cobas b 101

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

An evaluation of the measurement of CRP

Report from the evaluation SKUP/2019/116

organised by SKUP at the request of Roche Diagnostics

in Denmark and Norway

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Copyright © 2019 SKUP. The report was written by SKUP, September 2019.The main author was Anne Christin Breivik, SKUP in Norway. In order to use the SKUP name in marketing, it has to be referred to www.skup.org and the report code in question; SKUP/2019/116. For this purpose, the company can use a logotype containing the report code, available for the requesting company together with the final report. A correct format of referral in scientific publications will be "SKUP. Report from the evaluation SKUP/2019/116. cobas b 101 (Roche Diagnostics GmbH), a system for measurement of CRP, www.skup.org (*accessed date*)." The organization of SKUP is described in attachment 1.

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

1. Summary

Background
The **cobas b** 101 system is an in vitro diagnostic device for quantitative measurement of C-reactive protein (CRP), Haemoglobin A1c (HbA1c) and lipids. The product is intended for professional use. The sample material for CRP measurements can be capillary whole blood and serum, 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 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 CRP, 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 106 patients were measured on **cobas b** 101 CRP under optimal conditions. Under real-life conditions in each of two primary health care centres (PHCC1 and PHCC2) capillary whole blood samples from 55 and 50 patients, respectively, were measured on **cobas b** 101 CRP. Venous serum samples from the same patients were analysed on a comparison method (CRP Vario immunoturbidimetric assay, Architect plus c16000, Abbott). The analytical results and user-friendliness were assessed according to pre-set quality goals. The quality goal for precision was a repeatability (coefficient of variation, CV) ≤10,0 %. The quality goal for accuracy was that ≥95 % of the results should be within the deviation limits of ±2,0 mg/L for CRP concentrations <10 mg/L and ±20,0 % for CRP concentrations ≥10 mg/L 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
The CV achieved under optimal conditions was between 2,1 and 2,6 % depending on the concentration level. The PHCCs achieved a CV between 1,9 and 2,7 %. All the results were within the allowable deviation limits for accuracy both under optimal conditions and in the PHCCs. At the medical decision point of 40 mg/L there was a small but statistically significant bias between **cobas b** 101 CRP and the comparison method of approximately –3 %. The user-friendliness was rated as satisfactory.

Conclusion
The quality goal for repeatability was fulfilled both under optimal conditions and when the measurements were performed by intended users. The quality goal for accuracy was fulfilled both under optimal conditions and by intended users. The quality goal for user-friendliness was fulfilled.

Comments from Roche Diagnostics
Roche Diagnostics has accepted the report without further comments.

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
CI	Confidence Interval
CRP	C-reactive protein
CV	Coefficient of Variation
DEKS	Danish Institute of External Quality Assurance for Laboratories in Health Care
EDTA	Ethylenediaminetetraacetic acid
EFLM	European Federation of Clinical Chemistry and Laboratory Medicine
ERM	European Reference Materials
EQA	External Quality Assessment
Equalis	External quality assessment in laboratory medicine in Sweden
HbA1c	Haemoglobin A1c
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
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 cartridges 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

cobas b 101 for measurement of C-reactive protein (CRP), Haemoglobin A1c (HbA1c) and a lipid panel is produced by Roche Diagnostics GmbH. The product is intended for professional use. The system was launched into the Scandinavian market April 2013. This SKUP evaluation was carried out in Spring 2019 at the request of Roche Diagnostics Denmark and Roche Diagnostics Norway. This report describes the evaluation of **cobas b** 101 CRP. Evaluations of **cobas b** 101 HbA1c and **cobas b** 101 Lipid Panel are described in the in the reports SKUP/2019/117 and SKUP/2019/118, respectively.

3.3. The aim of the evaluation

The aim of the evaluation was to assess the analytical quality and user-friendliness of **cobas b** 101 CRP, 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 CRP

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

The evaluation included:

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

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

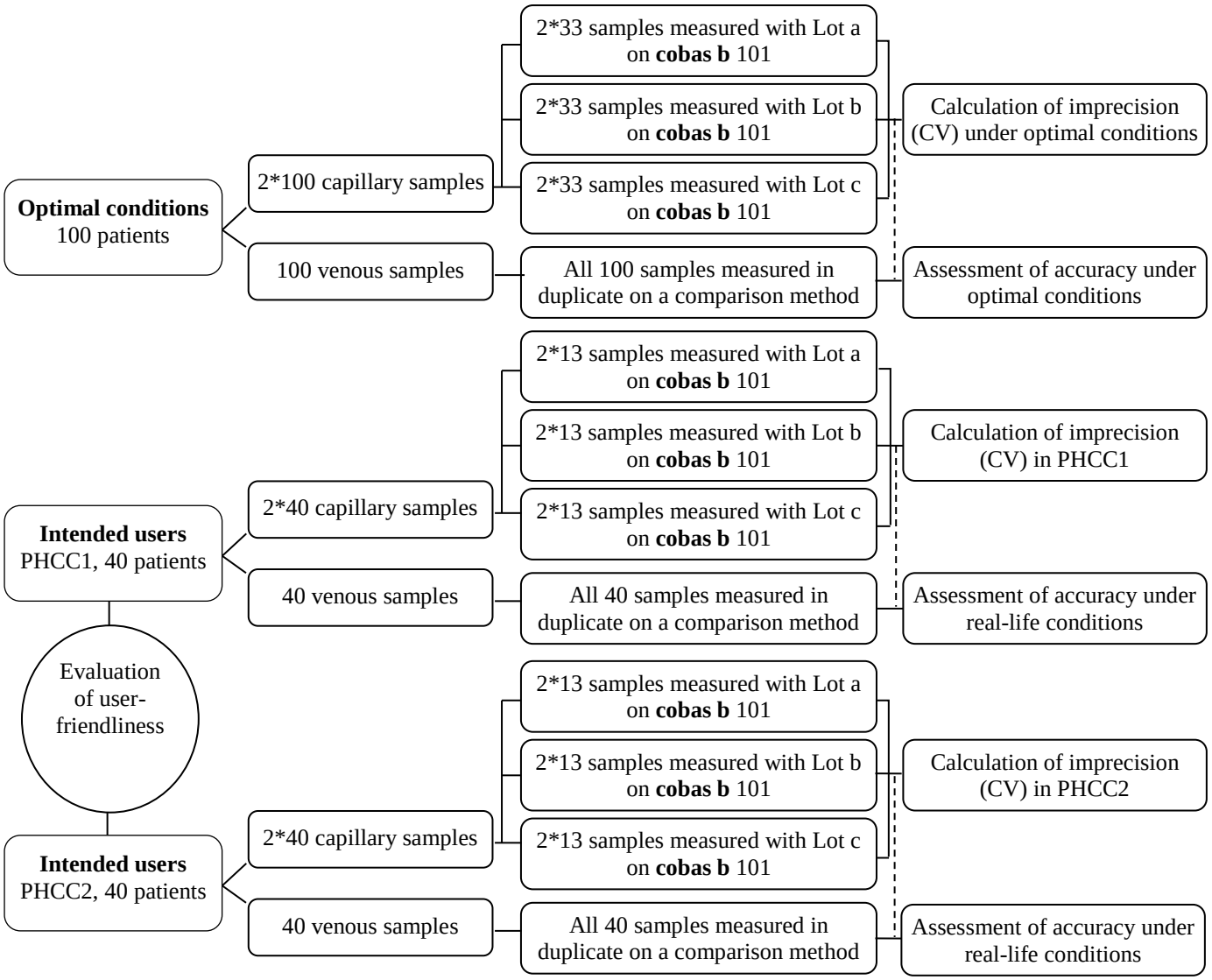

Figure 1. Flowchart illustrating the model for the evaluation of **cobas b** 101 CRP.

