/HDL-cholesterol ratio as well as the non-HDL-cholesterol (cholesterol minus HDL-cholesterol) from the measured values. If measured values are not available, the cholesterol/HDL-cholesterol ratio or non-HDL-cholesterol values are not calculated.

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** cholesterol and HDL-cholesterol test disc are traceable to the designated CDC reference methods (Abell-Kendall as reference method for cholesterol) and triglycerides are traceable to the ID/MS method.

Every **cobas b** Lipid 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** Lipid Panel test.

For technical details about the **cobas b** 101, see table 3. 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 3. Technical details from the manufacturer

Sample volume	19 µL
Measuring time	6 minutes
Measuring range	Cholesterol: 2,28 – 12,95 mmol/L (50–500 mg/dL) Triglycerides: 0,50 – 7,35 mmol/L (45–650 mg/dL HDL-cholesterol: 0,38 – 2,60 mmol/L (15–100 mg/dL)
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 methods

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 methods in this evaluation

The selected comparison method for samples taken under optimal conditions and by intended users (PHCCs) was **cobas** 8000 modul c702, Roche Diagnostics GmbH. For the evaluation under optimal conditions the comparison method at the Clinical Biochemistry laboratory at Aalborg University Hospital (KB-AaUH) was used and for the evaluation of intended users the comparison method at the Clinical Biochemistry and Pharmacology laboratory at Odense University hospital (KBF-OUH) was used.

The **cobas** 8000 use a colorimetric method (the principle is enzymatic) to analyse cholesterol, HDL-cholesterol and triglycerides. LDL-cholesterol is calculated.

Internal analytical quality control
Internal analytical quality control samples were measured daily on the comparison methods.
KB-AaUH: PreciControl ClinChem Multi 1 and Multi 2 (Roche Diagnostics GmbH)
KBF-OUH: Auto Clin Chem Liquid Level 1 and Level 2 (SERO AS)

External analytical quality control
KB-AaUH participates in the EQA scheme for general chemistry with two levels (2050 Serum B and C, Labquality Oy) in six rounds per year, organised by Labquality. The control material is liquid human serum samples.
KBF-OUH participates in the Reference Institute for Bioanalytics External quality assessment scheme for lipoproteins with two levels in four rounds per year (data not shown). The control material is lyophilised serum. In addition, the laboratory participated in the EQA scheme for general chemistry from Labquality for this evaluation.

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
Certified reference materials from LNE (Laboratorie National de Métrologie et d'Essais, France (National testing laboratory)) were analysed on the comparison methods. The trueness of the comparison methods was also verified with EQA results and in addition fifteen venous samples with lithium heparin plasma were measured in duplicate on both the comparison method in KB-AaUH and the comparison method in KBF-OUH to verify the agreement between the methods.

5.4. The evaluation

5.4.1. Planning of the evaluation

Inquiry about an evaluation
Roche Diagnostics 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 Clinical Biochemistry in Aalborg University Hospital, Denmark were assigned to do the practical work with **cobas b** 101 in the evaluation under optimal conditions. Two primary health care centres from the Region of Southern Denmark agreed to represent the intended users in this evaluation.

Training
Roche Diagnostics Denmark demonstrated **cobas b** 101 Lipid Panel 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.

5.4.2. Evaluation sites and persons involved

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

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

Two BLSs in PHCC1 and one BLS and one nurse in PHCC4 were involved in the practical work for sampling and measurements on **cobas b** 101. In PHCC1 duplicate measurements were performed using two **cobas b** 101 instruments and in PHCC4 only one **cobas b** 101 instrument was used for duplicate measurements. Both PHCCs are large centres with four and six physicians, respectively. None of the PHCCs have a routine method for Lipid Panel measurement.

Two BLSs at the Department of Clinical Biochemistry, Aalborg University Hospital 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.

5.4.3. The evaluation procedure

Internal analytical quality control

Internal analytical quality control samples for **cobas b** 101 Lipid Panel, two levels (**cobas** Lipid internal analytical quality control kit, Roche Diagnostics GmbH), were measured each evaluation day on **cobas b** 101 Lipid Panel. 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 Lipid Panel 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.

Handling of the samples and measurements

Fresh capillary whole blood samples were used for the measurements on the **cobas b** 101 Lipid Panel system. All measurements were performed in duplicate, i.e. two separate fingersticks. Under optimal conditions and in PHCC1, who each had two **cobas b** 101 instruments, the duplicate measurements were not performed on the same cobas b 101 instruments because these evaluation sites also contributed to the evaluation of **cobas b** 101 HbA1c.

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 $\underline{\leq}$8 minutes after application. The complete sampling and measurement procedure were repeated for the second measurement on **cobas b** 101 Lipid Panel.

For patients at PHCC1 where both HbA1c and Lipid Panel 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 BD Vacutainer® tubes with lithium-heparin. The tubes were inverted ten times to ensure thorough mixing and kept in climate cabinet (20,5-21,5^{o}C) until transported to KB-AaUH (samples from optimal conditions) or KBF-OUH (samples from the PHCCs) the same day. In the laboratories the tubes were centrifuged for ten minutes at 2200 g within ten hours from sampling, and the plasma samples were measured in duplicate on the comparison method within 24 hours from sampling. All samples were treated according to the internal procedures of the hospital laboratory regarding potential interfering substances.

6. Number of samples Lipid Panel

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 199 patients were enrolled.

Under optimal condition, 111 patients were recruited (SKUP ID 1 – 100 and F101 – F111).

PHCC1 recruited 48 patients (SKUP ID 101 – 140, 142 – 145, 147 – 150) and PHCC4 recruited 40 patients (SKUP ID 401 – 440).

An account of the number of samples not included in the calculations (missing, omitted and excluded results), are given in the chapters for each measurand.

Recorded error codes, technical errors and failed measurements.
The following error codes were reported from **cobas b** 101:
Four times W-321: Reaction failure - Repeat test with new cassette
One time: I-207: Printer is missing paper
One time: I-203: Remove cassette
Two times no error code: The analyze was interrupted
One time: no error code: Cassette error
One time: W-308: Outside the measuring range (HDL >2,6 mmol/L)

On six different days the QC control had to be reanalyzed (up to three times) - no error codes. Ten samples were aborted (no error codes). New samples were not analyzed due to the patients had gone home.

Only six technical error codes were reported related to measurement of Lipid Panel.
The SKUP recommendation of fraction of <2% tests wasted due to technical errors was achieved

7. Results and discussion cholesterol

7.1. Number of samples cholesterol

For number of samples see 6.1.

Missing results

- ID 1, 2, 11, 13, 22, 37, 42, 63, 64, 84, 103, 104, 105, 126, 143; only single measurements from **cobas b** 101. The single values were not included in the calculation of repeatability but were included in the calculation of bias and the assessment of accuracy.
- ID 93; there was no measurement from **cobas b** 101 due to time limit for analysis exceeded.
- ID 4, 5, 7, 8, 33, 36, 45, 50, 51, 52, 63, 64, 71, 72, 74, 98, F104, F105, F106 and F109; only single measurement from the comparison method. The single values were not included in the calculation of repeatability of the comparison method but were included in the calculation of bias and the assessment of accuracy.
- ID 20, 30, 31; there were no measurements from the comparison method. The results from **cobas b** 101 were included in calculation of repeatability but not included in the calculation of bias and the assessment of accuracy.
- From optimal condition the internal analytical quality control result for level 1 for one evaluation day was missing. The results from patient samples that day were still included in the calculations.

Omitted results

- ID 434, 435, 436; were analysed with the comparison method >4 days after sampling. The results from **cobas b** 101 were included in calculation of repeatability but not included in the calculation of bias and the assessment of accuracy.

Excluded results (statistical outliers)

Statistical outliers in SKUP evaluations are detected by the criterion promoted by Burnett [9]

- ID 53; 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 assessment of repeatability and accuracy (the first of the duplicate measurements).

7.2. Analytical quality of the selected comparison methods cholesterol

7.2.1. Internal analytical quality control for cholesterol

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

7.2.2. The precision of the comparison methods

Duplicate measurements of each venous patient sample were performed on the comparison method. The results were checked to meet the imposed condition for using formula 1 in attachment 5.

cobas 8000 KB-AaUH: The paired measurements at the high level showed a small, but statically significant difference (data not shown). When using highly precise methods, even negligible differences are easily pointed out as statistically significant. The systematic difference pointed out lead to a minor overestimation of the CV of the comparison method at the high cholesterol level.

cobas 8000 KBF-OUH: 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 tables 4a and 4b. 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 attachments 6 and 7.

Table 4a. Repeatability (CV) of the comparison method **cobas** 8000 KB-AaUH for cholesterol measured in venous plasma samples.

Level	Cholesterol interval, mmol/L	n	Excluded results (statistical outliers)	Mean value Cholesterol, mmol/L	CV (90% CI), %
Low	2,42 – 4,09	28	0	3,4	1,4 (1,2 – 1,8)
Medium	4,11 – 4,99	30	0	4,6	1,1 (0,9 – 1,4)
High	5,05 – 7,38	30	0	5,8	1,1 (0,9 – 1,4)

An account of the number of samples is given in sections 6.1 and 7.1.

Table 4b. Repeatability (CV) of the comparison method **cobas** 8000 KBF-OUH for cholesterol measured in venous plasma samples.

Level	Cholesterol interval, mmol/L	n	Excluded results (statistical outliers)	Mean value Cholesterol, mmol/L	CV (90% CI), %
Low	1,93 – 4,09	29	0	3,3	0,9 (0,7 – 1,1)
Medium	4,18 – 4,93	20	0	4,5	0,8 (0,6 – 1,1)
High	5,02 – 7,46	36	0	5,8	0,7 (0,6 – 0,9)

An account of the number of samples is given in sections 6.1 and 7.1.

Discussion

The CV for the comparison method **cobas** 8000 KB-AaUH for cholesterol was between 1,1 and 1,4 % and the CV for the comparison method **cobas** 8000 KBF-OUH for cholesterol was between 0,7 and 0,9 %.

7.2.3. The trueness of the comparison methods for cholesterol

To demonstrate the trueness of the two comparison methods in KB-AaUH and KBF-OUH, certified reference material LNE CRM Bio 101a level 1 and level 2 were analysed (tables 5a, 5b). Furthermore, samples from EQA programme "Serum B and C, general clinical chemistry" from Labquality (two levels, round 2 2019, table 5c) were analyzed on both methods (specified in section 5.3.1).

Table 5a. Cholesterol measured on LNE CRM on **cobas** 8000 module c702 at KB-AaUH.

Date: 22.05.2019		Site: KB-AaUH		
Level	Certified values by LNE k=2, mmol/L	n	KB-AaUH mean cholesterol, mmol/L	Deviation from target value, mmol/L
LNE CRM Bio 101a level 1	3,610 (0,057)	5	3,69	0,080
LNE CRM Bio 101a level 2	5,934 (0,127)	5	5,88	-0,054

Table 5b. Cholesterol measured on LNE CRM on **cobas** 8000 module c702 at KBF-OUH.

Date: 22.05.2019		Site: KBF-OUH		
Level	Certified values by LNE k=2, mmol/L	n	KBF-OUH mean cholesterol, mmol/L	Deviation from target value, mmol/L
LNE CRM Bio 101a level 1	3,610 (0,057)	5	3,54	-0,066
LNE CRM Bio 101a level 2	5,934 (0,127)	5	5,80	-0,138

Table 5c. Results for cholesterol from Labquality's EQA programme measured on the comparison methods.

April 2019 Sample	Assigned values cholesterol, mmol/L (±5 % acceptance limits)	n	KB-AaUH **cobas** 8000 c702 cholesterol, mmol/L	KBF-OUH **cobas** 8000 c702 cholesterol, mmol/L
S001	4,8 (4,6 – 5,1)	1	4,6	4,7
S002	3,2 (3,1 – 3,4)	1	3,2	3,1

Discussion

Tables 5a and 5b show that results on LNE CRM obtained in KB-AaUH were slightly higher at level 1 than the LNE CRM certified values, while level two was found within the uncertainty limits. Results on the LNE CRM obtained in KBF-OUH were slightly lower than the LNE certified values and outside the uncertainty limits at both levels. Fifteen patient samples were also measured in duplicate on both comparison methods to verify the agreement between the methods. This comparison showed that samples measured in KB-AaUH gave slightly higher results than

corresponding samples measured in KBF-OUH (attachment 8), which confirmed the measurements on the reference materials. The EQA results from both comparison methods were within the acceptance limits.

7.3. Analytical quality of cobas b 101 cholesterol under optimal conditions

The results below reflect the analytical quality of **cobas b** 101 cholesterol under optimal conditions. The results document the quality of the system under conditions as favourable as possible for achieving good analytical quality.

7.3.1. Internal analytical quality control for cholesterol

All results from the internal analytical quality control (**cobas** Lipid Panel kit) two levels were within the allowable control limits (data not shown). The reproducibility (CV) achieved with the internal analytical quality control samples were 1,7 % for level 1 (n=86) and 2,0 % for level 2 (n=87). Raw data is attached for the requesting company only, see attachment 9.

7.3.2. The precision of cobas b 101 cholesterol

Duplicate measurements from each patient sample were performed on **cobas b** 101 cholesterol. 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 6. The results were sorted and divided into three concentration levels according to the mean of the results of **cobas b** 101 cholesterol. Raw data is attached for the requesting company only, see attachment 10.

Table 6. Repeatability (CV) of **cobas b** 101 cholesterol measured in capillary whole blood samples. Results achieved under optimal conditions.

