Eurolyser *smart* 546 instrument with the *smart* CRP test
A system for measurement of P—CRP

manufactured by Eurolyser Diagnostica GmbH
Salzburg/Austria

Report from an evaluation
organised by SKUP

Evaluated at the request of ILS-Laboratories Scandinavia AB, Sweden

SKUP/2011/70*

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The organisation of SKUP

Scandinavian evaluation of laboratory equipment for primary health care, *SKUP*, is a co-operative commitment of NOKLUS[1] in Norway, DAK-E[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 on analytical quality and user-friendliness of laboratory equipment. This information is generated by organising SKUP *evaluations*.

SKUP offers manufacturers and suppliers evaluations of equipment for primary healthcare and also of devices for self-monitoring. Provided the equipment has not been launched into 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 prepared in cooperation with the manufacturer or their representatives. SKUP signs *contracts* with the requesting company and the evaluating laboratories. A *complete evaluation* requires one part performed by experienced laboratory personnel as well as one part performed by the intended users.

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 and a serial number. A report code, followed by an asterisk (*), indicates a special evaluation, not complete according to the guidelines, e.g. the part performed by the intended users was not included in the protocol. If suppliers use the SKUP name in marketing, they have to refer to www.skup.nu and to the report code in question. For this purpose the company can use a logotype available from SKUP containing the report code.

SKUP reports are published at www.skup.nu and www.skup.dk. A detailed list of previous SKUP evaluations is included in this report.

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[1] NOKLUS (Norwegian Quality Improvement of Primary Care Laboratories) is an organisation founded by Kvalitetsforbedringsfond III (Quality Improvement Fund III), which is established by The Norwegian Medical Association and the Norwegian Government. NOKLUS is professionally linked to “Seksjon for Allmennmedisin” (Section for General Practice) at the University of Bergen, Norway.

[2] SKUP in Denmark is placed in Hillerød Hospital. SKUP in Denmark reports to DAK-E (Danish Quality Unit of General Practice), an organisation that is supported by KIF (Foundation for Quality and Informatics) and Faglig udvalg (Professional Committee), which both are supported by DR (The Danish Regions) and PLO (The Organisation of General Practitioners in Denmark).

[3] EQUALIS AB (External quality assurance 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).

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A detailed list of previous SKUP evaluations is included in the attachments.
Attachments with raw data are included only in the copy to ILS-Laboratories Scandinavia AB, Sweden

1. Summary

Background
The Eurolyser ***smart*** system (**S**ingle **M**ethode **A**utomated **R**eading **T**echnology) is a family of near- patient testing instruments which can be used for several different tests. This evaluation is about the Eurolyser *smart* 546 instrument together with the *smart* CRP test (*smart* CRP system) used for measuring the concentration of CRP in whole blood, serum or plasma. The system is primarily intended for use in primary health care. The system is based on kinetic determination of the concentration of CRP by turbidimetric measurement at 546 nm (or at 700 nm in other Eurolyser instruments) of the antigen-antibody reaction between antibodies to human CRP, bound to polystyrene particles, and CRP present in the sample.

The aim of the evaluation
- To get a measure of the analytical quality of the *smart* CRP system in the concentration interval of 2,0 to 302 mg/L achieved under standardised and optimal conditions in a hospital laboratory by an experienced laboratory technologist.
- To assess the achieved analytical quality with the quality goals specified by SKUP: Bias <±10%, repeatability <10 CV% and total error <±26%.
- To evaluate the user-friendliness when used in a hospital laboratory

To investigate the influence of haematocrit was not part of the protocol; however it was measured because hospitalised patients were used in order to get a wide range of CRP-concentrations.

Materials and methods
Bias and repeatability were calculated from the test results from 101 individuals tested with both capillary whole blood samples and venous samples (EDTA-whole blood) in duplicates. The designated comparison method was an immunoturbidimetric plasma method, using mouse monoclonal Anti-CRP antibodies. The agglutination was measured turbidimetrically in a Modular P instrument from Roche. To check the calibration of the comparison method the 1st international standard of human C-Reactive Protein 85/506 was used before and after the evaluation. The comparison method needed no adjustment.

Results
97% of the venous whole blood sample results >4,0 mg/L were within the total error goal while 84% of the capillary blood sample results were within the goal. With venous whole blood samples the bias goal was fulfilled for CRP >4 mg/L. With capillary whole blood samples the bias goal was not fulfilled. The repeatability of *smart* CRP system in the range 4,5 to 36 mg/L was lower in venous sample results (5 CV%) than in capillary blood sample results (10 CV%). The user-friendliness was satisfactory; however there were comments about how to prepare the sample in order to get the correct volume.

Conclusion
With venous whole blood samples the CRP results between 4,0 to 302 mg/L fulfilled the analytical quality goals specified by SKUP. With capillary whole blood samples the quality goal for bias was not fulfilled. The total error goal was fulfilled between 8 and 302 mg/L. The user-friendliness was assessed as satisfactory; however, there were comments about application of the sample. As the *smart* CRP system was evaluated in a hospital laboratory, it is so far unknown how the system performs under less standardised conditions in the primary health care.

2. Analytical quality goals

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. The number of invalid tests due to errors must not exceed 2%.

2.1. Traceability for CRP results

All CRP tests should produce results traceable to a CRP reference material. The results in this evaluation are traceable to the 1st international standard of human C-Reactive Protein 85/506[1] that was run in three levels on the comparison method before, during and after the evaluation.
For the capillary samples measured with the *smart* CRP system it is assumed that the haematocrit (EVF) for all the samples are 0,40.

2.2. Quality goals for user-friendliness

The quality of the tested equipment in the user-friendliness questionnaires is separated in four sub-areas:

- Rating of information in manuals and inserts
- Rating of time factors of both measurement and preparation
- Rating of performing internal and external quality control
- Rating of operation facilities. Is the system handy?