4. Quality goals

4.1. Analytical quality

The 1st European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Strategic Conference, held in 2014 in Milan, defined three models to be used to derive analytical performance specifications [2]. Ceriotti *et al.* [3] give criteria for allocating measurands to the different models for analytical performance specifications recognized in the EFLM Strategic Conference and propose a theoretical rationale for selecting the best model that should be applied to a specific measurand.

International guidelines for analytical quality requirements for CRP are few. According to the discussion about advantages and disadvantages of the three models for various measurands defined by the EFLM Strategic Conference, the quality goals for CRP in this SKUP evaluation will be based on Model 3; state of the art. There is no official agreement on how to set analytical quality specifications based on this model, but a possible way is to derive them from external quality assessment (EQA) programs [3].

The *National Danish Committee for general practice Laboratory testing* appointed by the National Ministry of health has specified the demands to analytical quality; bias and the coefficient of variation (CV), for CRP instruments used in primary health care [4]. The Danish goals also include demands to the comparison method.
Analytical quality goals for CRP >15 mg/L:

Near patient tests used in primary health care centres	bias ≤±10 % and CV ≤10 %
Hospital laboratory methods used as a comparison method	bias ≤±3 % and CV ≤5 %

In the external quality assessment programme offered by the Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus), the following limits for deviation are in use for CRP in primary health care: To achieve the assessment *very good*, the maximum deviation from the control target value should be less than approximately ±15 %, depending on the CRP concentration in the control sample. A deviation between 15 and 20 % gives the assessment *acceptable*.

For near patient tests used in primary health care centres the expert group for protein analysis in the External quality assessment in laboratory medicine in Sweden (Equalis) suggest that the maximum deviation for a single result measured in whole blood should be ±15 % when compared to an assigned value set by five agreeing hospital laboratory methods for separated plasma. For hospital methods the maximum deviation for a single result measured in plasma should be ±10 % when compared to an assigned value set as the mean of five agreeing group means.

Based on recommendations from professionals and results in the Equalis and Noklus EQA programs, SKUP's quality goals for CRP in this evaluation are as presented in section 4.4.

4.2. User-friendliness

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

Technical errors

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

4.3. Principles for the assessments

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

4.3.1. Assessment of the analytical quality

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

Precision

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

Table 1. The rating of precision.

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

Bias

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

Bias with three lots of test discs

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

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

4.3.2. Assessment of the user-friendliness

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

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

4.4. SKUP's quality goals in this evaluation

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

Repeatability (CV)..... ≤10,0 %

Allowable deviation of the individual result from the comparison method result
for CRP concentrations <10 mg/L..... ≤±2,0 mg/L
and for CRP concentrations ≥10 mg/L..... ≤±20,0 %

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 mass concentration of C-reactive protein in blood 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 serum. The results are traceable to the European Reference Material (ERM)-DA472/International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) [5] and are expressed in the unit mg/L. The Committee on Nomenclature, Properties and Units (C-NPU) systematically describes clinical laboratory measurands in a database [6]. The NPU code related to the measurand in this evaluation is NPU19748. In this report the term CRP will be used for the measurand.

5.2. The evaluated measurement system cobas b 101 CRP

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® CRP system includes:

- **cobas b** 101 analyser
- **cobas b** 101 CRP test discs
- **cobas b** 101 CRP internal analytical quality control kit
- **cobas** CRP quality control (QC) info disc (included in the control kit)

Figure 2. cobas b 101 analyser and the three different test discs.

cobas b 101 CRP is an in vitro diagnostic test system designed to quantitatively determine CRP in human capillary whole blood and serum, as well as in venous K_2/K_3-ethylenediaminetetra-acetic acid (EDTA) and lithium heparin anticoagulated whole blood and plasma.

cobas b 101 CRP is an immunoturbidimetric assay. First, the erythrocytes of the capillary or venous blood sample is separated from the plasma by centrifugation, thus the CRP measurement is not affected by various levels of haematocrit in whole blood samples. In the next step, the plasma sample is diluted with buffer and transferred into a reaction chamber where it is mixed with CRP antibody-latex reagent. The CRP in the diluted plasma binds with the CRP antibody on the latex particle. The concentration of CRP is calculated as a function of the changed absorbance measured at 525 and 625 nm, which is in related to the quantity of agglutinated latex particles. Results <100 mg/L are reported with one decimal place and results ≥100 mg/L as whole numbers.

The instrument automatically reads 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** CRP test disc are traceable to the ERM-DA472/IFCC reference material.

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

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

Table 2. Technical details from the manufacturer

Technical details for cobas b 101 CRP	
Sample volume	12 µL
Measuring time	3 – 4 minutes
Measuring range	3,0 – 400 mg/L
Haematocrit range	20 – 60 %
Storage capacity	5 000 test results

5.3. The selected comparison method

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

5.3.1. The selected comparison method in this evaluation

The selected comparison method in this evaluation is the routine method for CRP measurement in the Centre for Laboratory Medicine, Østfold Hospital in Kalnes, Norway, hereafter called "the comparison method".

Instrument:	Architect plus c16000, Abbott
Reagent:	CRP Vario, Abbott
Principle:	Latex immunoassay and quantitative immunoturbidimetric determination of CRP due to changes in absorbance value at 572 nm
Traceability:	Traceable to ERM-DA472/IFCC
Calibrators:	Commercial CRP calibrators from Abbott (Six levels)
Reportable range:	0,2 – 320 mg/L. Results >320 mg/L is automatically diluted 1:5 and reanalysed

Internal analytical quality control

Internal analytical quality control samples, two levels (Autonorm Human Liquid L-1 and Sero Immunoprotein L-2, Sero AS), were measured daily on the comparison method.

External analytical quality control

The hospital laboratory participates in Noklus EQA scheme for CRP with two levels in four rounds per year. The material is fresh frozen pooled plasma from healthy Norwegian donors with

added purified human CRP. The assigned values for CRP are based on transferred reference values from ERM-DA474/IFCC [7].

5.3.2. Verification of the analytical quality of the comparison method

Precision
The repeatability (CV) of the comparison method was calculated from duplicate measurements of the venous serum samples from the patient participating under optimal conditions.

Trueness
ERM-DA474/IFCC from the Institute for Reference Materials and Measurements was analysed on the comparison method on different occasions during the evaluation. The trueness of the comparison methods was also verified with EQA results.