Level	Cholesterol interval, mmol/L	n	Excluded results (statistical outliers)	Mean value Cholesterol, mmol/L	CV (90% CI), %
Low	2,49 – 4,01	30	0	3,4	2,0 (1,6 – 2,5)
Medium	4,11 – 4,99	32	0	4,5	1,3 (1,1 – 1,6)
High	5,01 – 6,91	38	0	5,7	1,5 (1,3 – 1,8)

An account of the number of samples is given in sections 6.1. and 7.1.

Discussion

The CV achieved under optimal conditions was between 1,3 and 2,0 % depending on the concentration level. The CV's for all the three levels were statistically significant lower than the quality goal. As two instruments were used for duplicate measurements the difference between the two **cobas b** 101 instruments is included in the CV's given in table 6.

Conclusion

Under optimal conditions the quality goal for repeatability (CV ≤3,0 %) was fulfilled.

7.3.3. The bias of cobas b 101 cholesterol

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 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 attachments 7 and 10.

Table 7. Bias of **cobas b** 101 cholesterol measured in capillary whole blood samples. Results achieved under optimal conditions.

Level	Cholesterol interval comparison method, mmol/L	n*	Excluded results (statistical outliers)	Mean value Cholesterol comparison method, mmol/L	Mean value Cholesterol cobas b 101, mmol/L	Bias (95 % CI), mmol/L	Bias, %
Low	2,4 – 4,0	35	1**	3,9	3,5	0,03 (0,00 – 0,06)	0,9
Medium	4,1 – 5,0	37	0	4,6	4,7	0,06 (0,02 – 0,10)	1,3
High	5,0 – 6,8	35	0	5,7	5,8	0,11 (0,06 – 0,15)	1,9

*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 sections 6.1. and 7.1.
**ID 53 was a statistical outlier according to Burnett´s model [9] in the calculation of bias and therefore excluded.

Discussion

For medium and high level there was a small but statistically significant bias between **cobas b** 101 cholesterol and the comparison method. The results from **cobas b** 101 were systematically higher than the results from the comparison method. The bias was between 0,03 and 0,11 mmol/L, depending on the concentration level.

7.3.4. The accuracy of cobas b 101 cholesterol

To evaluate the accuracy of cholesterol results on **cobas b** 101, the agreement between **cobas b** 101 cholesterol and the comparison method is illustrated in a difference plot (figure 3). The limits for the allowable deviation according to the quality goal (±9 %) 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 attachments 6 and 10.

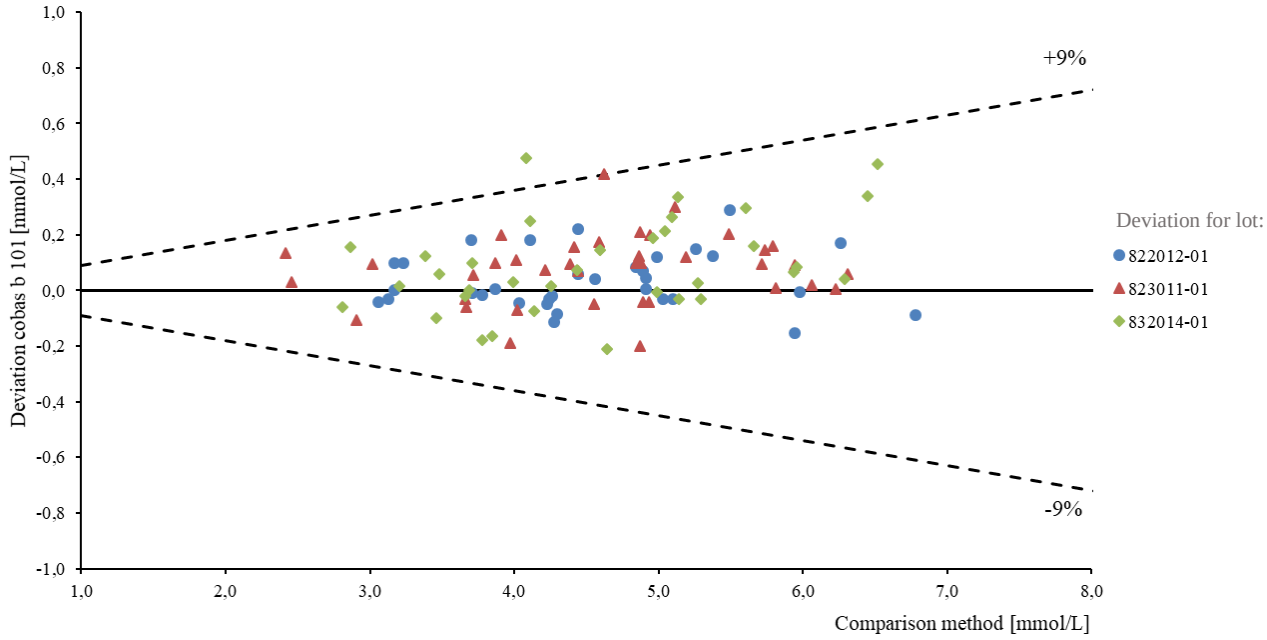

Figure 3. Accuracy of cholesterol results on **cobas b** 101 under optimal conditions. The x-axis represents the mean cholesterol result of the comparison method. The y-axis represents the cholesterol deviation in mmol/L of the capillary whole blood measurement on **cobas b** 101 from the mean result of the corresponding sample of the comparison method. The different lots of test discs are illustrated with the symbols ● (lot 822012-01), ▲ (lot 823011-01) and ♦ (lot 832014-01). Stippled lines represent the allowable deviation limits of ±9 %. Number of results (n) = 107. An account of the number of samples is given in sections 6.1 and 7.1.

Discussion

As shown in figure 3, the **cobas b** 101 cholesterol results tend to be slightly higher than the results from the comparison method which is consistent with the calculated bias (table 7). Of the 107 results 105 were inside the allowable deviation limits (±9 %) amounting to 98 %. The quality goal for individual results within the limits is ≥95 %. The figure also shows that there was no visible difference between the test disc lots.

Conclusion

Under optimal conditions the quality goal for accuracy was fulfilled.

7.4. Analytical quality of cobas b 101 cholesterol achieved by intended users

The results below reflect the analytical quality of **cobas b** 101 cholesterol under real-life conditions in the hands of intended users in PHCCs. The results may deviate from the results achieved under optimal conditions.

7.4.1. Internal analytical quality control cholesterol

All results from the internal analytical quality control (**cobas** Lipid Panel Control), two levels, were within the allowable control limits (data not shown). The reproducibility (CV) achieved with the internal analytical quality control samples were 1,6 % for level 1 (n=37) and 1,4 % for level 2 (n=37). Raw data is attached for the requesting company only, attachment 11.

7.4.2. The precision of cobas b 101 cholesterol

Duplicate measurements of each capillary whole blood sample were performed on **cobas b** 101 cholesterol. 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 in PHCC1. The CV with a 90 % CI is shown in table 8. The results were sorted and divided into three concentration levels according to the mean of the results of **cobas b** 101 cholesterol system. Since the variances between the two PHCCs were significantly different (F-test, 5 % significance level) the results from the two PHCCs were not combined before the calculation of CV. Raw data is attached for the requesting company only, see attachment 12.

Table 8. Repeatability (CV) of **cobas b** 101 for cholesterol measured in capillary whole blood samples. Results achieved by intended users.

Place	Level	Cholesterol interval, mmol/L	n	Excluded results (statistical outliers)	Mean value Cholesterol, mmol/L	CV (90% CI), %
PHCC 1	Low	1,9 – 4,0	11	0	3,2	1,9 (1,4 – 3,0)
	Medium	4,2 – 4,8	8	0	4,5	2,4 (1,7 – 4,3)
	High	5,1 – 8,0	24	0	5,9	2,0 (1,6 – 2,6)
PHCC 4	Low	2,5 – 4,1	10	0	3,6	0,8 (0,6 – 1,3)
	Medium	4,1 – 5,0	13	0	4,6	1,2 (0,9 – 1,8)
	High	5,1 – 7,5	17	0	5,9	1,5 (1,2 – 2,2)

An account of the number of samples is given in sections 6.1 and 7.1.

Discussion

The CV achieved by PHCC1 was between 1,9 and 2,4 % and in PHCC4 the CV was between 0,8 and 1,5 % depending on the concentration levels. However, the higher CV in PHCC1 may be caused by the use of two instruments for the duplicate measurements.

The CV's for all levels were statistically significantly lower than the quality goal, however the medium level at PHCC1 was not statistically significantly lower.

Conclusion
Since two instruments were used for duplicate measurements in PHCC1 only results from PHCC4 are included in this conclusion. When measurements were performed by the intended users in PHCC4 the quality goal for repeatability (CV ≤3 %) was fulfilled.

7.4.3. The bias of cobas b 101 cholesterol

The mean deviation (bias) of **cobas b** 101 cholesterol results from the comparison method was calculated. The bias is presented with a 95 % CI in table 9. The results were sorted and divided into two concentration levels according to the mean results of the comparison method. Raw data is attached for the requesting company only, see attachments 7 and 12.

Table 9. Bias of **cobas b** 101 for cholesterol measured in capillary whole blood samples. Results achieved by intended users.

Place	Level	Cholesterol interval comparison method, mmol/L	n	Excluded results (statistical outliers)	Mean value Cholesterol comparison method, mmol/L	Mean value Cholesterol cobas b 101, mmol/L	Bias (95 % CI), mmol/L	Bias, %
	Low	1,9 – 4,0	17	0	3,19	3,31	0,13 (0,08 – 0,18)	4,0
PHCC 1	Medium	4,2 – 4,9	9	0	4,49	4,65	0,17 (0,09 – 0,24)	3,7
	High	5,1 – 7,5	22	0	5,76	5,98	0,22 (0,15 – 0,29)	3,8
	Low	2,6 – 4,1	12	0	3,57	3,74	0,17 (0,09 – 0,25)	4,8
PHCC 4	Medium	4,2 – 4,9	11	0	4,60	4,79	0,19 (0,12 – 0,26)	4,1
	High	5,0 – 7,3	14	0	5,86	6,09	0,23 (0,16 – 0,31)	4,0

An account of the number of samples is given in sections 6.1 and 7.1.

Discussion
For all three levels there were a statistically significant bias between **cobas b** 101 cholesterol and the comparison method. For PHCC1 the bias was between 0,13 and 0,22 mmol/L and for PHCC4 the bias was between 0,17 and 0,23 mmol/L depending on the concentration level.

7.4.4. The accuracy of cobas b 101 cholesterol

To evaluate the accuracy of cholesterol results on **cobas b** 101, the agreement between **cobas b** 101 cholesterol and the comparison method is illustrated in a difference plot (figure 4). The limits for the allowable deviation according to the quality goal (±9 %) are shown with stippled lines. In PHCC1 the samples were measured in parallel on 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 PHCC4 the samples were measured on the same **cobas b** 101 instrument. The plot illustrates both random and systematic errors, reflecting the total measuring error in the **cobas b** 101 cholesterol results. Raw data is attached for the requesting company only, see attachments 7 and 12.

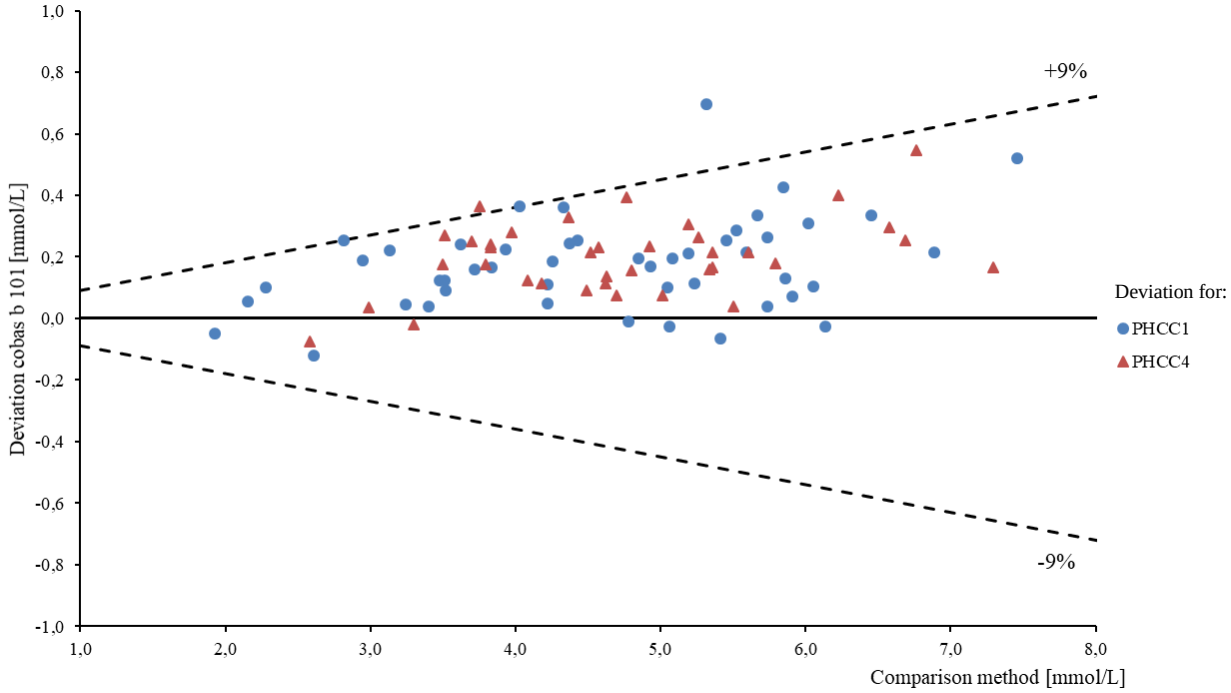

Figure 4. Accuracy of cholesterol results on **cobas b** 101 achieved by intended users. The x-axis represents the mean cholesterol result of the comparison method. The y-axis represents the cholesterol deviation in mmol/L of the capillary whole blood sample measurement on **cobas b** 101 cholesterol from the mean result of the corresponding sample of the comparison method. The different PHCC's are illustrated with the symbols ● (PHCC1), ▲ (PHCC4). Stippled lines represent the allowable deviation limits of ±9 %. Number of results (n) = 85. An account of the number of samples is given in sections 6.1 and 7.1.