Evaluation of user-friendliness is graded as
Satisfactory: ”2 points”
Less satisfactory: ”l point”
Un-satisfactory: ”0 points”

The tested equipment must reach the total rating of ”2 points” in all four sub-areas of characteristics mentioned above, to achieve the overall rating ”satisfactory”.

2.3. Analytical quality goals

International guidelines for analytical quality requirements for CRP are few. The biological within-subject-variation is 42,2% and the biological between-subject-variation is 76,3% for healthy individuals[2]. The reference interval is <3 mg/L. The desirable quality specifications[2-4] calculated from the biological variation gives high figures, imprecision 21,1% CV, bias ±21,8% and Total Error 56,6%. As the CRP test is mostly used for non-healthy individuals with higher CRP-concentrations, narrower quality limits are justified, as proposed below by SKUP for the present evaluation. In Denmark the CRP analyses used in primary healthcare and in hospital laboratories have different requirements to quality[5]. Norway and Sweden have no similar requirements.

In Denmark:

For CRP >15 mg/L:

Point Of Care Tests used in primary health care:	Bias ≤±10% and CV ≤10%
Hospital laboratory methods, used as comparison methods:	Bias ≤±3% and CV ≤5%

SKUP:

Total Error TE ≤ ± [│bias│ + 1,65 x CV], where bias < 10% and CV < 10%

2.4. SKUP's quality goals for the present evaluation

Based on the discussion about quality goals above, SKUP has decided to assess the results from the evaluation of the *smart* CRP system against the quality goals in table 1.

Table 1. Goals in the evaluation for the *smart* CRP system

		Goal
1	Imprecision	≤10% CV
2	Bias	≤±10%
3	Total Error (allowable deviation)	≤±26%
4	Fraction of technical errors	2% or less
5	User-friendliness	satisfactory

3. Materials and methods

3.1. Definition of CRP

Table 2. Name and codes for the CRP test according to C-NPU

Method	Formal full name of test	NPU code
	Plasma—C-reactive protein; mass concentration	NPU19748

3.2. The evaluated *smart* CRP system

Figure 1. The Eurolyser *smart* laboratory photometer

The Eurolyser *smart* laboratory photometer (figure 1) is an open measuring system, which means that various reagents from different producers can be applied. For measuring, the *smart* laboratory photometer is loaded with Eurolab reagent system (ERS) cassettes, in which the reagents of the particular producers are filled.

The instrument can process endpoint tests as well as kinetic tests. There are different types of *smart* instruments, using different wavelengths of the light source. For example: the name ”*smart* 546“ refers to a photometer with a 546 nm light source is used. The *smart* instruments can have one or two light sources. The instrument is equipped with a **R**adio **F**requency **ID**entification (RFID) card-reader module. The RFID cards are necessary to perform the test routine. The cards provide all test specific work schedules, the lot data as well as the calibration data. The instrument executes the test automatically, according to the data stored in the cards. Several components can be read out.

The sample and the reagent are mixed automatically. The photometer unit with either one or two light diodes executes the measuring. In the process, the absorption of light rays is measured, which can then be transformed into the test result. The measuring result is then shown on the touch display. The results can be exported to an external personal computer, or can be printed with an external printer.
When the user confirms the result, the test lid is automatically opened; the ERS cassette can be removed and disposed. After this procedure the instrument is ready for the next measurement. The principle of the measurement is shown in the figures below.

3.2.1. *Eurolab reagent system (ERS)*

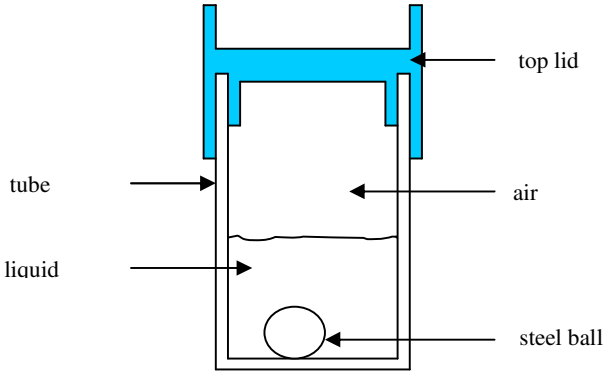


Figure 2. Pre-filled tube. Top lid: to be opened manually to add sample. Tube: contains pre-filled liquid and will be measured in analyser. Liquid: buffer for CRP. Steel ball: ball used for mixing liquids.

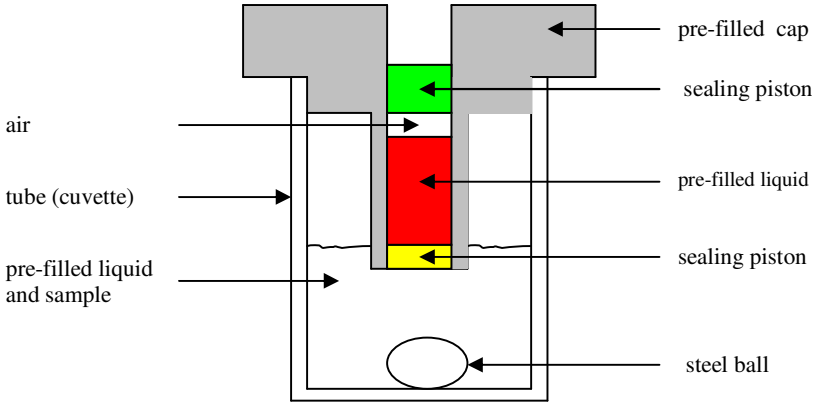
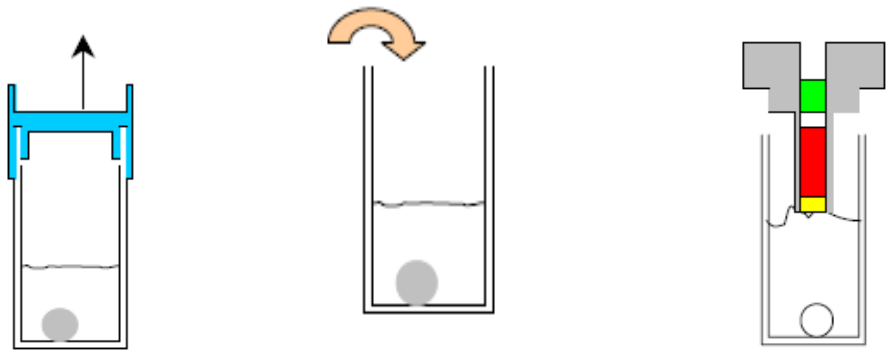