5.4. The evaluation

5.4.1. Planning of the evaluation

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

Protocol, arrangements and contract
In February 2019, the protocol for the evaluation was approved, and Roche Diagnostic in Norway and Denmark and SKUP signed a contract for the evaluation. Aleris Medical centre and Noklus in Oslo, Norway, were assigned to do the practical work with **cobas b** 101 CRP in the evaluation under optimal conditions. Two primary health care centres, Jeløy and Borge primary health care centres from Østfold county, Norway, agreed to represent the intended users in this evaluation.

Training
Reza Gordan in Roche Diagnostics Norway demonstrated **cobas b** 101 CRP for all the evaluation sites. The training in the PHCCs reflected the training usually given to the end-users. Roche Diagnostics 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 CRP was carried out for 15 weeks, ending in June 2019. Centre for Laboratory Medicine in Østfold Hospital was responsible for the comparison method as described in section 5.3.1. The laboratory has approximately 35 employees of which two BLSs were involved in the evaluation. Østfold Hospital is a local hospital. Under optimal conditions, two Biomedical laboratory scientists (BLSs) participated. The evaluation started in the Department of Medical Biochemistry, Oslo University Hospital at Ullevål, but was soon relocated to Aleris Medical centre in order to improve the recruitment of patients. The laboratory of Aleris in Oslo has five employees of which one BLS were involved in the evaluation. Aleris Medical centre is a private health care company covering most medical disciplines. From PHCC1 one health secretary and one medical secretary participated in the evaluation. PHCC1 has six physicians. From PHCC2 two nurses participated in the evaluation. PHCC2 has five physicians. Both PHCCs use capillary blood samples in their routine method for measurements of CRP.

5.4.3. The evaluation procedure

Internal analytical quality control

Internal analytical quality control samples for **cobas b** 101 CRP, two levels (**cobas** CRP Control Kit, Roche Diagnostics GmbH), were measured each evaluation day on **cobas b** 101 under optimal conditions, and one level per day alternating between the two levels in the PHCCs. The reproducibility (CV) as achieved with the quality control material was calculated.

Recruitment of patients

Patients, 18 years or older, coming to the laboratory or PHCCs for CRP 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. The patients were selected to cover a wide range of CRP concentrations.

Handling of the samples and measurements

Fresh capillary whole blood samples were used for the measurements on the **cobas b** 101 CRP system. All measurements were performed in duplicate, i.e. two separate fingersticks. The participants washed and dried their hands, and the puncture site was disinfected with alcohol pads and 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, and the second drop of blood was applied to the test disc in accordance with the instructions from the manufacturer. The test disc was inserted into the instrument immediately after sampling (within 120 seconds). The complete sampling and measurement procedure were repeated for the second measurement on **cobas b** 101. Three lot numbers of test discs were used, alternating between the lot numbers during the test period. In case of error codes, the test was repeated until a result was obtained, if the patient agreed.

The venous samples for the comparison method were treated according to the internal procedures of Centre for Laboratory Medicine, Østfold Hospital. The samples were obtained from venous puncture and collected into 5,0 mL Vacuette tubes with serum separator and clot activator (Greiner-Bio-One). The sample tubes were inverted eight times to ensure thorough mixing and allowed to clot for at least 30 min at room temperature in an upright position. The tubes were centrifuged for 10 minutes at 1800 – 2200 g within two hours from sampling and kept in refrigerator until transported to the hospital laboratory. Confirmed specimen stability was 11 days at room temperature and two months in refrigerator, but most of the serum samples in this evaluation were measured in duplicate for CRP on the comparison method within 72 hours of collection.

6. Results and discussion

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

6.1. Number of samples

Scheduled number of samples in this evaluation was 100 patient samples measured in duplicate under optimal conditions and 80 patient samples measured in duplicate by intended users in the PHCCs. At the end of the evaluation, a total of 211 patients were enrolled. Under optimal conditions, 106 patients were recruited (SKUP ID 1 – 100 and SKUP ID 101OPT – 106OPT). PHCC1 recruited 55 patients (SKUP ID 101 – 155) and PHCC2 recruited 50 patients (SKUP ID 201 – 250). The results from the comparison method covered a CRP interval from 0,40 – 293,4 mg/L. An account of the number of samples not included in the calculations, is given below.

Missing results

- From PHCC1 internal analytical quality control results for two evaluation days were missing. From PHCC2 internal analytical quality control result for one evaluation day was missing. The results from the patient samples these days were still included in the calculations.
- **cobas b** 101 reports CRP below 3,0 mg/L as <3,0 mg/L. Due to this, 41 samples were not included in any calculations;12 from optimal conditions, 16 from PHCC1 and 13 from PHCC2.
- ID 213; only single measurement from **cobas b** 101 as one of the duplicates were reported to be <3,0 mg/L. The single value was included in the calculation of bias and the assessment of accuracy.
- ID 113; only single measurements from **cobas b** 101 due to the error code I-203 (=Disc Present). The single value was included in the calculation of bias and the assessment of accuracy.
- ID 242 and ID 246; the results from **cobas b** 101 were not included in the calculation of repeatability due to the use of two lot numbers, i.e. not identical conditions, but the results were included in the calculation of bias and the assessment of accuracy.

Omitted results

There were no omitted results.

Excluded results (statistical outliers)

Statistical outliers in SKUP evaluations are detected by the criterion promoted by Burnett [8].

- ID 56; the results from the comparison method were classified as outliers according to Burnett's model in the calculation of repeatability. The results were not included in the calculation of bias and the assessment of accuracy, but the results from **cobas b** 101 were included in the calculation of repeatability.

Recorded error codes, technical errors and failed measurements

Only one error code was reported from **cobas b** 101 CRP during the evaluation. The SKUP recommendation of a fraction of ≤2 % tests wasted due to technical errors was achieved.

6.2. Analytical quality of the selected comparison method

6.2.1. Internal analytical quality control

All results from the internal analytical quality control (Autonorm Human Liquid L-1 and Sero Immunoprotein L-2, Sero AS), were within the allowable control limits (data not shown).

6.2.2. The precision of the comparison method

Duplicate measurements of the venous serum samples from the patients participating under optimal conditions 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 (data not shown).

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

Table 3. Repeatability (CV) of the comparison method for CRP measured in venous serum samples.

Level	CRP interval, mg/L	n*	Excluded results (statistical outliers)	Mean value CRP, mg/L	CV (90 % CI), %
Low	0,4 – 20,0	39	1	8,7	1,5 (1,2 – 1,8)
Medium	20,3 – 57,9	47	0	37,4	1,0 (0,9 – 1,2)
High	65,1 – 293,4	20	0	176,4	0,8 (0,6 – 1,1)

*The given number of results (n) were counted before the exclusion of statistical outliers. Mean and CV were calculated after the exclusion of statistical outliers. An account of the number of samples is given in section 6.1.
**ID 56 was statistical outliers according to Burnett's model [8] in the calculation of repeatability and therefore excluded.