Discussion

As shown in figure 4, the **cobas b** 101 cholesterol results tend to be higher than the results from the comparison method. This is consistent with the calculated bias (table 9).

Of the 85 results 81 were inside the allowable deviation (±9 %) amounting to 95 %. The quality goal for individuals results within the limits is ≥95 %.

Conclusion

When measurements were performed by the intended users the quality goal for accuracy was fulfilled.

8. Results and discussion HDL-cholesterol

8.1. Number of samples HDL-cholesterol

For numbers of samples see 6.1.

Missing results

- ID 1, 2, 11, 13, 22, 33, 37, 42, 63, 64, 84, 103, 104, 105, 126, 143; only single measurements from **cobas b** 101. The single values were not included in the calculation of repeatability but in the calculation of bias and the assessment of accuracy.
- ID 4, 5, 7, 8, 33, 36, 45, 50, 51, 52, 63, 64, 71, 72, 74, 98, F104, F105, F106, F109; only single measurement from the comparison method. The single values were not included in the calculation of repeatability of the comparison method but in the calculation of bias and the assessment of accuracy.
- ID 20, 30, 31; there were no measurements from the comparison method. The results from **cobas b** 101 were included in the calculations of repeatability, but not included in the calculation of bias and the assessment of accuracy.
- From optimal condition the internal analytical quality control result for level 1 for one evaluation day was missing. The results from patient samples that day were still included in the calculations.
- ID 40, 436; **cobas b** 101, first measurement was above measurement range (>2,60 mmol/L) and the results are not included in the calculation of repeatability but were included in the calculation of bias and the assessment of accuracy.
- ID 71, 150; **cobas b** 101, both measurements above measurement range (>2,60 mmol/L) and therefore not included in any calculations.
- ID 76, 425; **cobas b** 101, both measurements reported N/A.
- ID 93; no results from **cobas b** 101 due to time limit for analysis exceeded.

Omitted results

- ID 434, 435, 436; were analysed with the comparison method >4 days after sampling. The results from **cobas b** 101 were included in the calculations of repeatability, but not included in the calculation of bias and the assessment of accuracy.

Excluded results (statistical outliers)

Statistical outliers according to Burnett [9]:

- ID 139; the results from the comparison method was classified as outliers according to Burnett's model in the calculation of repeatability. The result was 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.

8.2. Analytical quality of the selected comparison methods HDL-cholesterol

8.2.1. Internal analytical quality control for HDL-cholesterol

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

8.2.2. The precision of the comparison methods

Duplicate measurements of each venous patient sample were performed on the comparison method. The results were checked to meet the imposed condition for using formula 1 in attachment 5.

cobas 8000 KB-AaUH: There was no systematic difference between the paired measurements.

cobas 8000 KBF-OUH: The paired measurements at the high level showed a small, but statically significant difference (data not shown). When using highly precise methods, even negligible differences are easily pointed out as statistically significant. The systematic differences pointed out lead to a minor overestimation of the CV of the comparison method at the high HDL-cholesterol level.

The precision is presented as repeatability (CV). The CV with a 90 % CI is shown in tables 10a and 10b. 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 attachments 13 and 14.

Table 10a. Repeatability (CV) of the comparison method **cobas** 8000 KB-AaUH for HDL-cholesterol measured in venous plasma samples.

Level	HDL-cholesterol interval, mmol/L	n	Excluded results (statistical outliers)	Mean value HDL-cholesterol, mmol/L	CV (90% CI), %
Low	0,57 – 1,20	35	0	1,0	1,9 (1,6 – 2,4)
Medium	1,24 – 1,60	32	0	1,4	1,5 (1,2 – 1,9)
High	1,65 – 2,51	29	0	2,0	1,7 (1,4 – 2,1)

An account of the number of samples is given in sections 6.1 and 8.1

Table 10b. Repeatability (CV) of the comparison method **cobas** 8000 KBF-OUH for HDL-cholesterol measured in venous plasma samples.

Level	HDL-cholesterol interval, mmol/L	n*	Excluded results (statistical outliers)	Mean value HDL-cholesterol, mmol/L	CV (90% CI), %
Low	0,54 – 1,20	26	1**	1,0	0,9 (0,7 – 1,2)
Medium	1,21 – 1,60	40	0	1,4	1,4 (1,2 – 1,7)
High	1,61 – 2,72	19	0	2,1	0,8 (0,6 – 1,1)

*The given number of results (n) were counted before the exclusion of statistical outliers. Mean and repeatability were calculated after the exclusion of statistical outliers. An account of the number of samples is given in sections 6.1 and 8.1.

**ID 139 was a statistical outlier according to Burnett´s model [9] in the calculation of repeatability and therefore excluded.

Discussion

The CV for the comparison method **cobas** 8000 KB-AaUH for HDL-cholesterol was between 1,5 and 1,9 % and the CV for the comparison method **cobas** 8000 KBF-OUH HDL-cholesterol was between 0,9 and 1,4 %.

8.2.3. The trueness of the comparison methods HDL-cholesterol

To demonstrate the trueness of the two comparison methods in KB-AaUH and KBF-OUH (both methods are **cobas** 8000 module c702), certified reference material LNE CRM Bio 101a level 1 and level 2 were analysed (tables 11a, 11b). Furthermore, controls from EQA programme "Serum B and C, general clinical chemistry" from Labquality (two levels, round 2 2019, table 11c) were analysed on both methods (specified in section 5.3.1).

Table 11a. HDL-cholesterol measured on LNE CRM on **cobas** 8000 module c702 at KB-AaUH.

Date: 22.05.2019		Site: KB-AaUH		
Level	Certified values by LNE k=2, mmol/L	n	KB-AaUH mean HDL-cholesterol, mmol/L	Deviation from target value, mmol/L
LNE CRM Bio 101a level 1	1,290 (0,038)	5	1,27	-0,018
LNE CRM Bio 101a level 2	1,531 (0,053)	5	1,47	-0,059

Table 11b. HDL-cholesterol measured on LNE CRM on **cobas** 8000 module c702 at KBF-OUH.

Date: : 22.05.2019		Site: KBF-OUH		
Level	Certified values by LNE k=2, mmol/L	n	KB-OUH mean HDL-cholesterol, mmol/L	Deviation from target value, mmol/L
LNE CRM Bio 101a level 1	1,290 (0,038)	5	1,24	-0,048
LNE CRM Bio 101a level 2	1,531 (0,053)	5	1,45	-0,077

Table 11c. Results for HDL-cholesterol from Labquality's EQA programme measured on the comparison methods.

Sample	Assigned values HDL-cholesterol, mmol/L (±10 % acceptance limits)	n	KB-AaUH **cobas** 8000 c702 HDL-cholesterol, mmol/L	KBF-OUH **cobas** 8000 c702 HDL-cholesterol, mmol/L
S001	1,17 (1,05 –1,28)	1	1,20	1,20
S002	0,74 (0,66 – 0,81)	1	0,71	0,70

Discussion

Tables 11a and 11b show that results obtained on the reference material in KB-AaUH and KBF-OUH were slightly lower than the LNE certified values and outside the uncertainty limits except for level 1 in KB-AaUH. Fifteen patient samples were also measured in duplicate on both comparison methods to verify the agreement between the methods This comparison showed that samples measured in KB-AaUH gave slightly higher results than corresponding samples

measured in KBF-OUH (attachment 15), which confirmed the measurements on the reference materials. The EQA results from both comparison methods were within the acceptance limits.

8.3. Analytical quality of cobas b 101 HDL-cholesterol under optimal conditions

The results below reflect the analytical quality of **cobas b** 101 HDL-cholesterol under optimal conditions. The results document the quality of the system under conditions as favourable as possible for achieving good analytical quality.

8.3.1. Internal analytical quality control for HDL-cholesterol

All results from the internal analytical quality control (**cobas** Lipid Panel kit) two levels were within the allowable control limits (data not shown). The reproducibility (CV) achieved with the internal analytical quality control samples were 5,0 % for level 1 (n=85) and 3,0 % for level 2 (n=87). Raw data is attached for the requesting company only, see attachment 16.

8.3.2. The precision of cobas b 101 HDL-cholesterol

Duplicate measurements from each patient sample were performed on **cobas b** 101 HDL-cholesterol. 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 12. The results were sorted and divided into three concentration levels according to the mean of the results of the **cobas b** 101 HDL-cholesterol method. Raw data is attached for the requesting company only, see attachment 17.

Table 12. Repeatability (CV) of **cobas b** 101 for HDL-cholesterol measured in capillary whole blood samples. Results achieved under optimal conditions.

Level	HDL-cholesterol interval, mmol/L	n	Excluded results (statistical outliers)	Mean value HDL-cholesterol, mmol/L	CV (90% CI), %
Low	0,57 – 1,20	35	0	1,0	1,9 (1,6 – 2,4)
Medium	1,24 – 1,60	32	0	1,4	1,5 (1,2 – 1,9)
High	1,65 – 2,51	29	0	2,0	1,7 (1,4 – 2,1)

An account of the number of samples is given in sections 6.1. and 8.1.

Discussion

The CV achieved under optimal conditions was between 1,5 and 1,9 % depending on the concentration level. The CV for the three levels was statistically significantly lower than the quality goal. As two instruments were used for duplicate measurements the difference between the two **cobas b** 101 instruments is included in the CV's given in table 12.

Conclusion

Under optimal conditions the quality goal for repeatability (CV ≤4,0 %) was fulfilled.

8.3.3. The bias of cobas b 101 HDL-cholesterol

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 13. 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 attachments 13 and 17.

Table 13. Bias of **cobas b** 101 for HDL-cholesterol measured in capillary whole blood samples. Results achieved under optimal conditions.

Level	HDL-cholesterol interval comparison method, mmol/L	n	Excluded results (statistical outliers)	Mean value HDL-cholesterol comparison method, mmol/L	Mean value HDL-cholesterol cobas b 101, mmol/L	Bias (95 % CI), mmol/L	Bias, %
Low	0,6 – 1,2	35	0	1,0	0,9	-0,04 (-0,06 – -0,03)	-4,4
Medium	1,2 – 1,6	37	0	1,4	1,4	-0,01 (-0,03 – 0,01)	-0,8
High	1,6 – 2,8	33	0	2,0	2,0	-0,01 (-0,04 – 0,02)	-0,7

An account of the number of samples is given in sections 6.1. and 8.1.

Discussion

For the low level, there was a statistically significant bias (-0,04 mmol/L) and for the medium and high levels no statistically significant bias was seen.

8.3.4. The accuracy of cobas b 101 HDL-cholesterol

To evaluate the accuracy of HDL-cholesterol results on **cobas b** 101, the agreement between **cobas b** 101 HDL-cholesterol and the comparison method is illustrated in a difference plot (figure 5). The limits for the allowable deviation according to the quality goal (±13,0 %) 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 attachments 13 and 17.

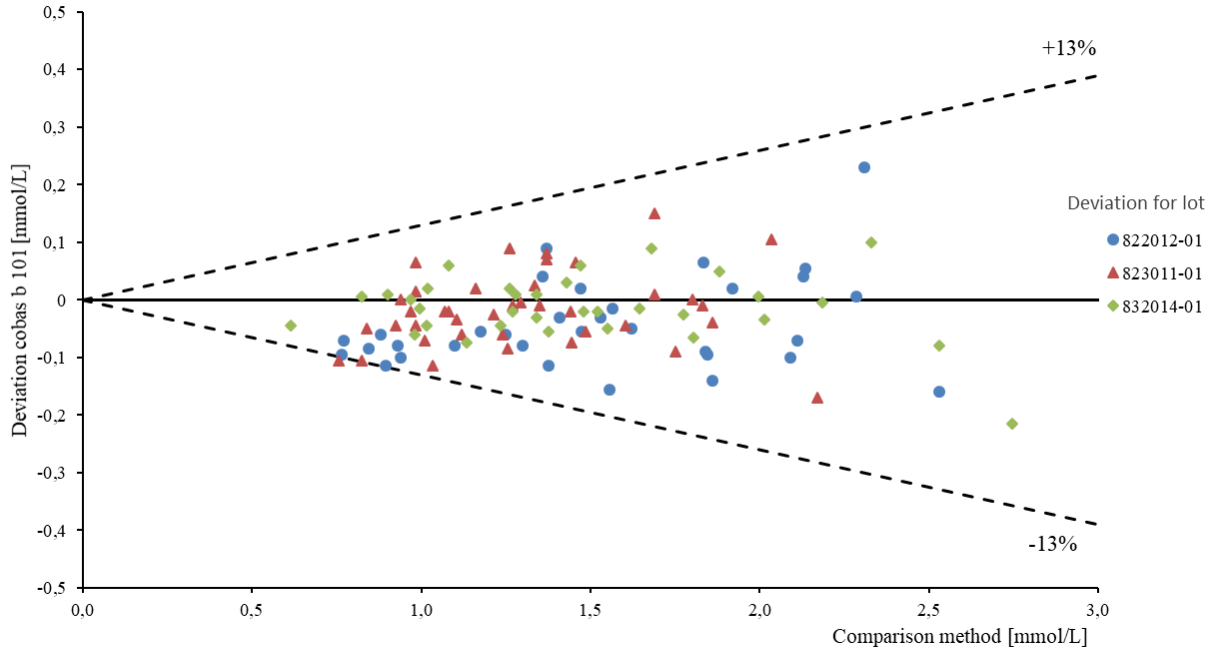

Figure 5. Accuracy of HDL-cholesterol results on **cobas b** 101 under optimal conditions. The x-axis represents the mean HDL-cholesterol result of the comparison method. The y-axis represents the HDL-cholesterol deviation in mmol/L of the capillary whole blood measurement on **cobas b** 101 from the mean result of the corresponding sample of the comparison method. The different lots of test discs are illustrated with the symbols ● (lot 822012-01), ▲ (lot 823011-01) and ♦ (lot 832014-01). Stippled lines represent the allowable deviation limits of ±13 %. Number of results (n) = 105. An account of the number of samples is given in sections 6.1. and 8.1.