Figure 3. ERS after applying the pre-filled cap. Pre-filled tube after adding sample and putting on the cap. Cap: to be pre-filled with any chemical (i.e. starter reagent). Sealing piston: for example buffer for CRP or other chemistry.

3.2.2. *Application for CRP test*



open the top lid add sample apply the pre-filled cap

Figure 4. Procedures before the tube including the cap are placed into the analyser.

The *smart* laboratory instrument is based on photometer technology to perform turbidimetric tests. An LED (Light Emitting Diode) generates a light beam that passes through the liquid-filled cuvette. At the opposite end of the photometer a photo diode receives the light beam and transfers the signal into an electronic value. The instrument measures the difference in optical density of the liquid before and after the reaction of the liquids within the cuvette. It then calculates the measured values with the tests specific formula and displays the result on the instrument screen.

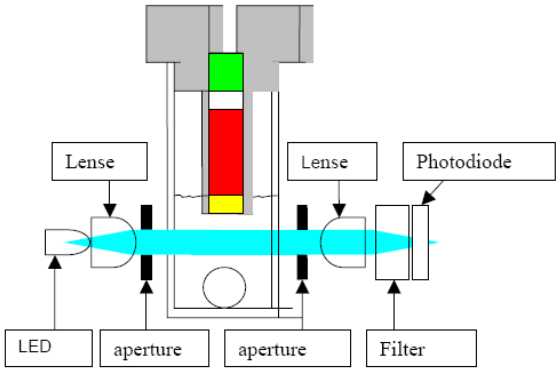


Figure 5. The measurement

The figures 1 to 5 are created by the ILS-company[6,7] as well as some of the text.

Before analysing with the *smart* system, the operator press 'whole blood' or 'serum' on the screen to indicate the nature of the sample, se attachment E. It is possible to make corrections for a high or a low haematocrit (EVF); however in the evaluation the *smart* instrument was set with a fixed haematocrit (EVF) 0,40 for all patients.

3.2.3. *Technical data*

Technical data from the producer is shown in Table 3.

Table 3. Technical specifications for *smart* from the manufacturer

TECHNICAL DATA FOR THE *smart*	
Working temperature	37˚C
Sample	Capillary, heparin or EDTA whole blood, serum or plasma
Sample volume	5 µL
Units	µmol/L or mg/L
Measuring time	4 minutes for whole blood 3 minutes for serum or plasma
Measuring range	<2,6 mg/L to 316 mg/L
Memory	100 results
Data output	On-board screen / Printer
Power supply	100-240V AC, 50/60Hz, 0.5-1.3A
Operating time with battery	none
Dimensions	14 (L) x 14 (W) x 24 (H) cm
Weight	3,5 kg

See further details in attachment E

3.2.4. *Product information, smart*

smart instrument	EUROLyser DiagnosticaGmbH 4 units: No Ab 0594, Ab0595, Ab 0596, Ab 0596 No Ab 0594 was used in the evaluation
Instructions for use	4 units
Printer	DPU-414 Thermal Printer Seiko Instruments Inc. Assembled in Malaysia. 4 units: 5010545 B-30B, 5010541B-30B, 5010544B-30B, 3024426B-30B no. 3024426 was used in the evaluation
Calibrator	2 units, lot BMD 7085, 1x1 mL
Lot, reagent Content in the reagent box:	657055 and 757051-1 32 test cassettes 1 ID card 1 insert sheet
Smart CRP-Control Kit	lot 417061. % units of 2 x 1 mL (low and high range)
Capillary Pipette 5 µL	*smart* EUROLyser DiagnosticaGmbH

	Art code: SZ0302. lot 2007-25 expiry 2012-08
Pipette 5 µL (non capillary samples)	CRP 5 µL pipette EUROlyser tested 19-April-2007 in FINAS-accredited calibration laboratory. No. 6137068 was used.
Pipette tips	Pipet tips, TXL-10 0,1-10 µL extra long, lot no. 070703-144 Axygen scientific, Union City, California, USA

3.2.5. *Manufacturer of smart*

Eurolyser Diagnostica GmbH
Bayernstrasse 11a
5020 Salzburg/Austria
Tel. +43 (0) 662 43 21 00
Fax. +43 (0) 662 43 21 00 50
www.eurolyser.com

3.2.6. *The suppliers of smart in the Scandinavian countries*

ILS-Laboratories Scandinavia AB, Sweden was the agent of *smart* in Denmark, Norway and Sweden during the evaluation but had finalised that agency mission when this report was published. For contact information of the current suppliers, please contact the manufacturer (see above).

3.3. The designated comparison method

3.3.1. Definition

A designated comparison method is a fully specified method which, in the absence of a reference method, serves as the common basis for the comparison of a field method.