Discussion

The CV for the comparison method was between 0,8 and 1,5 %.

6.2.3. The trueness of the comparison method

To demonstrate the trueness of the comparison method ERM-DA474/IFCC from the Institute for Reference Materials and Measurements was analysed on the comparison method on three different occasions; at start-up, halfway and at the end of the evaluation. The results achieved are shown in table 4. The trueness of the comparison methods was also verified with EQA results, and the results from two CRP EQA surveys from Noklus (specified in section 5.3.1) are shown in table 5.

Table 4. ERM-DA474/IFCC measured on the comparison method.

Date of measurement	Assigned value, CRP mg/L (uncertainty)	n	Architect plus c16000 Mean value, CRP mg/L
12.03.2019	**41,2** (38,7 – 43,7)	5	40,6
18.05.2019		5	40,8
21.06.2019		5	43,3*

*The increase observed for ERM-DA474/IFCC towards the end of the evaluation may be due to quarterly maintenance (18.06.2019) or change in CRP reagent lot number (19.06.2019)

Table 5. EQA control material from Noklus measured on the comparison method.

Date of survey	Assigned value, CRP mg/L (±15 acceptance limits)	n	Architect plus c16000 CRP mg/L
21.01.2019	35,5 (30,2 – 40,8)	2	36,0
	64,1 (54,5 – 73,7)	2	63,5
27.05.2019	28,4 (24,1 – 32,7)	2	28,0
	54,0 (45,9 – 62,1)	2	54,0

Discussion
The ERM-DA474/IFCC results from the comparison method were in agreement with the assigned value for the Reference material, and the trueness of the comparison method was confirmed by the results in the national EQA programme for HbA1c.

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

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

6.3.1. Internal analytical quality control

All results from the internal analytical quality control (**cobas** CRP Control Kit), two levels, were within the allowable control limits (data not shown). The reproducibility (CV) achieved with the internal analytical quality control samples were 4,5 % for level 1 and 3,7 % for level 2 (n=31). Raw data is attached for the requesting company only, see attachment 7.

6.3.2. The precision of cobas b 101 CRP

Duplicate measurements from each capillary whole blood sample were performed on **cobas b** 101 CRP. 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). 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 from the **cobas b** 101 CRP system. Raw data is attached for the requesting company only, see attachment 8.

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

Level	CRP interval, mg/L	n	Excluded results (statistical outliers)	Mean value CRP, mg/L	CV (90 % CI), %
Low	3,3 – 19,8	28	0	12,0	2,3 (1,9 – 3,0)
Medium	21,0 – 57,7	47	0	37,0	2,1 (1,8 – 2,5)
High	81,4 – 283,0	19	0	171,2	2,6 (2,1 – 3,7)

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

Discussion
The CV achieved under optimal conditions was between 2,1 and 2,6 % depending on the concentration level. The upper CI values were within the quality goal for all concentration levels.

Conclusion
Under optimal conditions the quality goal for repeatability (CV ≤10,0 %) was fulfilled.

6.3.3. The bias of cobas b 101 CRP

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 attachment 6 and 8.

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

Level	CRP interval comparison method, mg/L	n	Excluded results (statistical outliers)	Mean CRP comparison method, mg/L	Mean CRP cobas b 101, mg/L	Bias (95 % CI), mg/L	Bias %
Low	3,7 – 19,9	26	0	11,8	11,6	–0,22 ((–0,41) – (–0,04))	–1,9
Medium	20,6 – 57,8	47	0	37,4	36,2	–1,19 ((–1,63) – (–0,74))	–3,2
High	65,6 – 292,7	20	0	176,4	165,5	–10,91 ((–14,25) – (–7,56))	–6,2

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

Discussion
For all three CRP levels there was a statistically significant bias between **cobas b** 101 CRP and the comparison method. The results from **cobas b** 101 were systematically lower than the results from the comparison method. For the low CRP level, the bias was –0,22 mg/L, for the medium CRP level –1,19 mg/L and for the high CRP level –10,91 mg/L.

6.3.4. The accuracy of cobas b 101 CRP

To evaluate the accuracy of CRP results on **cobas b** 101 CRP, the agreement between **cobas b** 101 CRP and the comparison method is illustrated in difference plots (figure 3). The limits for the allowable deviation according to the quality goal, are shown with stippled lines.

All the first measurements from **cobas b** 101 CRP are included in the plots. The plots illustrate both random and systematic errors, reflecting the total measuring error in the **cobas b** 101 CRP results. Raw data is attached for the requesting company only, see attachment 6 and 8.