Discussion

As shown in figure 5, the **cobas b** 101 HDL-cholesterol are lower than the results from the comparison method which is consistent with the calculated bias (table 13). Of the 105 results 104 were within the allowable deviation limits (±13 %) amounting to 99 %. The quality goal for individual results within the limits is ≥95 %.

Discs with lot no 822012-01 (●) tend to differ more from the comparison method compared to the discs with lot number 823011-01 and 832014-01. Separate lot calculations were not performed.

Conclusion

Under optimal conditions the quality goal for accuracy was fulfilled.

8.4. Analytical quality of cobas b 101 HDL-cholesterol achieved by intended users

The results below reflect the analytical quality of **cobas b** 101 HDL-cholesterol under real-life conditions in the hands of intended users in PHCCs. The results may deviate from the results achieved under optimal conditions.

8.4.1. Internal analytical quality control for HDL-cholesterol

All results from the internal analytical quality control (**cobas** Lipid Panel Control), two levels, were within the allowable control limits (data not shown). The reproducibility (CV) achieved with the internal analytical quality control samples were 5,1 % for level 1 (n=37) and 2,1 % for level 2 (n=37). Raw data is attached for the requesting company only, attachment 18.

8.4.2. The precision of cobas b 101 HDL-cholesterol

Duplicate measurements of each capillary whole blood sample were performed on **cobas b** 101 HDL-cholesterol. 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 in PHCC1. The CV with a 90 % CI is shown in table 14. The results were sorted and divided into three concentration levels according to the mean of the results of **cobas b** 101 HDL-cholesterol system. Since the variances between the two PHCCs were significantly different (F-test, 5 % significance level) the results from the two PHCCs were not combined before the calculation of CV. Raw data is attached for the requesting company only, see attachment 19.

Table 14. Repeatability (CV) of **cobas b** 101 for HDL-cholesterol measured in capillary whole blood samples. Results achieved by intended users.

Place	Level	HDL-cholesterol interval, mmol/L	n	Excluded results (statistical outliers)	Mean value HDL-cholesterol, mmol/L	CV (90% CI), %
PHCC 1	Low	0,6 – 1,2	16	0	1,0	1,6 (1,2 – 2,2)
	Medium	1,2 – 1,6	16	0	1,4	1,7 (1,3 – 2,4)
	High	1,7 – 2,5	10	0	2,1	1,9 (1,4 – 3,1)
PHCC 4	Low	0,5 – 1,2	11	0	1,0	2,2 (1,6 – 3,5)
	Medium	1,2 – 1,6	18	0	1,4	1,0 (0,8 – 1,4)
	High	1,6 – 2,3	9	0	2,0	1,1 (0,8 – 1,9)

An account of the number of samples is given in sections 6.1. and 8.1.

Discussion

The CV achieved by PHCC1 was between 1,6 and 1,9 % and in PHCC4 the CV was between 1,0 and 2,2 %, depending on the concentration levels. As two instruments were used for duplicate measurements in PHCC1 the difference between the two **cobas b** 101 instruments is included in the CV's given in table 14.

Conclusion
When measurements were performed by the intended users the quality goal for repeatability (CV ≤4 %) was fulfilled.

8.4.3. The bias of cobas b 101 HDL-cholesterol

The mean deviation (bias) of **cobas b** 101 HDL-cholesterol results from the comparison method was calculated. The bias is presented with a 95 % CI in table 15. The results were sorted and divided into two concentration levels according to the mean results of the comparison method. Raw data is attached for the requesting company only, see attachments 14 and 19.

Table 15. Bias of **cobas b** 101 for HDL-cholesterol measured in capillary whole blood samples. Results achieved by intended users.

Place	Level	HDL-cholesterol interval comparison method, mmol/L	n	Excluded results (statistical outliers)	Mean value HDL-cholesterol comparison method, mmol/L	Mean value HDL-cholesterol cobas b 101, mmol/L	Bias (95 % CI), mmol/L	Bias, %
PHCC 1	Low	0,7 – 1,2	16	0	1,0	1,0	-0,04 (-0,07 – -0,02)	-4,3
	Medium	1,2 – 1,6	21	0	1,4	1,4	0,00 (-0,02 – 0,02)	0,1
	High	1,9 – 2,5	9	0	2,2	2,2	-0,01 (-0,06 – 0,04)	-0,4
PHCC 4	Low	0,6 – 1,2	8	0	1,0	1,0	-0,02 (-0,06 – 0,02)	-2,1
	Medium	1,2 – 1,6	20	0	1,4	1,4	0,01 (-0,02 – 0,04)	0,7
	High	1,6 – 2,3	8	0	2,0	2,0	0,03 (-0,04 – 0,09)	1,3

An account of the number of samples is given in sections 6.1. and 8.1.

Discussion
For both PHCC1 and PHCC4 no statistically significant bias was seen except for the low level

8.4.4. The accuracy of cobas b 101 HDL-cholesterol

To evaluate the accuracy of HDL-cholesterol results on **cobas b** 101, the agreement between **cobas b** 101 HDL-cholesterol and the comparison method is illustrated in a difference plot (figure 6). The limits for the allowable deviation according to the quality goal (±13 %) 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 PHCC4 the samples were measured on the same **cobas b** 101 instrument. The plot illustrates both random and systematic errors, reflecting the total measuring error in the **cobas b** 101 HDL-cholesterol results. Raw data is attached for the requesting company only, see attachments 14 and 19.

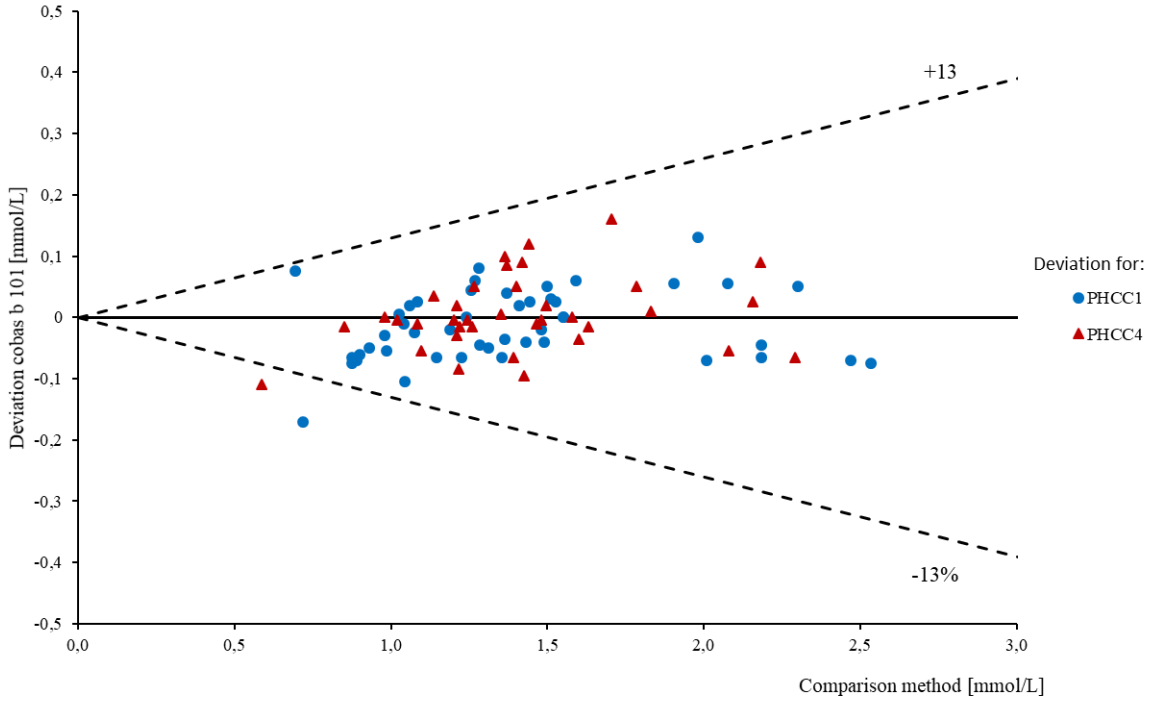

Figure 6. Accuracy of HDL-cholesterol results on **cobas b** 101 achieved by intended users. The x-axis represents the mean HDL-cholesterol result of the comparison method. The y-axis represents the HDL-cholesterol deviation in mmol/L of the capillary whole blood sample measurement on **cobas b** 101 HDL-cholesterol from the mean result of the corresponding sample of the comparison method. The different PHCC's are illustrated with the symbols ● (PHCC1) and ▲ (PHCC4). Stippled lines represent the allowable deviation limits of ±13 %. Number of results (n) = 83. An account of the number of samples is given in sections 6.1. and 8.1.

Discussion

As shown in figure 6, no visible difference was seen between the comparison method and **cobas b** 101 HDL cholesterol. Of the 83 results 81 were inside the limits for allowable deviation (±13 %) amounting to 98 %. The quality goal for individual results within the limits is ≥95 %. The figure also shows that there was no visible difference between the two PHCCs.

Conclusion

When measurements were performed by the intended users the quality goal for accuracy was fulfilled.

9. Results and discussion triglycerides

9.1. Number of samples

For numbers of samples see 6.1.

Missing results

- ID 1, 2, 11, 13, 22, 37, 42, 63, 64, 84, 103, 104, 105, 126, 143; only single measurements from **cobas b** 101. The single values were not included in the calculation of repeatability but in the calculation of bias and the assessment of accuracy.
- ID 4, 5, 7, 8, 33, 36, 45, 50, 51, 52, 63, 64, 71, 72, 74, 98, F104, F105, F106, F109; only single measurement from the comparison method. The single values were not included in the calculation of repeatability of the comparison method but in the calculation of bias and the assessment of accuracy.
- ID 20, 30, 31; there were no measurements from the comparison method. The results from **cobas b** 101 were included in the calculations of repeatability, but not included in the calculation of bias and the assessment of accuracy.
- From optimal condition the internal analytical quality control result for level 1 for one evaluation day was missing. The results from patient samples that day were still included in the calculations.
- ID 409; **cobas b** 101, both measurements were below measurement range (<0,50 mmol/L) and therefore not included in any calculations.
- ID 76, 425; **cobas b** 10, both measurements above measurement range (>7,35 mmol/L) and therefore not included in any calculations.
- ID 93; no results from **cobas b** 101 due to time limit for analysis exceeded.

Omitted results

- ID 434, 435, 436; were analysed with the comparison method >4 days after sampling. The results from **cobas b** 101 were included in the calculations of repeatability, but not included in the calculation of bias and the assessment of accuracy.
- ID 33; **cobas b** 101, was manually excluded from all calculations because big different between the two measurements.

Excluded results (statistical outliers)

Statistical outliers according to Burnett [9]:

- ID 4, 41, F102, 108, 117, 405; these results from **cobas b** 101 were classified as outliers to Burnett's model in the calculation repeatability. The results were removed before calculation of repeatability and bias but were included in the assessment of accuracy.

- ID 29, 75, 93, 128, 140; these results from the comparison method were classified as outliers to Burnett's model in the calculation repeatability. The results were not included in the of bias and the assessment of accuracy, but the results from cobas b 101 were included in the calculation of repeatability.

- ID 19, 61, 67, 106; these results were classified as outliers according to Burnett's model in the calculation of bias. The results were removed before calculation of bias but were included in the assessment of accuracy.

9.2. Analytical quality of the selected comparison methods triglycerides

9.2.1. Internal analytical quality control for triglycerides

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

9.2.2. The precision of the comparison methods

Duplicate measurements of each venous patient sample were performed on the comparison method. 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 from KB-AaUH or KBF-OUH (data not shown).

The precision is presented as repeatability (CV). The CV with a 90 % CI is shown in tables 16a and 16b. 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 attachments 20 and 21.

Table 16a. Repeatability (CV) of the comparison method **cobas** 8000 KB-AaUH for triglycerides measured in venous plasma samples.