The designated comparison method[8] is called the comparison method in the following text.

3.3.2. *Description of the comparison method in this evaluation*

Instrument: Modular P, Roche

Sample: Venous plasma collected in Li-heparin tubes.

Traceability: 1st International Standard of Human C-reactive protein, code 85/506, 0,049 International Units per ampoule or 50 micrograms Human C-reactive protein from NIBSC (National Institute for Biological Standards and Control).

The method was calibrated with Calibrator for automated systems (C.f.a.s.) from Roche. C.f.a.s. is traceable to a master lot calibrator, which is traceable to SI-units via the reference material – Certified Reference Material (CRM) 470.

Method principle: Immunoturbidimetric analysis, mouse monoclonal anti-CRP antibodies bound to latex micro particles react with CRP in the sample and creates a new antigen/antibody complex. The agglutination is measured turbidimetrically.

It is a two-point endpoint measurement. The first endpoint is just before reagent 2 is added. After adding reagent 2 (the antibody) the agglutination begins and the absorbance is read after about 5 minutes. The difference between measurements is used in the calculation of the measured result. A bi-chromatic measurement is done to minimise interference.

Calculation of a measurement result: The concentration in a sample is calculated from the formula:

$$Cx = [\{K(Ax-Ab)+Cb\}\bullet IFA]+ IFB,$$ where

Cx	=	concentration in a sample
K	=	factor of calibration
Ax	=	absorbance of actual sample
Ab	=	absorbance of Std. 1/Blank*
Cb	=	concentration of Std. 1/Blank
IFA, IFB	=	the constant of the instrument for slope and intercept

*Blank = Background absorbance before measurement

3.3.3. *Verification of the analytical quality of the comparison method*

Traceability:
1st International Standard of Human C-reactive protein, code 85/506, 0,049 International Units per ampoule or 50 micrograms Human C-reactive protein from NIBSC.
Before and after the testing, the comparison method was checked with the 1st International Standard 85/506 in 3 levels: 2, 10 and 50 mg/L. The bias was calculated as the deviation of the mean of 8 measurements (two instruments) from the calculated concentrations of 1st International Standard 85/506.

Internal quality control 1:
Three pools of human plasma sample were produced for the evaluation, Low, Medium and Very High. They were run daily in the period 15-05-2007 to 13-09-2007

Low concentration:	<5 mg/L
Medium	15 – 20 mg/L
Very High	>100 mg/L

Internal quality control 2:
Two control materials from ILS, Sweden were run daily in the period 1-04-2007 to 3-07-2007

Low concentration:	~ 6 mg/L
High	~90 mg/L

3.3.4. *Product information, the comparison method*

Instruments:
For CRP: Modular P, serial number HQ 1360-30 and HQ 1360-20
For haematocrit: Coulter®LH 750, 755 workcell, series number AJ11184, AJ11186, AJ11190

Reagent :
CRP LX, Tina-quant®
Lot number before 21 May 2008: 696967
Lot number after 21 of May 2008: 698201

Calibrators:
Calibrator C.f.a.s. from Roche, lot numbers: 178428. Modular calibrated October 2007 for the evaluation.

3.4. Planning of the evaluation

Background for the evaluation
ILS-Laboratories Scandinavia AB, Sweden wanted to distribute *smart* in Scandinavia. The *smart* system was already in use in Germany.

3.4.1. *Meetings, protocol and contract*
November 1st 2007, Eva Carlson, Product Manager, ILS-Laboratories Scandinavia AB contacted SKUP in Denmark and asked for a protocol for evaluation of the *smart* instrument for CRP analysis..
11th of December 2007 Eva Carlson brought 4 instruments and one lot of CRP test kit to Odense. The protocol was discussed and Nina Brøgger was taught to operate the *smart* instrument. Capillary samples, venous samples and control samples were analysed. It was agreed to send the upgraded protocol and a contract to ILS the following week.

The contract was signed 18th of December 2007. 17th of January 2008 lot 757051-1 was received. The 29th of February 2008 ILS, Sweden was in Odense for troubleshooting because the results including the control samples deviated systematically and too much from the comparison method. The instrument had the calibration function changed by ILS. The evaluation in the hospital restarted 29th of February and had the first patient included 1st of April 2008.

3.4.2. *Time schedule*
The first evaluation period:

Hospital laboratory January 2008

The second evaluation period:

Hospital laboratory 29th of February to 3rd of July 2008

Writing of Report:
September to December 2008 and December 2010

Pause of evaluation
February 2009 – October 2010

Based on the capillary results and the comments in the user-friendliness evaluation it was agreed to wait for new caps. It was agreed with SKUP that when the caps arrived, the evaluation should continue.
The aim of the evaluation with the new caps:

- Determination of the imprecision with 100 venous patient samples in a hospital laboratory
- Determination of the imprecision with 40 patient samples at two primary care centres.
- Comparison with the Modular P results for CRP and the 1st International Standard Human C-reactive protein code 85/506 0,049 International Units per ampoule. Determination of trueness and accuracy
- Evaluation of user-friendliness

Stop of evaluation

September 2010

In a mail Emma Broberg, Clinical Diagnostics, ThermoFisher Scientific, Jönköping, Sweden informed SKUP that the evaluation of the *smart* CRP had changed from 'pause' to 'stop'.

3.4.3. *Evaluation sites and persons involved*

The hospital evaluation took place in Odense University Hospital. Nina Brøgger, SKUP/Odense, did the practical work and collected the capillary and venous samples for the evaluation.