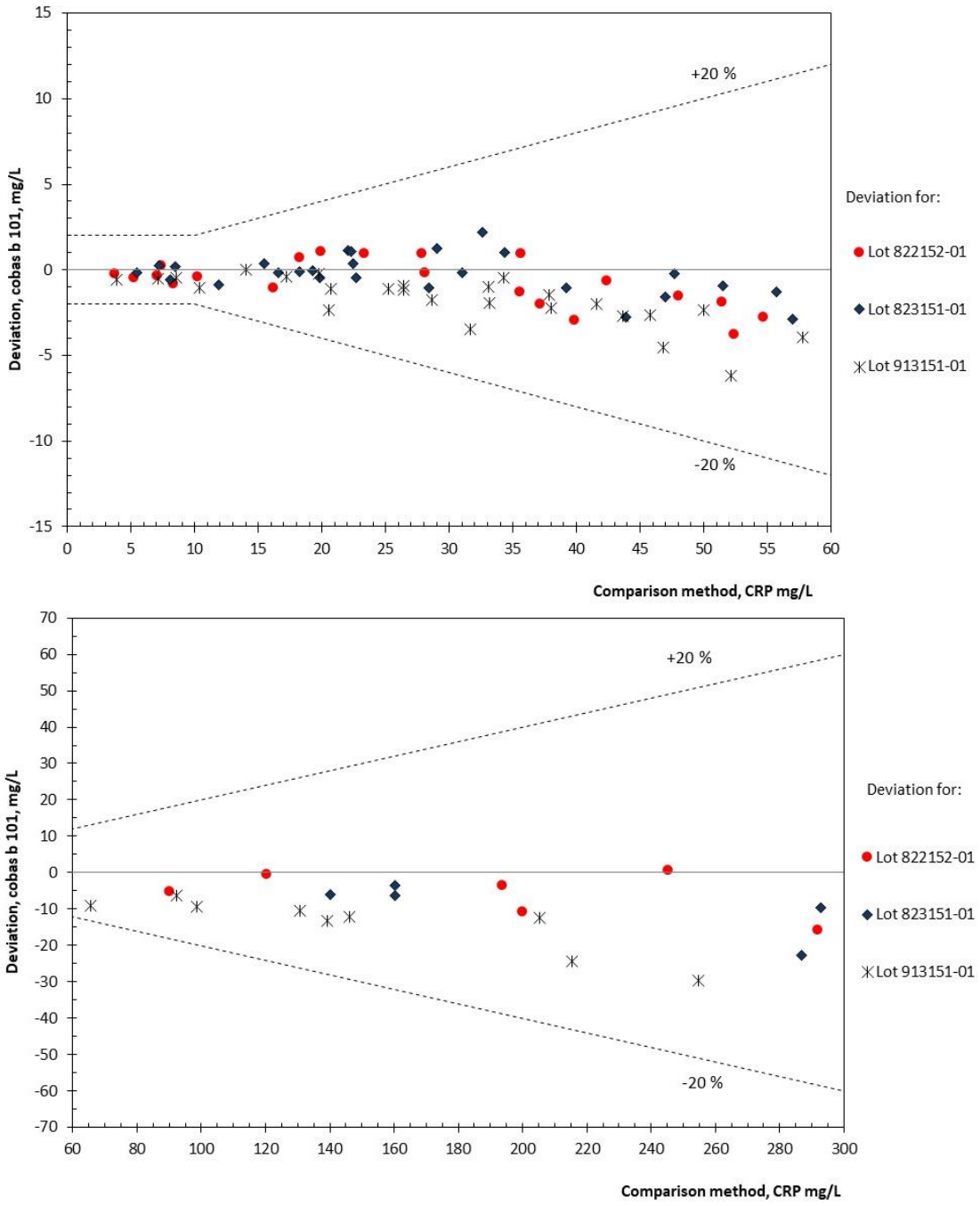

Figure 3. Accuracy of CRP results on **cobas b** 101 CRP achieved under optimal conditions. Low and medium CRP results are shown in the upper plot and high CRP results in the lower plot. The x-axis represents the mean CRP result of the comparison method. The y-axis represents the CRP deviation in mg/L of the first capillary whole blood sample measurement on **cobas b** 101 CRP from the mean result of the corresponding sample of the comparison method. The different lots of test discs are illustrated with the symbols ● (lot 822152-01), ♦ (lot 823151-01) and * (lot 913151-01). Stippled lines represent the allowable deviation limits of ≤±2,0 mg/L for CRP concentrations <10 mg/L and ≤±20,0 % for CRP concentrations ≥10 mg/L. Number of results (n) = 93. Results reported from **cobas b** 101 as <3,0 mg/L are not included in the plot. An account of the number of samples is given in section 6.1.

Reportable range for **cobas b** 101 is 3,0 – 400 mg/L, and 12 of the results achieved under optimal conditions were reported as <3,0 mg/L. These results are not included in figure 3. The corresponding results from the comparison method varied between 0,7 – 3,0 mg/L.

Discussion
As shown in figure 3, the **cobas b** 101 CRP results tend to be lower than the results from the comparison method, the results in the medium and high CRP levels in particular. This is consistent with the calculated bias (table 7). The figure also shows that the test discs with lot number 919151-01 differ more from the comparison method compared to the discs with lot number 822152-01 and 823151-01. Separate lot calculations were not performed. **cobas b** 101 results reported as <3,0 mg/L were in agreement with the results from the comparison method. All the results achieved under optimal conditions were inside the allowable deviation limits of ±2,0 mg/L for CRP concentrations <10 mg/L and ±20,0 % for CRP concentrations ≥10 mg/L.

Conclusion
Under optimal conditions the quality goal for accuracy was fulfilled.

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

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

6.4.1. Internal analytical quality control

All results from the internal analytical quality control (**cobas** CRP Control Kit), two levels, were within the allowable control limits (data not shown). From the PHCCs three quality control results were missing as described in section 6.1. The reproducibility (CV) achieved with the internal analytical quality control samples were 6,2 % for level 1 (n=26) and 4,8 % for level 2 (n=27). Raw data is attached for the requesting company only, see attachment 9.

6.4.2. The precision of cobas b 101 CRP

Duplicate measurements from each capillary whole blood patient sample were performed on **cobas b** 101 CRP. The results were checked to meet the imposed condition for using formula 1 in attachment 5. A systematic difference was pointed out between the paired measurements for the low and high concentration level (data not shown). The differences were small, but statistically significant. The second result of the duplicate measurements was on average lower than the result of the first measurements. The differences were on average –0,2 mg/L for the low CRP level and –2,0 mg/L for the high CRP level. No explanation for these systematic differences has been found. The sampling procedure, as well as the measurement procedure, were identical for all samples and measurements throughout the evaluation. The differences pointed out lead to a slightly overestimation of the CVs for the low and high CRP levels. Since the differences pointed out have no impact on the final assessment of the precision, the CVs are calculated without taking the systematic differences into account. For the medium level, no systematic difference between the paired measurements was found.

The precision is presented as repeatability (CV). 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 from the **cobas b** 101 CRP system. Since the variances between the two PHCCs are not significantly different (F-test, 5 % significance level) the results from the two PHCCs are combined before the calculation of CV. Raw data is attached for the requesting company only, see attachment 10.

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

Place	Level	CRP interval, mg/L	n	Excluded results (statistical outliers)	Mean value CRP, mg/L	CV (90 % CI), %
PHCC1 + *PHCC2*	Low	3,7 – 20,2	20	0	9,1	2,4* (1,9 – 3,3)
	Medium	20,3 – 61,0	23	0	42,2	1,9 (1,5 – 2,5)
	High	60,8 – 272,0	29	0	114,8	2,7* (2,2 – 3,5)

An account of the number of samples is given in section 6.1.
* The CVs for these CRP levels are calculated without taking the systematic difference described above into account. In a simulated set of data, the average systematic difference at each level were removed for all paired results and the CVs were estimated to 1,9 % and 2,4 %, respectively. Due to increased uncertainty in these estimates, CI are not given.

Discussion
The CV achieved by intended users was between 1,9 and 2,7 depending on the concentration level. The upper CI values were within the quality goal for all concentration levels.

Conclusion
When measurements were performed by the intended users the quality goal for repeatability (CV ≤10 %) was fulfilled.

6.4.3. The bias of cobas b 101 CRP

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 9. The results were sorted and divided into three concentration levels according to the mean results of the comparison method. Raw data is attached for the requesting company only, see attachment 6 and 10.

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

	Level	CRP interval comparison method, mg/L	n	Excluded results (statistical outliers)	Mean CRP comparison method, mg/L	Mean CRP cobas b 101, mg/L	Bias (95 % CI), mg/L	Bias %
PHCC1	Low	4,0 – 17,6	12	0	8,5	8,3	–0,24 ((–0,46) – (–0,03))	–2,9
	Medium	20,5 – 58,1	10	0	41,1	39,0	–2,16 ((–4,52) – (+0,20))	–5,3
	High	62,0 – 197,9	17	0	109,0	101,3	–7,70 ((–10,15) – (–5,26))	–7,1
PHCC2	Low	3,0 – 19,4	10	0	9,4	9,3	–0,05 ((–0,42) – (+0,31))	–0,6
	Medium	23,9 – 55,7	9	0	39,7	38,5	–1,24 ((–2,98) – (+0,49))	–3,1
	High	64,5 – 286,3	18	0	118,5	113,0	–5,48 ((–7,97) – (–2,98))	–4,6

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

Discussion

For the medium CRP level, no statistically significant bias was pointed out in the PHCCs. For the low CRP level, there was a statistically significant bias between **cobas b** 101 CRP and the comparison method of –0,24 mg/L in PHCC1, and no statistically significant bias for this level in PHCC2. For the high CRP level there was a statistically significant bias of –7,70 mg/L and –5,48 mg/L in PHCC1 and PHCC2, respectively.