Level	Triglycerides interval, mmolL	n*	Excluded results (statistical outliers)	Mean value Triglycerides, mmolL	CV (90% CI), %
Low	0,53 – 1,44	47	2**	1,04	1,2 (1,0 – 1,4)
Medium	1,51 – 1,96	18	0	1,71	1,4 (1,1 – 1,9)
High	2,03 – 7,48	23	1**	2,85	1,5 (1,2 – 2,1)

*The given number of results (n) were counted before the exclusion of statistical outliers. Mean and repeatability were calculated after the exclusion of statistical outliers. An account of the number of samples is given in sections 6.1. and 9.1.
**ID 29, 75, 93 were statistical outliers according to Burnett´s model [9] in the calculation of repeatability and therefore excluded.

Table 16b. Repeatability (CV) of the comparison method **cobas** 8000 KBF-OUH for triglycerides measured in venous plasma samples.

Level	Triglycerides interval, mmol/L	n*	Excluded results (statistical outliers)	Mean value Triglycerides, mmol/L	CV (90% CI), %
Low	0,40 – 1,48	44	0	1,03	1,0 (0,9 – 1,3)
Medium	1,55 – 1,98	17	1**	1,70	0,7 (0,5 – 1,0)
High	2,11 – 8,45	24	1**	2,93	0,7 (0,6 – 0,9)

*The given number of results (n) were counted before the exclusion of statistical outliers. Mean and repeatability were calculated after the exclusion of statistical outliers. An account of the number of samples is given in sections 6.1. and 9.1.
**ID 128, 140 were statistical outliers according to Burnett´s model [9] in the calculation of repeatability and therefore excluded.

Discussion
The CV for the comparison method **cobas** 8000 KB-AaUH for triglycerides was between 1,2 and 1,5 % and the CV for the comparison method **cobas** 8000 KBF-OUH for triglycerides was between 0,7 and 1,0 %.

9.2.3. The trueness of the comparison methods triglycerides

To demonstrate the trueness of the two comparison methods in KB-AaUH and KBF-OUH (both methods are **cobas** 8000 module c702), certified reference material LNE CRM Bio 101a level 1 and level 2 were analysed (tables 17a, 17b). Furthermore, controls from EQA programme "Serum B and C, general clinical chemistry" from Labquality (two levels, round 2 2019, table 17c) were analysed on both methods (specified in section 5.3.1).

Table 17a. Triglycerides measured on LNE CRM on **cobas** 8000 module c702 at KB-AaUH.

Date: 22.05.2019		Site: KB-AaUH		
Level	Certified values by LNE k=2, mmol/L	n	KB-AaUH mean triglycerides, mmol/L	Deviation from target value, mmol/L
LNE CRM Bio 101a level 1	0,741 (0,021)	5	0,78	0,037
LNE CRM Bio 101a level 2	1,607 (0,047)	5	1,66	0,057

Table 17b. Triglycerides measured on LNE CRM on **cobas** 8000 module c702 at KBF-OUH.

Date: 22.05.2019		Site: KBF-OUH		
Level	Certified values by LNE k=2, mmol/L	n	KBF-OUH mean triglycerides, mmol/L	Deviation from target value, mmol/L
LNE CRM Bio 101a level 1	0,741 (0,021)	5	0,747	0,006
LNE CRM Bio 101a level 2	1,607 (0,047)	5	1,609	0,002

Table 17c. Results for triglycerides from Labquality's EQA programme measured on the comparison methods.

Sample	Assigned values triglycerides, mmol/L (±10 % acceptance limits)	n	KB-AaUH **cobas** 8000 c702 triglycerides, mmol/L	KBF-OUH **cobas** 8000 c702 triglycerides, mmol/L
S001	1,86 (1,58 – 2,14)	1	2,00	1,99
S002	0,92 (0,78 – 1,06)	1	1,00	1,00

Discussion
Tables 17a and 17b show that results obtained in KB-AaUH were slightly higher than the LNE certified values and outside the LNE uncertainty limits. Results obtained on the LNE reference material in KBF-OUH were very close to the LNE certified values. Fifteen patient samples were also measured in duplicate on both comparison methods to verify the agreement between the methods (attachment 22). These samples also showed that KB-AaUH found slightly higher results than KBF-OUH. The EQA results from the two comparison methods were within the acceptance limits.

9.3. Analytical quality of cobas b 101 triglycerides under optimal conditions

The results below reflect the analytical quality of **cobas b** 101 triglycerides under optimal conditions. The results document the quality of the system under conditions as favourable as possible for achieving good analytical quality.

9.3.1. Internal analytical quality control for triglycerides

All results from the internal analytical quality control (**cobas** Lipid Panel kit) two levels were within the allowable control limits (data not shown). The reproducibility (CV) achieved with the internal analytical quality control samples were 1,9 % for level 1 (n=86) and 1,4 % for level 2 (n=87). Raw data is attached for the requesting company only, see attachment 23.

9.3.2. The precision of cobas b 101 triglycerides

Duplicate measurements from each patient sample were performed on **cobas b** 101 triglycerides. 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 18. The results were sorted and divided into three concentration levels according to the mean of the results of the **cobas b** 101 triglycerides method. Raw data is attached for the requesting company only, see attachment 24.

Table 18. Repeatability (CV) of **cobas b** 101 for triglycerides measured in capillary whole blood samples. Results achieved under optimal conditions.

Level	Triglycerides interval, mmol/L	n*	Excluded results (statistical outliers)	Mean value Triglycerides, mmol/L	CV (90% CI), %
Low	0,68 – 1,49	39	1**	1,12	6,3 (5,3 – 7,8)
Medium	1,54 – 1,95	22	2**	1,73	4,0 (3,2 – 5,4)
High	2,01 – 4,84	37	0	2,95	8,0 (6,7 – 10,0)

*The given number of results (n) were counted before the exclusion of statistical outliers. Mean and repeatability were calculated after the exclusion of statistical outliers. An account of the number of samples is given in sections 6.1. and 9.1.
**ID 4, 41, F102 were statistical outliers according to Burnett´s model [9] in the calculation of repeatability and therefore excluded.

Discussion
The CV achieved under optimal conditions was between 4,0 and 8,0 % depending on the concentration level. The CV for the medium level was lower than the quality goal, but not statistically significant lower as the upper CI is above the quality goal. The CV for low and high levels was statistically significantly higher than the quality goal. As two instruments were used for duplicate measurements the difference between the two **cobas b** 101 instruments is included in the CV's given in table 18.

Conclusion
Since two **cobas b** 101 instruments were used for duplicate measurements, the difference between the two instruments is included in the CVs in table 18 and therefore it cannot be concluded whether the quality goal (CV ≤5,0 %) was met.

9.3.3. The bias of cobas b 101 triglycerides

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 19. 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 attachments 20 and 24.

Table 19. Bias of **cobas b** 101 for triglycerides measured in capillary whole blood samples. Results achieved under optimal conditions.

Level	Triglycerides interval comparison method, mmol/L	n*	Excluded results (statistical outliers)	Mean value Triglycerides comparison method, mmol/L	Mean value Triglycerides cobas b 101, mmol/L	Bias (95 % CI), mmol/L	Bias, %
Low	0,53 – 1,44	51	2**	1,02	1,26	0,24 (0,20 – 0,27)	23,0
Medium	1,51 – 1,96	21	0	1,70	2,01	0,31 (0,22 – 0,40)	18,1
High	2,03 – 4,47	28	1**	2,76	3,06	0,31 (0,23 – 0,38)	11,1

*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 sections 6.1. and 9.1.
**ID 19, 61, 67 were statistical outliers according to Burnett´s model [9] in the calculation of bias and therefore excluded.

Discussion
For all three levels there was a statistically significant bias between **cobas b** 101 triglycerides and the comparison method. The result from **cobas b** 101 were systematically higher than the results from the comparison method. For the low triglyceride level, the bias was 0,24 mmol/L, for the medium and high triglyceride levels the bias was 0,31 mmol/L.

9.3.4. The accuracy of cobas b 101 triglycerides

To evaluate the accuracy of triglycerides results on **cobas b** 101, the agreement between **cobas b** 101 triglycerides and the comparison method is illustrated in a difference plot (figure 7). The limits for the allowable deviation according to the quality goal (±16,0 %) 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 attachments 20 and 24.

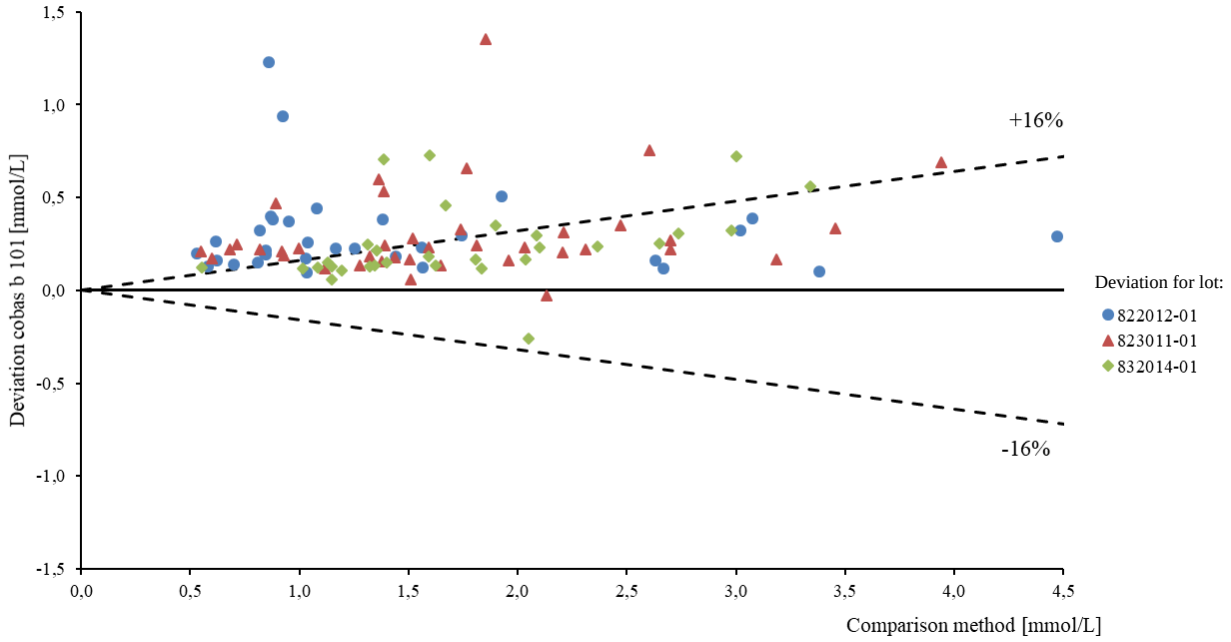

Figure 7. Accuracy of triglycerides results on **cobas b** 101 under optimal conditions. The x-axis represents the mean triglycerides result of the comparison method. The y-axis represents the triglycerides deviation in mmol/L of the capillary whole blood measurement on **cobas b** 101 from the mean result of the corresponding sample of the comparison method. The different lots of test discs are illustrated with the symbols ● (lot 822012-01), ▲ (lot 823011-01) and ♦ (lot 832014-01). Stippled lines represent the allowable deviation limits of ±16 %. Number of results (n) = 105. An account of the number of samples is given in sections 6.1 and 9.1.

Discussion

As shown in figure 7, the **cobas b** 101 triglycerides results are higher than the results from the comparison method, which is consistent with the calculated bias (table 19). Of the 105 results 53 were inside the limits for allowable deviation (±16 %) amounting to 50 %. The quality goal for individual results within the limits is ≥95 %.

Conclusion

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

9.4. Analytical quality of cobas b 101 triglycerides achieved by intended users

The results below reflect the analytical quality of **cobas b** 101 triglycerides under real-life conditions in the hands of intended users in PHCCs. The results may deviate from the results achieved under optimal conditions.

9.4.1. Internal analytical quality control for triglycerides

All results from the internal analytical quality control (**cobas** Lipid Panel kit) two levels were within the allowable control limits (data not shown). The reproducibility (CV) achieved with the internal analytical quality control samples were 1,4 % for level 1 (n=37) and 1,1 % for level 2 (n=37). Raw data is attached for the requesting company only, see attachment 25.

9.4.2. The precision of cobas b 101 triglycerides

Duplicate measurements from each patient sample were performed on **cobas b** 101 triglycerides. 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 in PHCC1. The CV with a 90 % CI is shown in table 20. The results were sorted and divided into three concentration levels according to the mean of the results of the **cobas b** 101 triglycerides method. Since the variances between the two PHCCs were significantly different (F-test, 5 % significance level) the results from the two PHCCs were not combined before the calculation of CV. Raw data is attached for the requesting company only, see attachment 26.

Table 20. Repeatability (CV) of **cobas b** 101 for triglycerides measured in capillary whole blood samples. Results achieved by intended users.

Place	Level	Triglycerides interval, mmol/L	n*	Excluded results (statistical outliers)	Mean value Triglycerides, mmol/L	CV (90% CI), %
PHCC 1	Low	0,63 – 1,47	15	1**	1,02	2,0 (1,5 – 3,0)
	Medium	1,56 – 1,96	11	1**	1,76	1,4 (1,0 – 2,3)
	High	2,01 – 4,10	17	0	2,81	7,3 (5,7 – 10,3)
PHCC 4	Low	0,79 – 1,47	14	1**	1,19	2,2 (1,7 – 3,4)
	Medium	1,51 – 1,97	10	0	1,79	8,4 (6,1 – 13,8)
	High	2,19 – 3,83	14	0	2,92	8,5 (6,5 – 12,6)

*The given number of results (n) were counted before the exclusion of statistical outliers. Mean and repeatability were calculated after the exclusion of statistical outliers. An account of the number of samples is given in sections 6.1. and 9.1.