Table 4. Evaluation sites and persons involved

Place	**Person**	**Title**	**Task**
Hillerød Hospital	Esther A Jensen	Physician	Author of report
OUH	Nina Brøgger	Biomedical laboratory scientist	Hospital testing
OUH	Ole Blaabjerg	Clinical Biochemist MSc.	Responsible for 1st International Standard of Human C-Reactive Protein 85/506
OUH	Poul Jørgen Jørgensen	Civil engineer	Responsible for the comparison method

3.4.4. *Blood sampling devices*

The capillary punctures were made with the sampling tool the biomedical laboratory scientist was accustomed to.

The venous blood for *smart* was drawn into EDTA tubes (K2) and for the Modular P Lithium-heparin tubes were used.

3.5. Evaluation procedure in the hospital laboratory

Out-patients were recruited in addition to patients in the medical department for infectious disease in Odense University Hospital. Hospitalised patients were included in order to achieve a fraction of very high CRP results as a part of the evaluation.

3.5.1. *The aim of the evaluation*

- Determination of imprecision and total error of the *smart* CRP system with capillary whole blood samples and venous whole blood samples from 100 individuals measured in duplicates with the *smart* CRP system
- Comparison with the plasma CRP results on the Roche method for CRP in the instrument Modular P. Determination of trueness and accuracy
- Bias of the comparison method was checked by using the 1st international standard of human C - reactive protein 85/506.
- Evaluation of the user-friendliness of the *smart* CRP system
- After the hospital evaluation is completed an extension of the evaluation should be considered to be done in the primary care

Influence of the haematocrit

To investigate the influence of the haematocrit was not part of the protocol; however the distrubution of the CRP-concentrations were (table 5). The samples from the hospitalised patients in a university hospital would not be comparable with the CRP samples from the average primary care centre. SKUP in Denmark wanted to make sure, that an error was not introduced by including hospitalised patient – possibly they had low haematocrit values. If the instrument was sensitive to low haematocrit, the number of hospitalised patients could ruin the evaluation.

3.5.2. *Training*

Nina Brøgger was trained by ILS, Sweden, 11th of December 2007. Capillary samples, venous samples and control samples were analysed using the *smart* CRP system in the Department of Clinical Biochemistry, Odense University Hospital.
The 29th of February 2008 Werner Rademacher, ILS, Sweden was in Odense for troubleshooting. The instrument had the calibration function changed by the ILS Sweden. All agreed that Nina Brøgger performed the analysing correctly.

3.5.3. *Evaluation procedure in the hospital laboratory (standardised and optimal conditions)*

All data, specimen collection, days of analyses, lot numbers on test, results, etc. were reported. The *smart* capillary whole blood results were compared to the *smart* venous whole blood results and the comparison method results (plasma). Control samples were run on the *smart* CRP system and the comparison method.
The 1st international standard of human C-Reactive Protein 85/506 was run as check samples before and after the evaluation in the *smart* CRP system and the comparison method.

3.5.4. *Internal quality control*

The two ILS control materials as well as the three pools made in department of clinical biochemistry were run in duplicate every day samples were tested on the *smart* instrument. Every second day the high control was analysed and every second day the low control was analysed.

3.5.5. *Recruitment of the patients/samples*

Due to the short half-life of CRP in vivo the capillary whole blood sample for the *smart* CRP system and the venous plasma sample for the comparison method from the same individual were drawn within 30 minutes.
An optimal distribution of sample concentrations was achieved by including about 40 outpatients and 60 inpatients from the Department of Infectious Disease. The attempt was to reach the distribution of CRP results demonstrated in table 5.

Table 5. The comparison method, distribution of the concentrations in the samples

	% of total in group				
CRP (mg/L)	<5	>5 and<15	> 15	>50	>100
number at least	5	5-10	≥60	≥15	≥5

3.5.6. *Handling of specimens and measurements*

Blood samples were collected from patients that had the CRP measured in the out-patient clinic or in the Department of infectious disease.

Sample handling for the comparison method Modular P
The venous plasma samples were drawn and treated as routine samples. They were then analysed as usual with one of the Modular P instrument.

Analysing with the comparison method
After the routine analysing in Modular, the sample were reanalysed in the other Modular P instrument of the department if possible and then frozen at minus 70°C. Normally the samples are measured only once. The time from blood sampling to analysis was maximum 8 hours.

Comparison method, external QC
The 1st international standard of human C-Reactive Protein 85/506 was used before and after testing. External QC was not used.

Analysing with the *smart* CRP system
According to the manufacturer both capillary whole blood samples and serum/plasma samples can be used. In this evaluation whole blood was used for both capillary and venous samples. The control samples were all plasma samples. According to the manufacturer the sample volume, 5 µL, was the same for both capillary blood and serum/plasma.
The samples were analysed in duplicates with the *smart* CRP system, first the two capillary whole blood samples, then the two venous EDTA whole blood samples, in total four measurements on the *smart* instrument for each patient. For capillary samples the second blood drop was used. The instruction manual was followed, see attachment E.

Quality assurance on the *smart* CRP system
Pools of human serum were established. The CRP concentrations were <5, 15-20 and >100 mg/L. Two of the samples were run in duplicates every day of testing. Two control materials from ILS were analysed as well.

Analysing the haematocrit
After the analysing on the *smart* CRP system, an EDTA tube was analysed in Coulter for haematocrit.

3.5.7. *Evaluation of user-friendliness*
Nina Brøgger evaluated the user friendliness immediately after the testing in hospital ended. She used the evaluation form with the four categories; manual, time factors, Quality Assurance and operation facilities.

4. Statistical expressions and calculations

4.1. Statistical terms and expressions

The definitions in this section are taken from the International Vocabulary of Metrology, VIM[9]

4.1.1. *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 descriptive in general terms (e.g. good, acceptable or poor) and measured as imprecision. 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 and CV is usually reported in percent.