6.4.4. The accuracy of cobas b 101 CRP

To evaluate the accuracy of CRP results on **cobas b** 101 CRP, the agreement between **cobas b** 101 CRP and the comparison method is illustrated in difference plots (figure 4). The limits for the allowable deviation according to the quality goal, are shown with stippled lines.

All the first measurements from **cobas b** 101 CRP are included in the plots. The plots illustrate both random and systematic errors, reflecting the total measuring error in the **cobas b** 101 CRP results. Raw data is attached for the requesting company only, see attachment 6 and 10.

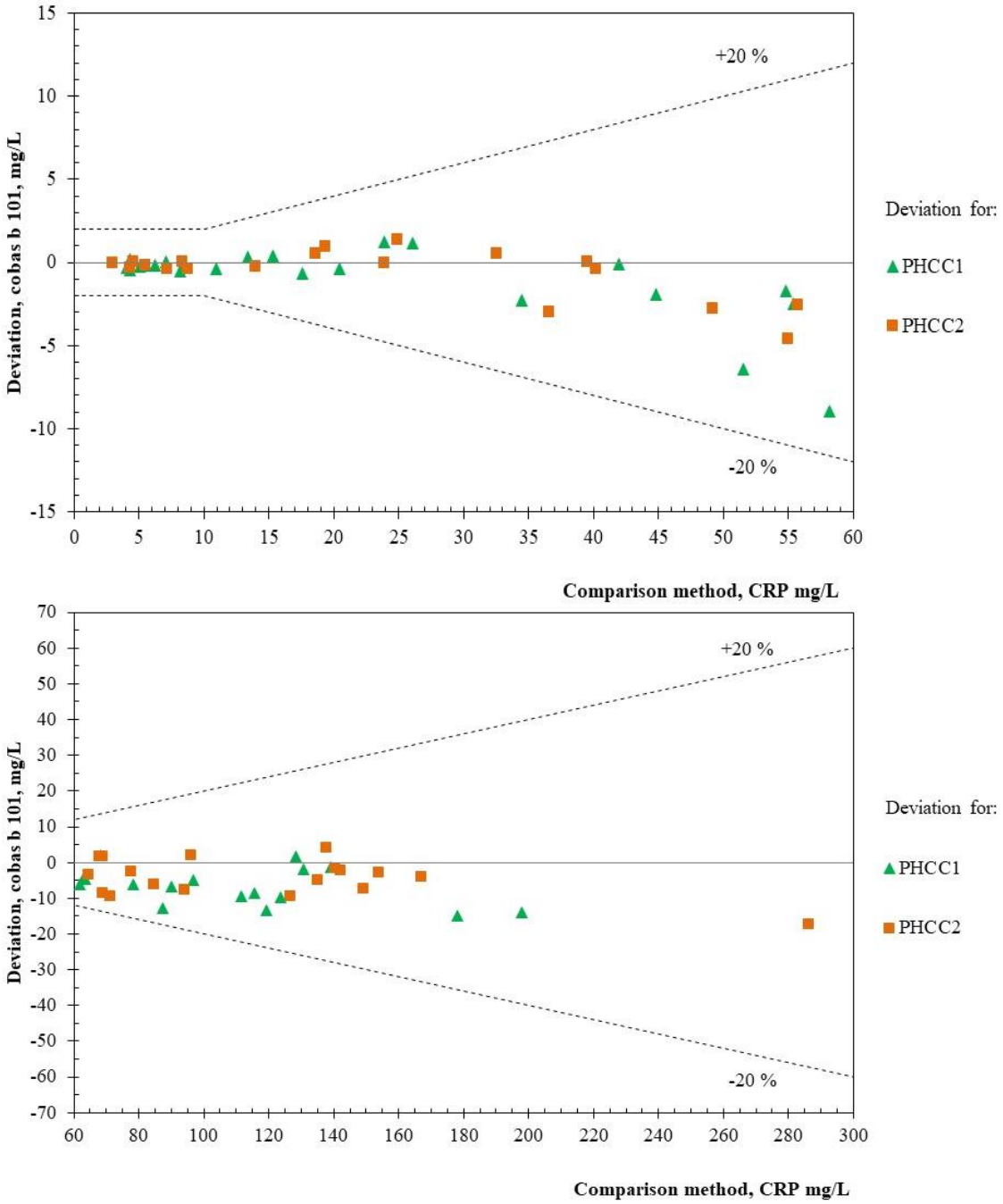

Figure 4. Accuracy of CRP results on **cobas b** 101 CRP achieved by intended users. Low and medium CRP results are shown in the upper plot and high CRP results in the lower plot. The x-axis represents the mean CRP result of the comparison method. The y-axis represents the CRP deviation in mg/L of the first capillary whole blood sample measurement on **cobas b** 101 CRP from the mean result of the corresponding sample of the comparison method. The different PHCCs are illustrated with the symbols ▲ (PHCC1) and ■ (PHCC2). Stippled lines represent the allowable deviation limits of ≤±2,0 mg/L for CRP concentrations <10 mg/L and ≤±20,0 % for CRP concentrations ≥10 mg/L. Number of results (n) = 76. Results reported from **cobas b** 101 as <3,0 mg/L are not included in the plot. An account of the number of samples is given in section 6.1.

Reportable range for **cobas b** 101 is 3,0 – 400 mg/L, and 29 of the results achieved by the intended users were reported as <3,0 mg/L. These results are not included in figure 4. The corresponding results from the comparison method varied between 0,3 – 3,1 mg/L.

Discussion

Figure 4 shows that in the PHCCs the **cobas b** 101 CRP results tend to be lower than the results from the comparison method, which is consistent with the calculated bias (table 9) and the results achieved under optimal conditions (Figure 3). All the results achieved in the PHCCs were inside the allowable deviation limits of ±2,0 mg/L for CRP concentrations <10 mg/L and ±20,0 % for CRP concentrations ≥10 mg/L.

Conclusion

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

6.5. Evaluation of user-friendliness

6.5.1. Questionnaire to the evaluators

The most important response regarding user-friendliness comes from the intended users themselves. The end-users often emphasise other aspects than those pointed out by more extensively trained laboratory personnel.

At the end of the evaluation period, the evaluating persons filled in a questionnaire about the user-friendliness of the measurement system. SKUP has prepared detailed instructions for this.

The questionnaire is divided into four subareas:

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, topics marked with grey colour in table A and B.

In the tables, the first column shows what is up 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 property seriously influences on the user-friendliness of the system.

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

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

Comment
In this evaluation, the user-friendliness was assessed by:
PHCC1, the opinion of one health secretary and one medical secretary
PHCC2, the opinion of two nurses
Optimal conditions, the opinion of one BLS

Table A. Rating of operation facilities.