**ID 108, 117, 405 were statistical outliers according to Burnett´s model [9] in the calculation of repeatability and therefore excluded.

Discussion

The CV achieved by PHCC1 was between 1,4 and 7,3 % and in PHCC4 the CV was between 2,2 and 8,5 % depending on the concentration levels. The CV for the low and medium level for PHCC1 and the low level for PHCC4 were statistically significantly lower than the quality goal. The CV for the high level for PHCC1 and the medium and high level for PHCC4 was statistically significantly higher than the quality goal.

Conclusion
Since two instruments were used for duplicate measurements in PHCC1 only results from PHCC4 are included in this conclusion. When measurements were performed by the intended users the quality goal for repeatability (CV ≤5,0 %) was not fulfilled.

9.4.3. The bias of cobas b 101 triglycerides

The mean deviation (bias) of **cobas b** 101 triglycerides results from the comparison method was calculated. The bias is presented with a 95 % CI in table 21. 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 attachments 21 and 26.

Table 21. Bias of **cobas b** 101 for triglycerides measured in capillary whole blood samples. Results achieved by intended users.

Place	Level	Triglycerides interval comparison method, mmol/L	n*	Excluded results (statistical outliers)	Mean value Triglycerides comparison method, mmol/L	Mean value Triglycerides cobas b 101, mmol/L	Bias (95 % CI), mmol/L	Bias, %
PHCC 1	Low	0,57 – 1,47	23	1**	1,0	1,3	0,26 (0,17 – 0,36)	26,4
	Medium	1,56 – 1,98	9	0	1,7	1,9	0,22 (0,14 – 0,29)	12,6
	High	2,11 – 3,54	12	0	2,7	3,1	0,37 (0,29 – 0,46)	13,9
PHCC 4	Low	0,74 – 1,48	17	0	1,2	1,5	0,30 (0,15 – 0,44)	25,7
	Medium	1,55 – 1,86	7	0	1,7	1,9	0,24 (0,16 – 0,33)	14,4
	High	2,13 – 3,29	10	0	2,7	3,1	0,40 (0,19 – 0,61)	15,0

*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 sections 6.1. and 9.1.
**ID 106 was a statistical outlier according to Burnett´s model [9] in the calculation of bias and therefore excluded.

Discussion
For both PHCC1 and PHCC4 there was a statistically significant bias between **cobas b** 101 and the comparison method at all three levels. The bias was between 0,22 and 0,40 mmol/L depending on the concentration level.

9.4.4. The accuracy of cobas b 101 triglycerides

To evaluate the accuracy of triglycerides results on **cobas b** 101, the agreement between **cobas b** 101 triglycerides and the comparison method is illustrated in a difference plot (figure 8). The limits for the allowable deviation according to the quality goal (±16 %) 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 PHCC4 the samples were measured on the same **cobas b** 101 instrument. The plot illustrates both random and systematic errors, reflecting the total measuring error in the **cobas b** 101 triglycerides results. Raw data is attached for the requesting company only, see attachments 21 and 26.

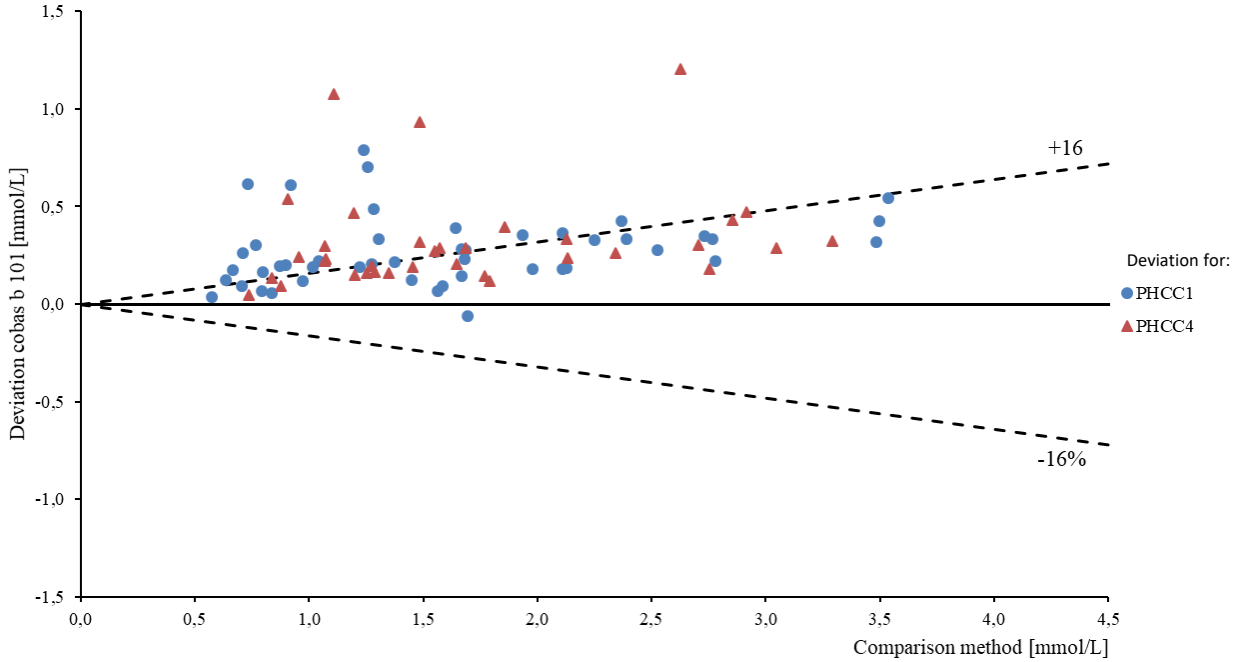

Figure 8. Accuracy of triglycerides results on **cobas b** 101 achieved by intended users. The x-axis represents the mean triglycerides result of the comparison method. The y-axis represents the triglycerides deviation in mmol/L of the capillary whole blood sample measurement on **cobas b** 101 triglycerides from the mean result of the corresponding sample of the comparison method. The different instruments are illustrated with the symbols ● (PHCC1) and ▲ (PHCC4). Stippled lines represent the allowable deviation limits of ±16 %.
Number of results (n) = 83. An account of the number of samples is given in sections 6.1. and 9.1.

Discussion

As shown in figure 8, the **cobas b** 101 triglycerides results are higher than the results from the comparison method, this is consistent with the calculated bias (table 21). Of the 83 results 45 were inside the limits for allowable deviation (±16 %) amounting to 54 %. The quality goal for individual results within the limits is ≥95 %.

Conclusion

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

10. Results and discussion LDL-cholesterol

LDL-cholesterol in **cobas b** 101 is calculated using the Friedewald formula [10] if triglycerides are <4,52 mmol/L
If triglycerides are ≥4,52 mmol/L LDL-cholesterol is not calculated.
If HDL-cholesterol is >2,6 mmol/L LDL-cholesterol is not calculated.

LDL-cholesterol results from **cobas** 8000 are calculated using Friedewald formula [10].

Friedewald formula: LDL-cholesterol = cholesterol – HDL-cholesterol – (triglycerides × 0,45)

10.1. Number of samples

For numbers of samples see 6.1.

Results excluded as outliers in cholesterol, HDL-cholesterol and triglycerides for comparison instruments (**cobas** 8000) are excluded before calculations of the LDL-cholesterol.

Missing results

- ID 1, 2, 11 ,13, 22, 23, 31, 33, 37, 40, 42, 63, 64, 72, 84, 103, 104, 105, 126, 143 only single results from **cobas b** 101. The single values were not included in the calculation of repeatability but in calculation of bias and the assessment of accuracy.
- ID 4, 5, 7, 8, 33, 36, 45, 50, 51, 52, 63, 64, 71, 72, 74, 98, F104, F105, F106, F109, F111; only single measurement from the comparison method. The single values were not included in the calculation of repeatability but in the calculation of bias and the assessment of accuracy.
- ID 20, 30, 31; there were no measurements on cholesterol, triglycerides and HDL-cholesterol from comparison method. The results from cobas b 101 were included in the calculations of repeatability.
- ID 31, 33, 36, 72, 76, 425; **cobas b** 101 reported LDL-cholesterol as N/A. The LDL-cholesterol is not calculated because triglycerides are ≥4,52 mmol/L.
- ID 409; **cobas b** 101 reported LDL-cholesterol as N/A. The LDL-cholesterol is not calculated because triglycerides are <0,50 mmol/L.
- ID 40, 71, 150, 436; **cobas b** 101 reported LDL-cholesterol as N/A. The LDL-cholesterol is not calculated because HDL-cholesterol >2,60 mmol/L.
- ID 76, 127: **cobas b** 101 HDL-cholesterol reported as N/A (out of range), LDL-cholesterol is not calculated.

Omitted results

- ID 434, 435, 436; were analysed with the comparison method >4 days after sampling, the measurements were included in the calculation of repeatability for **cobas b** 101 but not in calculation of repeatability, bias and the assessment of accuracy from the comparison method.

Manual outliers in all calculations

- ID 29, 75, 93, 128, 140; were statistical outliers in triglycerides on the comparison method.
- ID 139; was a statistical outlier in HDL-cholesterol on the comparison method.

Excluded results (statistical outliers)

Statistical outliers according to Burnett [9]:

- ID 21, 415; the results from **cobas b** 101 were classified as outliers according to Burnett's model in the calculation of LDL-cholesterol repeatability. The result was excluded in the assessment of bias but included in the assessment of accuracy.
- ID 33, 106; the results from **cobas b** 101 were classified as outliers according to Burnett's model in the calculation of LDL-cholesterol bias. The results were included on the assessment of accuracy (the first of the duplicate measurements).

10.2. Analytical quality of the selected comparison methods LDL-cholesterol

10.2.1. Internal analytical quality control for LDL-cholesterol

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

10.2.2. The precision of the comparison methods

Duplicate results were calculated from each venous patient sample analyzed on the comparison method. The results were checked to meet the imposed condition for using formula 1 in attachment 5.

cobas 8000 KB-AaUH: The paired measurements at the medium and high levels showed a small, but statically significant difference (data not shown). When using highly precise methods, even negligible differences are easily pointed out as statistically significant. The systematic differences pointed out lead to a minor overestimation of the CV of the comparison method at the medium and high LDL-cholesterol levels (data not shown).

cobas 8000 KBF-OUH: There were no systematic differences between the paired measurements. (data not shown).

The precision is presented as repeatability (CV). The CV with a 90 % CI is shown in tables 22a and 22b. 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 attachments 27 and 28.

Table 22a. Repeatability (CV) of the comparison method **cobas** 8000 KB-AaUH for LDL-cholesterol measured in venous plasma samples.

Level	LDL-cholesterol interval, mmol/L	n	Excluded results (statistical outliers)	Mean value LDL-cholesterol, mmol/L	CV (90% CI), %
Low	0,51 – 1,99	25	0	1,5	2,9 (2,4 – 3,9)
Medium	2,03 – 2,99	39	0	2,8	1,8 (1,5 – 2,2)
High	3,05 – 4,50	20	0	3,7	1,6 (1,3 – 2,2)

An account of the number of samples is given in sections 6.1. and 10.1.

Table 22b. Repeatability (CV) of the comparison method **cobas** 8000 KBF-OUH for LDL-cholesterol measured in venous plasma samples.

Level	LDL-cholesterol interval, mmol/L	n	Excluded results (statistical outliers)	Mean value LDL-cholesterol, mmol/L	CV (90% CI), %
Low	0,78 – 1,93	26	0	1,5	2,5 (2,0 – 3,2)
Medium	2,00 – 2,92	25	0	2,5	1,6 (1,3 – 2,1)
High	3,01 – 5,13	29	0	3,7	1,0 (0,8 – 1,3)

An account of the number of samples is given in sections 6.1. and 10.1.

Discussion

The CV for the comparison method **cobas** 8000 KB-AaUH for LDL-cholesterol was between 1,6 and 2,9 % and the CV for the comparison method **cobas** 8000 KBF-OUH LDL-cholesterol was between 1,0 and 2,5 %.

10.2.3. The trueness of the comparison methods LDL-cholesterol

To demonstrate the trueness of the two comparison methods in KB-AaUH and KBF-OUH (both methods are **cobas** 8000 module c702), certified reference material LNE CRM Bio 101a level 1 and level 2 were analysed (tables 23a, 23b). Furthermore, controls from EQA programme "Serum B and C, general clinical chemistry" from Labquality (two levels, round 2 2019, table 23c) were analysed on both methods (specified in section 5.3.1).

Table 23a. LDL-cholesterol calculated on LNE CRM from **cobas** 8000 module c702 at KB-AaUH.

Date: 22.05.2019		Site: KB-AaUH		
Level	Certified values by LNE, k=2, mmol/L	n	KB-AaUH mean LDL-cholesterol, mmol/L	Deviation from target value, mmol/L
LNE CRM Bio 101a level 1	2,001 (0,069)	5	2,07	0,065
LNE CRM Bio 101a level 2	3,518 (0,126)	5	3,66	0,145

Table 23b. LDL-cholesterol calculated on LNE CRM from **cobas** 8000 module c702 at KBF-OUH.