The frequently used terms within-series imprecision and between-series imprecision are often misinterpreted. Especially the terms between-series and between-day imprecision are often not precisely defined. To be able to interpret an assessment of precision, the precision conditions must be defined. The "specified conditions" can be, for example, repeatability, intermediate precision or reproducibility conditions of measurement.

Repeatability is the agreement between the results of consecutive measurements of the same component carried out under identical measuring conditions (within the measuring series). Reproducibility is the agreement between the results of discontinuous measurements of the same component carried out under changing measuring conditions over time. The reproducibility includes the repeatability.
The precision conditions in this evaluation are close to the defined *repeatability* and *reproducibility* conditions, and the imprecision is expressed as repeatability CV and reproducibility CV. The imprecision is summarised in tables.

4.1.2. *Accuracy*

Definition

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

Inaccuracy is a measure of the deviation of a single measurement from the true value, and implies a combination of random and systematic error (analytical imprecision and bias). Inaccuracy, as defined by a single measurement, is not sufficient to distinguish between random and systematic errors in the measuring system. Inaccuracy can be expressed as total error. The inaccuracy is illustrated by difference plots with quality goals for the total error shown as deviation limits in percent.

4.1.3. *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 measured as bias (systematic errors). Trueness is descriptive in general terms (good, poor), whereas bias is the estimate, reported in the same unit as the analytical result or in %. The bias at different CRP concentration levels is summarised in tables.

4.2. Statistical calculations

4.2.1. *Number of samples*

From 101 patient both capillary whole blood samples and venous EDTA whole blood samples were collected. The samples were measured in duplicates.

4.2.2. *Statistical outliers*

All the results are checked for outliers according to Burnett[10], with repeated truncations. The model takes into consideration the number of observations together with the statistical significance level for the test. The significance level is often set to 5%, also in this evaluation. Where the results are classified according to different concentration levels, the outlier testing is done at each level separately. Statistical outliers are excluded from the calculations.

4.2.3. *Missing or excluded results*

One sample was only measured in the *smart* CRP system – and not with the comparison method. Possible outliers will be commented on under each table.

4.2.4. *Calculations of imprecision based on duplicate results*

The imprecision was calculated with the following formula:

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

d = difference between duplicate measurements
m = mean of the duplicate measurements
n = number of differences

This formula is preferred when estimating CV over a large concentration interval within which the CV is assumed to be reasonable constant.

The assumption for using this formula is that there is no systematic difference between the 1st and the 2nd measurement. There is no such systematic difference in this evaluation, see table 11.

4.2.5. *Calculation of trueness*

To measure the trueness of the results at the *smart* CRP system, the average bias at three concentration levels is calculated based on the results obtained under standardised and optimal measuring conditions.

4.2.6. *Calculation of accuracy*

To evaluate the accuracy of the results from the *smart* CRP system, the agreement between the *smart* CRP system and the comparison method is illustrated in difference plots. In the plots the x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference in percent between the first measurement on the *smart* CRP system with two lots and the mean value of the duplicate results from the comparison method.

5. Results and discussion

50 men and 51 women, in total 101 patients participated in the evaluation. 55 outpatients were recruited and 46 patients from a medical department. The samples from the patients were measured on one *smart* instrument and two lot numbers were used. It was not a part of the evaluation to investigate if the instruments were in agreement with each other. The supplier guaranteed that the lot numbers gave corresponding results.

Table 6. The comparison method, distribution of the CRP concentrations in the samples

CRP (mg/L)	**<5**	**5 to <15**	**15 to <50**	**50 to <100**	**>100**
Number*	37	14	24	9	16

*one sample was only measured in the *smart* CRP system

5.1. Number of samples

In total 101 patients participated in the evaluation. The number of tests performed is seen in table 7. Nine capillary and 15 venous results were <2,6 mg/L on *smart.* The first result in one duplicate venous result was >316 mg/L on *smart*. One sample was only measured on *smart* and not on the comparison method.

Table 7. Number of test used in the *smart* CRP instrument in the February to July evaluation

The evaluation in a hospital laboratory	
Practise before the evaluation	10
Measurements on venous whole blood samples	101 x 2 = 202
Measurements on capillary whole blood samples	101 x 2 = 202
Measurements on control samples	130
Invalid tests	2
Measurements in experiments	
n total	***~546*** *+ experiments ~100*

5.1.1. *Failed measurements*

In total two errors occurred during the evaluation, both when measuring control samples.
The percent of invalid tests was therefore <1,0%.

5.2. Analytical quality of the comparison method

5.2.1. *The precision of the comparison method Modular P*

Table 8. Repeatability of the comparison method Modular P with venous plasma patient samples

Level	Modular P interval CRP, mg/L	n	Outliers	Modular P Dept. BFG mean CRP mg/L	CV % (95 % C.I.)
Low	0,2 — 4,4	33	0	1,8	21,8 (17,7— 28,8)
Medium	4,5 — 35,8	34	0	15,2	3,2 (2,7— 4,3)
High	36,7 — 301	33	0	123,0	2,6 (2,1— 5,4)
	2,0 — 301	80*	0	46,6	3,6 (3,1— 4,3)

* the concentrations 0,2 to 2,0 mg/L are not included.

Discussion: It is of no importance if a CRP result is 1,0 or 2,0 mg/L. The CV% for the 20 samples with a concentration between 0,2 and 2,0 mg/L was very high in Modular P. For the 80 samples >2,0 mg/L the CV% was 3,6%.
The laboratory normally reports the low Modular P results to clients as '<5,0 mg/L'.