Topic	Rating	Rating	Rating	Rating	Option
To prepare the test / instrument	**S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
To prepare the sample	**S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
Application of specimen	**U[1], S, I[2]**	**Satisfactory**	**Intermediate**	**Unsatisfactory**	No opinion
Specimen volume	**U[1], S, I[2]**	**Satisfactory**	**Intermediate**	**Unsatisfactory**	No opinion
Number of procedure step	**I[3], S, S**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Instrument / test design	**U[4], S, S**	**Satisfactory**	Intermediate	**Unsatisfactory**	No opinion
Reading of the test result	**E, E, E**	**Easy**	Intermediate	Difficult	No opinion
Sources of errors	**S, N, S**	**Satisfactory**	Intermediate	Unsatisfactory	**No opinion**
Cleaning / Maintenance	**S, N, S**	**Satisfactory**	Intermediate	Unsatisfactory	**No opinion**
Hygiene, when using the test	**I[1], S, S**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Size and weight of package	**I[5], S, S**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Storage conditions for tests, unopened package*	**S**	**+15 to +30°C**	+2 to +8°C	–20°C	
Storage conditions for tests, opened package	**S**	+15 to +30°C **or disposable**	+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**			

*Storage temperature for the **cobas b** 101 CRP test discs is +2 to +30°C

Comments from the evaluators:

[1]The suction of blood into the test discs is relatively slow, and the disc's suction point easily smears blood on the finger. During sampling it is difficult to observe whether the marked area is filled or not.

[2]The CRP test disc requires a large drop of blood (required volume is described in attachment 2)

[3]Time consuming to close the lid between each measurement (time thief) and long measurement time (measurement time is described in attachment 2)

[4]The system requires space for storage of the test discs and it generates a lot of waste

[5]No comment is given

Additional positive comments from the evaluators:
- Easy to check the sample volume
- Appreciated that the test discs can be stored at room temperature
- Convenient to have printer available
- Particularly satisfied with the CRP measuring range up to 400 mg/L
- Few error messages
- Clear display with straightforward instructions
- Generally satisfied with the system, although some practice was needed to get accustomed to the sampling technique of the test discs

Additional negative comments:
- Noise from the instrument, both during use and in standby

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

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

[1]Did not need to check for error messages and troubleshooting

Additional positive comments: Good instructions on how to get started
Additional negative comments: The user manual was not written in Norwegian (for which Scandinavian languages the manual is available in as per October 2019 see attachment 3)

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**		

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

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

6.5.2. Assessment of the user-friendliness

Assessment of the operation facilities (table A)
The operation facilities were in total assessed as satisfactory, but there were some intermediate and unsatisfactory ratings. The motivations for the lower ratings mainly concerned the handling of the test discs.

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

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

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

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

7. References

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2. Sandberg S. *et al.* Defining analytical performance specifications: consensus statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine, Clin Chem Lab Med 2015; **53**: 833 – 835.

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6. The IFCC – IUPAC terminology for properties and units. http://www.ifcc.org/ifcc-scientific-division/sd-committees/c-npu/npusearch/ (accessed 2019-09-11)

7. Commission of the European Communities. EUR 24922 EN – Joint Research Centre – Institute for Reference Materials and Measurements. Auclair G. *et al.* Certification report. The Certification of the Mass Concentration of C-Reactive Protein in Human Serum - Certified Reference Material ERM®-DA474/IFCC. 2011.

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

Attachments

1. The organization of SKUP
2. Facts about **cobas b** 101 CRP
3. Information about manufacturer, retailers and marketing
4. Product specifications for this evaluation, **cobas b** 101 CRP
5. Statistical expressions and calculations
6. Raw data, CRP results from the comparison method
7. Raw data, internal analytical quality control results, **cobas b** 101 CRP, optimal conditions
8. Raw data, **cobas b** 101 CRP results, optimal conditions
9. Raw data, internal analytical quality control results, **cobas b** 101 CRP, intended users
10. Raw data, **cobas b** 101 CRP results, intended users
11. List of previous SKUP evaluations

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

The organization of SKUP

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

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

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

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

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

SKUP reports are published at www.skup.org.

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

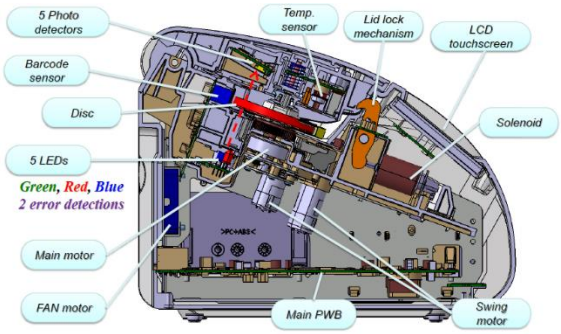
[2] DEKS (Danish Institute for External Quality Assurance for Laboratories in Health Care) is a non-profit organization owned by the Capital Region of Denmark on behalf of all other Regions in Denmark.

[3] Equalis AB (External quality assessment in laboratory medicine in Sweden) is a limited company in Uppsala, Sweden, owned by “Sveriges Kommuner och Landsting” (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 CRP

This form is filled in by Roche Diagnostics

Table 1. Basic facts.

Name of the measurement system	**cobas b** 101
Dimensions and weigh	Width: 135mm Depth: 184mm Height: 234mm Weight: 2,0 kg
Components of the measurement system	The measurement principle is a photometric measurement. The systems light sources are LED, and the instrument has three wavelengths of 460 nm, 525 nm and 625 nm. The system measures the absorbance by utilization of photodetectors placed in the lid of the instrument. The concentration of CRP is calculated by measuring the latex agglutination reaction with a wavelength of 525 nm and 625 nm. The attached picture shows the optical unit: LEDs and photo detectors. 
Measurand	CRP
Sample material	Capillary whole blood or serum, venous whole blood or plasma with anticoagulant (EDTA or heparin)
Sample volume	12 µL
Measuring principle	The erythrocytes of the capillary or venous blood sample are separated from the plasma by centrifugation. Then, the plasma sample is diluted with HEPES buffer and transferred into a reaction chamber where it is mixed with CRP antibody-latex reagent. The CRP in the diluted plasma binds with the CRP antibody on the latex particle. The concentration of CRP is calculated as a function of the changed absorbance measured at 525 nm and 625 nm which is in relation to the amount of agglutination.
Traceability	Each disc lot of the **cobas** CRP Test is traceable to ERM DA 472/IFCC reference material
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	3,0 – 400 mg/L or 0,30 – 40,0 mg/dL
Haematocrit range	20 – 60 %

Measurement time	Within 3 – 4 minutes
Operating conditions	Temperature range: 15 – 32 °C Relative humidity: 10 – 85 % (no condensation) Maximum altitude: 3000 m
Electrical power supply	Input: 100 ~ 240 V AC; 50/60 Hz Output: 12 V DC
Recommended regular maintenance	Maintenance- and service-free
Package contents	- **cobas b** 101 instrument - Power adapter - Power cable - Optical check disc - Expert Manual
Necessary equipment not included in the package	- Printer (Optional) - Barcode scanner (Optional)

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. Optional (via USB)
Can the instrument be connected to a printer?	YES. Optional (via USB)
What can be printed?	- Patient ID - Patient name - Patient date of birth - Operator ID - Operator name - Test name - Disc lot number - Results - Comments - Date and time when result was generated - Date and time when result was printed - Facility information
Can the instrument be connected to a PC?	YES. USB 1 terminal: Connection to a personal computer. BUH terminal: Connection to a network through a base unit hub.
Can the instrument communicate with LIS (Laboratory Information System)? If yes, is the communication bidirectional?	YES, to both questions. The main objectives of making the **cobas b** 101 POCT1-A compatible for communication with the DMS are: 1. Bi-directional communication – allow the **cobas b** 101 to send data to and receive data from an external DMS utilizing existing standards. 2. Device connection commonality – allow the **cobas b** 101 to be seen as a device on the network that the DMS can communicate with.