Date: : 22.05.2019		Site: KBF-OUH		
Level	Certified values by LNE, k=2, mmol/L	n	KBF-OUH mean LDL-cholesterol, mmol/L	Deviation from target value, mmol/L
LNE CRM Bio 101a level 1	2,001 (0,069)	5	1,97	-0,035
LNE CRM Bio 101a level 2	3,518 (0,126)	5	3,62	0,100

Table 23c. Results for LDL-cholesterol from Labquality's EQA programme measured on the comparison methods.

Sample	Assigned values LDL-cholesterol, mmol/L (±10 % acceptance limits)	n	KB-AaUH **cobas** 8000 c702 LDL-cholesterol, mmol/L Friedewald formula	KBF-OUH **cobas** 8000 c702 LDL-cholesterol, mmol/L
S001	Friedewald formula: 2,64 (2,38 – 2,91) Direct: 2,72 (2,45 – 3,00)	1	2,50	Calculated: 2,60* Direct: 2,67
S002	Friedewald formula: 2,01 (1,81 – 2,22) Direct: 2,35 (2,11 – 2,58)	1	2,00	Calculated: 1,95* Direct: 2,32

*Calculated by SKUP with Friedewald formula

Discussion
Tables 23a and 23b show that results obtained on LNE in KB-AaUH were close to the LNE certified values. Level 1 was within the uncertainty limits and level 2 was just slightly outside the uncertainty limits. Results obtained on the LNE reference material in KBF-OUH were within the uncertainty limits. Fifteen patient samples were also measured in duplicate on both comparison methods to verify the agreement between the methods. This comparison showed that samples measured in KB-AaUH gave slightly higher results than corresponding samples measured in KBF-OUH (attachment 29). The EQA results from both comparison methods were within the acceptance limits.

10.3. Analytical quality of cobas b 101 LDL-cholesterol under optimal conditions

The results below reflect the analytical quality of **cobas b** 101 LDL-cholesterol under optimal conditions. The results document the quality of the system under conditions as favourable as possible for achieving good analytical quality.

10.3.1. Internal analytical quality control for LDL-cholesterol

There is no internal quality control for **cobas b** 101 LDL-cholesterol.

10.3.2. The precision of cobas b 101 LDL-cholesterol

The precision is presented as repeatability (CV). The CV with a 90 % CI is shown in table 24. The results were sorted and divided into three concentration levels according to the mean of the results of the **cobas b** 101 LDL-cholesterol method. Raw data is attached for the requesting company only, see attachment 30.

Table 24. Repeatability (CV) of **cobas b** 101 for LDL-cholesterol measured in capillary whole blood samples. Results achieved under optimal conditions.

Level	LDL-cholesterol interval, mmol/L	n*	Excluded results (statistical outliers)	Mean value LDL-cholesterol, mmol/L	CV (90% CI), %
Low	0,27 – 1,97	30	0	1,4	10,3 (8,5 – 13,2)
Medium	2,04 – 2,97	42	1**	2,5	2,0 (1,7 – 2,4)
High	3,04 – 4,37	19	0	3,7	1,9 (1,5 – 2,7)

*The given number of results (n) were counted before the exclusion of statistical outliers. Mean and repeatability were calculated after the exclusion of statistical outliers. An account of the number of samples is given in sections 6.1. and 10.1.
**ID 21 was a statistical outlier according to Burnett´s model [9] in the calculation of repeatability and therefore excluded.

Discussion
The CV achieved under optimal conditions was 10,3 % at the low LDL-cholesterol level. This is statistically significantly higher than the quality goal. For the medium and high levels, the CVs were 2,0 % and 1,9 % respectively, and the upper CI for both levels was below the quality goal (CV ≤4,0 %). As two instruments were used for duplicate measurements the difference between the two **cobas b** 101 instruments is included in the CV's given in table 24.

Conclusion
Since two **cobas b** 101 instruments were used for duplicate measurements, the difference between the two instruments is included in the CVs in table 24 and therefore it cannot be concluded whether the quality goal is met for the low level, but under optimal conditions the quality goal for repeatability (CV ≤4,0 %) was fulfilled at the medium and high level.

10.3.3. The bias of cobas b 101 LDL-cholesterol

The mean deviation (bias) of **cobas b** 101 LDL-cholesterol results from the comparison method was calculated. The bias is presented with a 95 % CI in table 25. 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 attachments 28 and 30.

Table 25. Bias of **cobas b** 101 for LDL-cholesterol measured in capillary whole blood samples. Results achieved under optimal conditions.

Level	LDL-cholesterol interval comparison method, mmol/L	n*	Excluded results (statistical outliers)	Mean value LDL-cholesterol comparison method, mmol/L	Mean value LDL-cholesterol cobas b 101, mmol/L	Bias (95 % CI), mmol/L	Bias, %
Low	0,51 – 1,99	30	0	1,5	1,4	-0,10 (-0,17 – -0,04)	-6,6
Medium	2,03 – 2,99	47	1**	2,5	2,5	-0,03 (-0,06 – 0,00)	-1,2
High	3,05 – 4,50	23	0	3,7	3,6	-0,07 (-0,11 – -0,03)	-2,0

*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 sections 6.1. and 10.1.
**ID 33 was a statistical outlier according to Burnett´s model [9] in the calculation of bias and therefore excluded.

Discussion
A negative bias was seen at all three levels, however it was not statistically significant at the medium level (CI -0,06 – 0,00).
The bias was between -0,03 mmol/L and -0,10 mmol/L, depending on the concentration level.

10.3.4. The accuracy of cobas b 101 LDL-cholesterol

To evaluate the accuracy of LDL-cholesterol results on **cobas b** 101, the agreement between **cobas b** 101 LDL-cholesterol and the comparison method is illustrated in a difference plot (figure 9). The limits for the allowable deviation according to the quality goal (±13 %) 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 attachments 27 and 30.

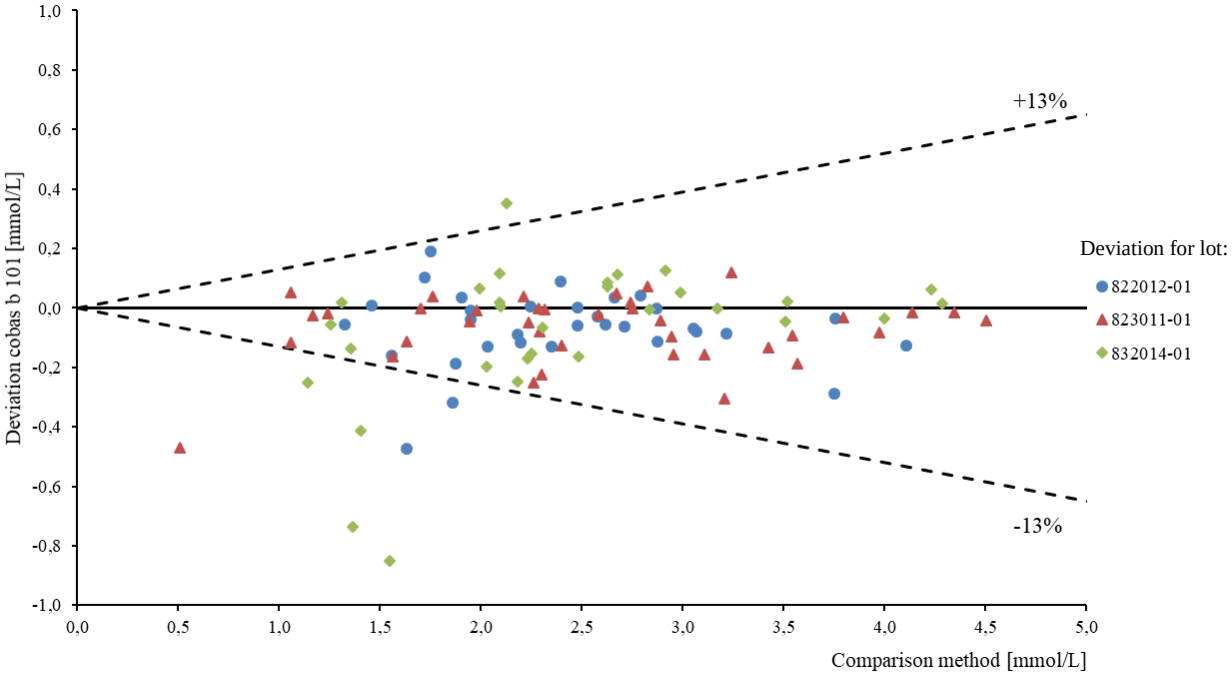

Figure 9. Accuracy of LDL-cholesterol results on **cobas b** 101 under optimal conditions. The x-axis represents the mean LDL-cholesterol result of the comparison method. The y-axis represents the LDL-cholesterol deviation in mmol/L of the capillary whole blood measurement on **cobas b** 101 from the mean result of the corresponding sample of the comparison method. The different lots of test discs are illustrated with the symbols ● (Lot 822012-01), ▲ (lot 823011-01) and ♦ (lot 832014-01). Stippled lines represent the allowable deviation limits of ±13 %. Number of results (n) = 101. An account of the number of samples is given in sections 6.1. and 10.1.

Discussion

As shown in figure 9, most of the **cobas b** 101 LDL-cholesterol results are lower than the results from the comparison method, especially in the low level which is consistent with the calculated bias (table 25). Of the 101 results, 92 were within the allowable deviation limits amounting to 91 %. The quality goal for individual results within the limits is ≥95 %.

Conclusion

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

10.4. Analytical quality of cobas b 101 LDL-cholesterol achieved by intended users

10.4.1. Internal analytical quality control for LDL-cholesterol

There is no internal quality control for **cobas b** 101 LDL-cholesterol.

10.4.2. The precision of cobas b 101 LDL-cholesterol

The precision is presented as repeatability (CV). The CV with a 90 % CI is shown in table 26. The results were sorted and divided into three concentration levels according to the mean of the results of **cobas b** 101 LDL-cholesterol system. Since the variances between the two PHCCs were significantly different (F-test, 5 % significance level) the results from the two PHCCs were not combined. Raw data is attached for the requesting company only, see attachment 31.

Table 26. Repeatability (CV) of **cobas b** 101 for LDL-cholesterol measured in capillary whole blood samples. Results achieved by intended users.

Place	Level	LDL-cholesterol interval, mmol/L	n*	Excluded results (statistical outliers)	Mean value LDL-cholesterol, mmol/L	CV (90% CI), %
PHCC 1	Low	0,05 – 1,93	12	0	1,3	3,7 (2,8 – 5,7)
	Medium	2,06 – 2,98	13	0	2,5	4,4 (3,3 – 6,6)
	High	3,01 – 5,05	17	0	3,7	1,9 (1,5 – 2,7)
PHCC 4	Low	1,2 – 1,91	12	1**	1,6	2,5 (1,8 – 3,9)
	Medium	2,03 – 3,00	13	0	2,6	5,1 (3,8 – 7,7)
	High	3,21 – 5,11	12	0	3,8	2,5 (1,9 – 3,9)

*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 sections 6.1. and 10.1.

**ID 415 was a statistical outlier according to Burnett´s model [9] in the calculation of repeatability and therefore excluded.

Discussion

The CV achieved by PHCC1 was between 1,9 and 4,4 % and for PHCC4 the CV was between 2,5 and 5,1 % depending on the concentration levels. For both PHCC1 and PHCC4 the CV for the medium level was statistically significantly higher than the quality goal (4,0 %) and the CV for the low and high levels was statistically significantly lower than the quality goal, except for the low level for PHCC1.

Conclusion

Since two instruments were used for duplicate measurements in PHCC1 only results from PHCC4 are included in this conclusion. The quality goal for repeatability (CV ≤4,0 %) was not fulfilled at the medium level but was fulfilled at the low and high level.

10.4.3. The bias of cobas b 101 LDL-cholesterol

The mean deviation (bias) of **cobas b** 101 LDL-cholesterol results from the comparison method was calculated. The bias is presented with a 95 % CI in table 27. 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 attachments 28 and 31.

Table 27. Bias of **cobas b** 101 for LDL-cholesterol measured in capillary whole blood samples. Results achieved by intended users.

Place	Level	LDL-cholesterol interval comparison method, mmol/L	n*	Excluded results (statistical outliers)	Mean LDL-cholesterol, comparison method, mmol/L	Mean LDL-cholesterol, cobas b 101, mmol/L	Bias (95 % CI), mmol/L	Bias, %
	Low	0,78 – 1,88	13	0	1,4	1,4	-0,02 (-0,09 – 0,06)	-1,1
PHCC 1	Medium	2,00 – 2,92	13	0	2,4	2,5	0,05 (-0,05 – 0,15)	2,2
	High	3,01 – 4,94	17	1**	3,7	3,8	0,09 (0,03 – 0,15)	2,3
	Low	1,25 – 1,93	11	0	1,6	1,6	0,02 (-0,02 – 0,06)	0,9
PHCC 4	Medium	2,18 – 2,89	11	0	2,6	2,7	0,08 (-0,01 – 0,16)	2,9
	High	3,08 - 5,13	12	0	3,8	3,8	0,05 (-0,05 – 0,14)	1,2

*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 sections 6.1. and 10.1.

**ID 106 was statistical outlier according to Burnett´s model [9] in the calculation of bias and therefore excluded.

Discussion

For PHCC1 there was no statistically significant bias at the low and medium level but for the high level a statistically significant bias was seen (+0,09 mmol/L). For PHCC4 there was no statistically significant bias at any of the three levels.