5.2.2. *The trueness of the comparison method Modular P, Roche*

Table 9. The bias of the comparison method

	1st international standard of human C-Reactive Protein 85/506		CV	bias	Comparison instrument Modular 1		Comparison instrument Modular 2	
Date	assigned	measured	%	%	result 1	result 2	result 1	result 2
15.05.07					1,9	1,9	1,7	1,8
23.07.07					1,8	1,8	1,5	1,6
13.09.07	2,0	1,97	27,7	-1,75	1,8	1,7	3,6	3,2
24.01.08					1,9	2,3	2,0	2,2
03.07.08					1,8	2,0	1,4	1,4
15.05.07					9,6	10,3	9,5	9,5
23.07.07					9,3	9,2	9,0	9,0
13.09.07	10,0	9,68	5,9	-3,25	9,6	9,4	11,0	11,2
24.01.08					9,6	9,6	9,8	9,3
03.07.08					9,4	9,6	9,7	9,9
15.05.07					52,1	47,8	52,2	51,6
23.07.07					52,3	51,8	49,6	51,1
13.09.07	50,0	52,16	4,3	4,32	51,4	50,1	56,0	55,9
24.01.08					53,6	53,9	55,4	55,6
03.07.08					50,7	49,9	50,7	51,5

Discussion: Table 9 shows that the bias of the comparison method at concentration level 10,0 and 50,0 mg/L is -3,25% to 4,32%, respectively. The CV% for the low concentration of 2,0 mg/L in Modular P is 27,7%. Low concentrations are routinely reported as <5,0 mg/L. The results are therefore acceptable and no adjustment has been done of the comparison method results in this report.

5.2.3. *The precision of the control samples on the comparison method*

Table 10. Internal quality control, patient pool Modular P from 1st of April to 3rd of July 2008

			Repeatability		Reproducibility
	N	**mean (mg/L)**	**CV (%)**	**CI 95%**	**CV (%)**
Control 1	9	4,4	3,5	2,4 — 6,8	5,8
Control 2	7	19,3	2,0	1,4 — 4,2	2,5
Control 3	7	191	0,7	0,6 — 1,4	2,6

Discussion: Repeatability and reproducibility of CRP in Modular P fulfilled the analytical quality goal presented in chapter 2.2 for the comparison method[4] at the concentrations about 19 and 191 mg/L. At 4,4 mg/L the reproducibility was 5,8% and thus higher than the goal of 5%. The laboratory normally reports low results to clients as '<5,0 mg/L'.

5.3. Analytical quality of the *smart* CRP system in the hospital laboratory

5.3.1. *Comparison of the 1st and 2nd measurements*

Of the 101 patients participating in the evaluation, 61 had a CRP concentration ≥5,0 mg/L. The results are checked to meet the assumption that there is no difference between the first and the second measurement. Table 11 shows that no systematic difference was pointed out between the paired measurements. A difference between the measurements would be unexpected because the two measurements are genuine duplicates from two skin-penetrations.

Table 11. Comparison of the 1st and 2nd measurements on *smart* CRP

	n	Mean 1st measurement CRP mg/L	Mean 2nd measurement CRP mg/L	Mean difference 1st – 2nd measurement CRP mg/L	95% CI for the mean difference, CRP mg/L
Capillary	101*	56,3	56,0	+0,29	-0,5 — +1,1
Venous	101*	53,2	52,6	+0,63	-0,4 — +1,7

* *smart* gave the result <2,6 mg/L for at least one duplicate result for six capillary samples.
** *smart* gave the result <2,6 mg/L for at least one duplicate result for 12 venous samples and CRP ≥316 mg/L for one duplicate result.

Conclusion: There is no significant difference between the first and the second measurements of either capillary or venous duplicates (table 11), however there is a difference between the capillary and venous results from the same patients.

5.3.2. *The precision of smart*

Repeatability under standardised and optimal measuring conditions in a hospital laboratory was obtained with capillary blood samples (table 12) and venous whole blood samples (table13). The raw data is not shown. The venous and the capillary results originate from the same 101 patients. Repeatability was calculated for three subgroups: the highest CRP-values (n=34), the lowest (n=33) and the middle level of CRP (n=34). The three groups were chosen according to their concentration with the comparison method.

Table 12. Repeatability for the *smart* CRP system with capillary whole blood samples

Level	CRP interval comparison method Modular (mg/L)	n	Outliers	CRP mean comparison method Modular (mg/L)	CV % (95 % C.I.)
Low	0,3 — 4,3	33*	0	3,0	12,0 (9,6— 16,5)
Medium	4,5 — 35,8	34	0	15,2	10,0 (8,2— 13,2)
High	36,7 — 302	34	0	123	4,9 (4,0— 6,5)
	2,0 — 302	80	0	46,6	8,4 (7,3— 10,0)

** 6 duplicate measurements with test results <2,6 mg/L were not included in the calculations. The results <2,6 mg/L were in good agreement with the concentrations on the comparison method.*

Table 13. Repeatability for the *smart* CRP system with venous whole blood samples

Level	CRP interval comparison method Modular (mg/L)	n	Outliers	CRP mean comparison method Modular (mg/L)	CV % (95 % C.I.)
Low	0,8 — 4,3	33*	0	3,0	10,6 (8,2 — 15,3)
Medium	4,5 — 35,8	34	0	15,2	5,0 (4,1 — 6,6)
High	36,7 — 302	34**	0	123	5,5 (4,2 — 6,9)
	2,0 — 302	80	0	46,6	6,7 (5,8—8,0)

**12 duplicate measurements with test results <2,6 mg/L were not included in the calculations. The results <2,6 mg/L were in good agreement with the concentrations on the comparison method. **one sample >316 mg/L*

Discussion: The samples with values <2,6 mg/L were in good accordance with the Modular P results, one high result was 266 and >316 mg/L in the *smart* CRP system; the values in Modular P were 249 and 256 mg/L.
The goal for repeatability, less than 10%, was fulfilled by the *smart* CRP system in all concentrations with comparison method results >2,0 mg/L with both capillary and venous samples. The CV% for CRP concentration on the comparison method between 2,0 and 302 mg/L was for both capillary and venous duplicate measurements between 5,8 to 10,0% for the *smart* CRP system.