	3. QC and regulatory compliance – allow **cobas b** 101 to send QC data to the DMS.
What is the storage capacity of the instrument and what is stored in the instrument?	5 000 patient test results 500 control test results 500 sets of patient information 50 sets of operator information (including 5 for administrators)
Is it possible to trace/search for measurement results?	YES

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

Name of the reagent/test strips/test cassettes	**cobas** CRP Test
Stability in unopened sealed vial	Until the expiration date printed on the pouch: 13 months shelf life (in spring 2019). Will be extended to 16 months in the near future.
Stability in opened vial	20 minutes
Package contents	One package of 10 tests. Each test is packed in sealed foil.

Table 4. Quality control.

Electronic self-check	YES
Recommended control materials and volume	**cobas** CRP Control: Level 1, 2 bottles 2 mL each, low range Level 2, 2 bottles 2 mL each, high range
Stability in unopened sealed vial	Up to the stated expiration date at 2 – 8 °C: 15 months shelf life (in spring 2019). Will be extended to 18 months in the near future.
Stability in opened vial	7 days at 20 – 25 °C or 30 days at 2 – 8 °C provided that the dispensing of the control occurs without microbial contamination and when stored tightly capped.
Package contents	▪ 2 x 2 mL Control Level 1 (low range) ▪ 2 x 2 mL Control Level 2 (high range) ▪ 1 x QC 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: OneMed, ABENA, Mediq Norway: Norengros AS Sweden: Not launced
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:	March 2nd 2018 – EC Declaration of Confirmity
In which Scandinavian languages is the manual available:	Danish Norwegian to become available soon

Product specifications for this evaluation, cobas b 101 CRP

cobas b *101 CRP instrument serial numbers*

Serial no	Used by
Q68101247	Optimal conditions
Q68101223	PHCC1
Q68101224	PHCC2
Q68101251	Spare (not included)

cobas b *101 CRP test discs*

Lot no	Expiry date	Used by
822152-01	2019-10-31	All evaluation sites
823151-01	2019-11-30	All evaluation sites
913151-01	2020-01-31	All evaluation sites

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

Control	Lot no	Expiry date	Used by
Control 1	020096-10	2019-12-31	All evaluation sites
Control 2	020096-20		

Other equipment used in the evaluation

Other equipment	Lot no	Expiry date	Used by
Greiner VACUETTE® TUBE 5 mL, REF no.:456073R	A18093PJ	2020-01-10	All evaluation sites
Accu-Chek Safe T pro plus	41518208	2022-12-31	All evaluation sites

Statistical expressions and calculations

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

Statistical terms and expressions

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

Precision

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

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

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

Trueness

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

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

Accuracy

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

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

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

Statistical calculations

Statistical outliers

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

Calculation of imprecision

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

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

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

(formula 1)

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

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

m = mean of paired measurements

(formula 2)

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

Calculation of bias

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

Assessment of accuracy

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

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

List of previous SKUP evaluations

The 30 latest SKUP evaluations.

Evaluation no.	Component	Instrument/test kit	Producer
SKUP/2019/116	CRP	**cobas b** 101	Roche Diagnostics GmbH
SKUP/2018/114	Strep A	DIAQUICK Strep A Blue Dipstick	DIALAB GmbH
SKUP/2018/115*	PT (INR)	*Confidential***	
SKUP/2017/113	Glucose[1]	Accu-Chek Instant	Roche Diabetes Care GmbH
SKUP/2017/111	Glucose[1]	*Confidential*	
SKUP/2017/112	Glucose[1]	Accu-Chek Guide	Roche Diabetes Care GmbH
SKUP/2016/110	PT (INR)	Xprecia Stride Coagulation system	Siemens Healthcare Diagnostics INC
SKUP/2015/107	Strep A	QuickVue Dipstick Strep A Test	Quidel Corporation
SKUP/2015/109	PT (INR)	microINR portable coagulometer	iLine Microsystems S.L.
SKUP/2015/108	HbA1c	*Confidential*	
SKUP/2015/102	HbA1c	*Confidential*	
SKUP/2015/106*	Strep A	QuikRead go	Orion Diagnostica Oy
SKUP/2014/101	HbA1c	InnovaStar analyzer	DiaSys Diagnostic Systems GmbH
SKUP/2014/104	PT (INR)	ProTime InRythm	ITC International Technidyne Corporation
SKUP/2014/105	Glucose[1]	Accu-Chek Aviva	Roche Diagnostics GmbH
SKUP/2014/103	PT (INR)	*Confidential*	
SKUP/2013/87	Glucose[1]	Wella Calla Light	Med Trust Handelsges.m.b.H.
SKUP/2013/100	Glucose[1]	Mylife Unio	Bionime Corporation
SKUP/2013/97	NT-proBNP	Cobas h 232 POC system	Roche Diagnostics GmbH
SKUP/2013/92	CRP	Eurolyser smart 700/340	Eurolyser Diagnostica GmbH
SKUP/2013/99*	Glucose	Accu-Chek Mobile	Roche Diagnostics
SKUP/2013/98*	Glucose	Accu-Chek Aviva	Roche Diagnostics
SKUP/2013/85	Glucose, β-Ketone	Nova StatStrip	Nova Biomedical Corporation, USA
SKUP/2013/96	Hemoglobin	DiaSpect Hemoglobin T	DiaSpect Medical GmbH
SKUP/2013/68	Allergens	ImmunoCap Rapid	Phadia AB Marknadsbolag Sverige
SKUP/2012/95	Glucose[1]	Mendor Discreet	Mendor Oy
SKUP/2012/94	Glucose[1]	Contour XT	Bayer Healthcare
SKUP/2012/91	HbA1c	Quo-Test A1c	Quoient Diagnostics Ltd
SKUP/2011/93*	Glucose	Accu-Chek Performa	Roche Diagnostics
SKUP/2011/90	CRP	*i*-Chroma	BodiTech Med. Inc.

*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 their evaluations to be kept confidential.

[1]Including a user-evaluation among diabetes patients.