10.4.4. The accuracy of cobas b 101 LDL-cholesterol

To evaluate the accuracy of LDL-cholesterol results on **cobas b** 101, the agreement between **cobas b** 101 LDL-cholesterol and the comparison method is illustrated in a difference plot (figure 10). The limits for the allowable deviation according to the quality goal (±13 %) 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 PHCC4 the samples were measured on the same **cobas b** 101 instrument. The plot illustrates both random and systematic errors, reflecting the total measuring error in the **cobas b** 101 LDL-cholesterol results. Raw data is attached for the requesting company only, see attachments 28 and 31.

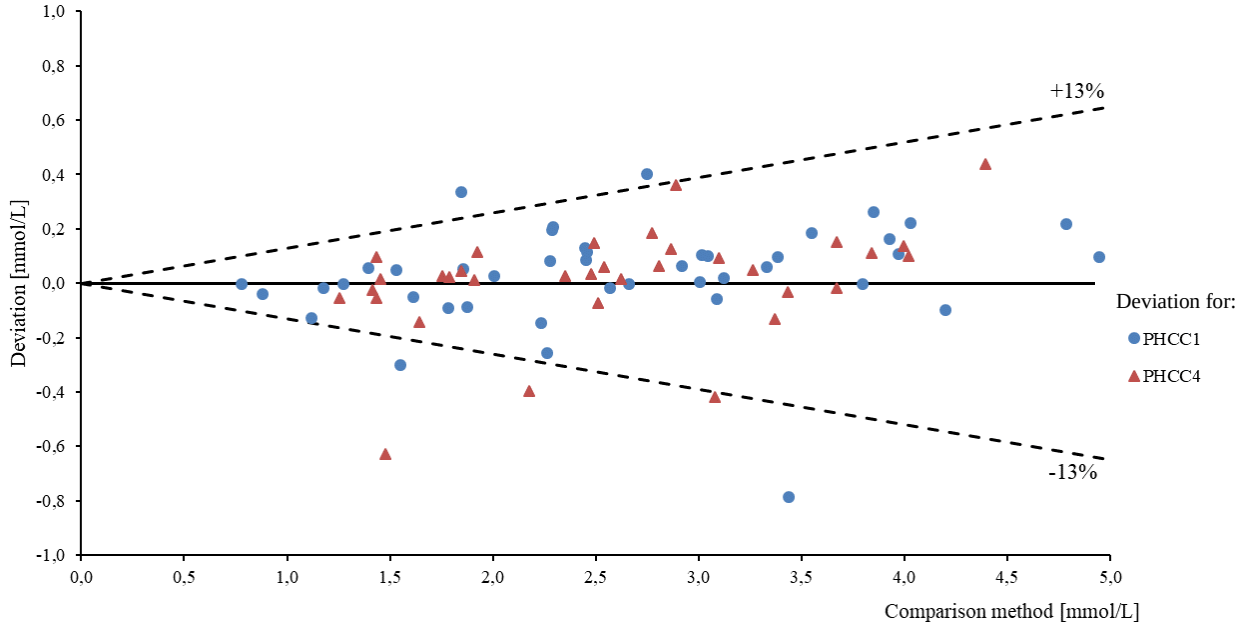

Figure 10. Accuracy of LDL-cholesterol results on **cobas b** 101 achieved by intended users. The x-axis represents the mean LDL-cholesterol result of the comparison method. The y-axis represents the LDL-cholesterol deviation in mmol/L of the capillary whole blood sample measurement on **cobas b** 101 LDL-cholesterol from the mean result of the corresponding sample of the comparison method. The different instruments are illustrated with the symbols ● (PHCC1) and ▲ (PHCC4). Stippled lines represent the allowable deviation limits of ±13 %.
Number of results (n) = 78. An account of the number of samples is given in sections 6.1. and 10.1.

Discussion

As shown in figure 10, the **cobas b** 101 LDL-cholesterol results tend to be slightly higher than the results from the comparison method, which is consistent with the calculated bias. Of the 78 results 71 were inside the limits for allowable deviation (±13 %) amounting to 91 %. The quality goal for individual results within the limits is ≥95 %.

Conclusion

The quality goal for accuracy was not fulfilled.

11. User-friendliness

11.1. 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 evaluation 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 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 property, 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 (evaluation of HbA1c and Lipid Panel), the opinion of two BLSs.
PHCC4 (evaluation of Lipid Panel), the opinion of one BLS and one nurse.

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	**I[1], S**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Specimen volume	**I[1], S**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Number of procedure step	**I[2] S**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Instrument / test design	**I, I[3]**	Satisfactory	**Intermediate**	Unsatisfactory	No opinion
Reading of the test result	**E, E**	**Easy**	Intermediate	Difficult	No opinion
Sources of errors	**I[4], 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]The application of the quality controls were more difficult than the application of the patient samples, because the liquid has no colour.
[2]Comments from SKUP: The PHCC evaluated both HbA1c and Lipid Panel, which might explain this PHCC's rating on procedure steps.
[3]Impractical not to touch the test disc without gloves.
[4]One of the instruments had «some» error reports.
Comments from SKUP: The PHCC had two instruments, SKUP has no further information about the error reports.

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	**N[1], S**	**Satisfactory**	Intermediate	Unsatisfactory	**No opinion**
Specimen collection	**N[1], S**	**Satisfactory**	Intermediate	Unsatisfactory	**No opinion**
Measurement procedure	**N[1], S**	**Satisfactory**	Intermediate	Unsatisfactory	**No opinion**
Reading of result	**N[1], S**	**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, S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
General impression	**I[3], 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**			

[1]We did not use the manual 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 were that we did not find any solution for the problem.
[3]SKUP has no further information about the error reports.

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 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**		

11.1.1. Assessment of the user-friendliness

Assessment of the operation facilities (table A)
The operation facilities were in total assessed as satisfactory, but there were several intermediate ratings. The motivations for the lower ratings mainly concerned the specimen volume, the application of the quality controls which was more difficult than the application of the patient samples because the controls have no colour, and to be careful not to touch the disc without gloves.

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 motivations for the lower ratings mainly concerned use of the manual for troubleshooting and not being able to find a solution.

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 Lipid Panel and its manual was rated as satisfactory. The quality goal for user-friendliness was fulfilled.

12. References

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Attachments

1. The organisation of SKUP
2. Facts about Facts about **cobas b** 101 Lipid Panel
3. Information about manufacturer, retailers and marketing
4. Product specifications for this evaluation, **cobas b** 101 Lipid Panel
5. Statistical expressions and calculations
6. Raw data, cholesterol results from the comparison method – KB-AaUH
7. Raw data, cholesterol results from the comparison method – KBF-OUH
8. Raw data, cholesterol results from patient samples for trueness of the comparison methods
9. Raw data, internal analytical quality control results, **cobas b** 101 cholesterol, optimal conditions
10. Raw data, **cobas b** 101 cholesterol results, optimal conditions
11. Raw data, internal analytical quality control results, **cobas b** 101 cholesterol, intended users
12. Raw data, **cobas b** 101 cholesterol results, intended users
13. Raw data, HDL-cholesterol results from the comparison method – KB-AaUH
14. Raw data, HDL-cholesterol results from the comparison method – KBF-OUH
15. Raw data, HDL-cholesterol results from patient samples for trueness of the comparison methods
16. Raw data, internal analytical quality control results, **cobas b** 101 HDL-cholesterol, optimal conditions
17. Raw data, **cobas b** 101 HDL-cholesterol results, optimal conditions
18. Raw data, internal analytical quality control results, **cobas b** 101 HDL-cholesterol, intended users
19. Raw data, **cobas b** 101 HDL-cholesterol results, intended users
20. Raw data, triglycerides results from the comparison method – KB-AaUH
21. Raw data, triglycerides results from the comparison method – KBF-OUH
22. Raw data, triglycerides results from patient samples for trueness of the comparison methods
23. Raw data, internal analytical quality control results, **cobas b** 101 triglycerides, optimal conditions
24. Raw data, **cobas b** 101 triglycerides results, optimal conditions
25. Raw data, internal analytical quality control results, **cobas b** 101 triglycerides, intended users
26. Raw data, **cobas b** 101 triglycerides results, intended users
27. Raw data, LDL-cholesterol results from the comparison method – KB-AaUH
28. Raw data, LDL-cholesterol results from the comparison method – KBF-OUH
29. Raw data, LDL-cholesterol results from patient samples for trueness of the comparison methods
30. Raw data, **cobas b** 101 LDL-cholesterol results, optimal conditions
31. Raw data, **cobas b** 101 LDL-cholesterol results, intended users
32. List of previous SKUP evaluations
33. Comments from Roche Diagnostics A/S

Attachments with raw 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 of 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).

Facts about cobas b 101 Lipid Panel

This form is filled in by Roche Diagnostics

Table 1. Basic facts Table

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 • **cobas b** 101 Lipid Panel Test • Optical check disc • Power adapter • Power cable
Measurand:	Total cholesterol (TC), high-density lipoprotein (HDL)-cholesterol, and triglycerides (TG). A calculated value for low-density lipoprotein (LDL), non-HDL and a TC/HDL ratio is provided by the **cobas b** 101 system.
Sample material:	Fresh capillary blood, K_2- or K_3-EDTA venous whole blood or plasma.
Sample volume:	19 µL
Measuring principle:	Total cholesterol, HDL-cholesterol, triglycerides: Enzymatic method.
Traceability:	Total cholesterol and HDL-cholesterol are traceable to the designated CDC reference methods (Abell-Kendall as reference method for total cholesterol). Triglycerides are traceable to the ID/MS method.
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:	Cholesterol: 50 – 500 mg/dL or 1,28 – 12,95 mmol/L Triglycerides: 45 – 650 mg/dL or 0,50 – 7,35 mmol/L HDL-cholesterol: 15 – 100 mg/dL or 0,38 – 2,60 mmol/L
Measurement time:	6 minutes
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 Patient name Operator ID Operator name Test name Disc lot number Results Date and time when result was generated Date and time when result was printed Comment Facility information
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, with bidirectional communications
What is the storage capacity of the instrument and what is stored in the instrument?	5000 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 Lipid Panel
Stability in unopened sealed vial:	Store 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. Uses Optical check disc every day
Recommended control materials and volume:	For quality control, use **cobas** Lipid Control The control intervals and limits should be adapted to each laboratory's individual requirements. Follow the applicable government regulations and local guidelines for quality control.
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 2 mL **cobas** Lipid Control Level 1 (below threshold) ▪ 2 x 2 mL **cobas** Lipid Control Level 2 (above threshold) ▪ 1 x Quality control information disc

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 Denmark 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, Swedish and Norwegian

Product specifications for this evaluation, cobas b 101 Lipid Panel

cobas b *101 instrument serial numbers*

Serial no	Used by
Q66111686	Optimal conditions
Q66111787	Optimal conditions
Q66111675	PHCC1
Q66111789	PHCC1
Q66111790	PHCC4

cobas b *101 Lipid Panel test discs*

Lot no	Expiry date	Used by
822012-01	2019-10	All evaluation sites
823011-01	2019-11	All evaluation sites
832017-01	2019-08	All evaluation sites

cobas b *101 Lipid Panel internal analytical quality control kit liquid controls*

Control	Lot no	Expiry date	Used by
Level 1	01009301	2019-08-31	All evaluation sites
Level 2	01009301		

Other equipment used in the evaluation

Other equipment	Used by
BD Vacutainer® tube, Lithium-heparin 3,0 mL, REF: 367374	PHCC1 and PHCC4
BD Vacutainer® tube, Lithium-heparin 4,0 mL, REF: 368884	Optimal conditions

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.
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List of previous SKUP evaluation

The 30 latest SKUP evaluation

Evaluation no.	Component	Instrument/test kit	Producer
SKUP/2020/118	Lipid Panel	**cobas b** 101	Roche Diagnostics GmbH
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

*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.

**Manufacturers of laboratory equipment which are not introduced on the Scandinavian market can ask for their evaluations to be kept confidential.

[1] Including a user-evaluation among diabetes patients

Comments from Roche diagnostic A/S

SKUP
Valdemar Hansens Vej 1-23
Indgang 8
2600 Glostrup

2 November 2020

Comments on the report from evaluation SKUP/2020/118 cobas b 101, a system for measurement of Lipid Panel

Roche would like to thank SKUP for the careful evaluation of the **cobas** Lipid Panel on **cobas b** 101. We are very pleased to obtain the best possible rating not only for the user-friendliness but also for the performance of Cholesterol and HDL-cholesterol. The quality goals for repeatability and accuracy were fulfilled both under optimal conditions and when the measurements were performed by intended users confirming the strong robustness of the system. These results in general confirm Roche's commitment to quality.

In contrast, the results for Triglycerides were disappointing. Not surprising, also results for LDL-cholesterol showed a similar pattern because those values are calculated from the Triglyceride values in combination with Cholesterol and HDL-cholesterol using the Friedewald formula.

A closer look at the data set reveals many positive outliers. Although a detailed root-cause analysis was not possible in the given timeframe, Roche believes (based on experience of other studies) that the outliers are the result of pre-analytic errors. These errors may occur when the test is not performed according to the instructions in the manual. If for example the prescribed hand washing procedure is omitted, traces from hand cream can interfere with Triglyceride measurement leading to false high results.

We would like to thank SKUP for going into discussions regarding reassessing the performance in a new controlled setting in Norway. It is in the interest of Roche and SKUP – and ultimately the patients – to have accurate measurement results they can trust in.

Kind regards,

Roche Diagnostics A/S

DocuSigned by:
Dorte Reffeldt Lund
F8297C1A0070431...
Dorte Reffeldt Lund
Customer Solutions Partner

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