5.3.3. *The trueness of the smart CRP system in a hospital laboratory*

The trueness of *smart* is calculated from results achieved by one biomedical laboratory scientist in a hospital laboratory. A total of 101 patients participated in the evaluation. The results are shown in Tables 14 and15. The raw data are shown in attachment B - for the supplier only.
Bias is the mean difference between the *smart* CRP system and the comparison method, based on the mean of each duplicate with both methods. The results are achieved under standardised and optimal conditions. Only samples with CRP results >2,5 mg/L and <316 mg/L in the *smart* CRP method are included. Table 14 demonstrates the results for capillary whole blood samples and Table 15 for venous samples from the same individuals.

Table 14. Bias with the *smart* CRP system. Capillary whole blood samples

Level	CRP interval comparison method Modular P (mg/L)	n	Outliers	comparison method mean CRP (mg/L)	Bias (95 % C.I.) %
Low	2,0 — 4,3	33*	0	3,0	+42,8 (28,0 — 57,0)
Medium	4,5 — 35,8	34	0	15,2	+10,8 (6,4 — 15,0)
High	36,7 — 302	34**	0	123,0	+13,0 (8,4 — 17,4)
	3,0 — 302	72	0	46,6	+12,7 (9,8 — 15,6)

* 20 samples were <2,0 mg/L in the comparison method.** one sample had a value >316 mg/L. These samples are not part of the calculations.

Table 15. Bias with the *smart* CRP system. Venous whole blood samples

Level	CRP interval comparison method Modular P (mg/L)	n	Outliers	comparison method mean CRP (mg/L)	Bias (95 % C.I.) %
Low	2,0 — 4,3	33*	0	3,0	+36,1(26,0 — 47,0)
Medium	4,5 — 35,8	34	0	15,2	+9,8 (6,1 — 13,4)
High	36,7 — 302	34**	0	123,0	+4,3 (0,6 — 8,1)
	3,0 — 302	72	0	60,7	+9,3 (6,0 — 12,4)

*21 duplicate samples had at least one sample <2,6 mg/L in the *smart* or the comparison method. ** one sample had one value >316 mg/L. These samples are not part of the calculations.

Discussion: The bias is high for the low values. It has, however, no consequences whether a CPR result is 2 or 4 mg/L. In the concentrations between 3 and 302 mg/L in the comparison method the bias is less than 10% for the venous samples and +12,7% for the capillary samples. Some of the positive deviation for the low values may originate from the comparison method, see Table 9. However, the 1st international standard of human C-Reactive Protein 85/506 was measured twice in the *smart* CRP system, and the results suggest that the *smart* CRP system does have a positive bias in the low area whereas there is no bias for the concentrations of 50 mg/L (table 16).

5.3.4. *External quality control with the smart CRP system in hospital laboratory*

Table 16. The 1st international standard of human C-Reactive Protein 85/506 in the *smart* CRP system

Date	N	Assigned value CRP (mg/L)	Measured value CRP (mg/L)	bias %
	2	2	2,9	+45,0
03.07.08	2	10	12,4	+24,5
	2	50	48,2	-3,5

5.3.5. *Internal quality control (ILS control samples) with the smart CRP system*

Two ILS control samples were run every day in duplicate.

Table 17. Internal quality control with ILS control samples from 1st of April to 3rd of July

The *smart* CRP system					
			Repeatability		**Reproducibility**
	N	**mean (mg/L)**	**CV (%)**	**C.I. 95%**	**CV (%)**
Control low	19*	6,0	6,1	4,6—9,3	8,1
Control high	19	93,6	4,9	3,8—7,2	7,7

* one duplicate measurement was excluded. The CRP results were 4,5 and 1,6 mg/L

5.3.6. *The smart CRP system, genuine plasma control material pools made by SKUP*

Table 18. Internal quality control (patient pool) measured from April to July 2008

The *smart* CRP system					
			Repeatability		**Reproducibility**
	N	**mean (mg/L)**	**CV (%)**	**CI 95%**	**CV (%)**
Control 1	16	3,7	11,7	8,0 — 22,6	12,0
Control 2	14	16,3	5,7	3,8 — 11,8	6,9
Control 3	12	165,3	4,1	2,7 — 9,1	3,6

Discussion: Repeatability and reproducibility of the *smart* CRP system fulfilled the goals for the control values at 16 and 165 mg/L. For the control at the low CRP concentration the repeatability was 11,7% which is above the quality goal of 10%; however, the confidence interval included 10%. A CV% of 12% at the concentration of 3,7 mg/L has less clinical importance.

5.3.7. *The accuracy of the smart CRP system*

To evaluate the accuracy of the results on the *smart* CRP system, the agreement between the *smart* CRP system and the comparison method is illustrated in three difference-plots. The plots show the deviations of single measurement results on the *smart* CRP system from the true value, and give a picture of both random and systematic deviation, reflecting the accuracy of *smart*. The deviation is shown for the first measurements of the duplicate results only. Under standardised and optimal conditions two lots of tests were used. The allowed deviation in this evaluation was <±26%.

The accuracy of capillary samples on the *smart* CRP system, with two lots of tests is shown in figure 6 and 7. The accuracy of venous samples on the *smart* CRP system is shown in figure 8 and 9, and the accuracy of capillary and venous samples and the influence of the haematocrit, gender and outpatients/hospitalised patients are shown in figure 10-14. In figure 15-6 the influence of the lot number are visualised.

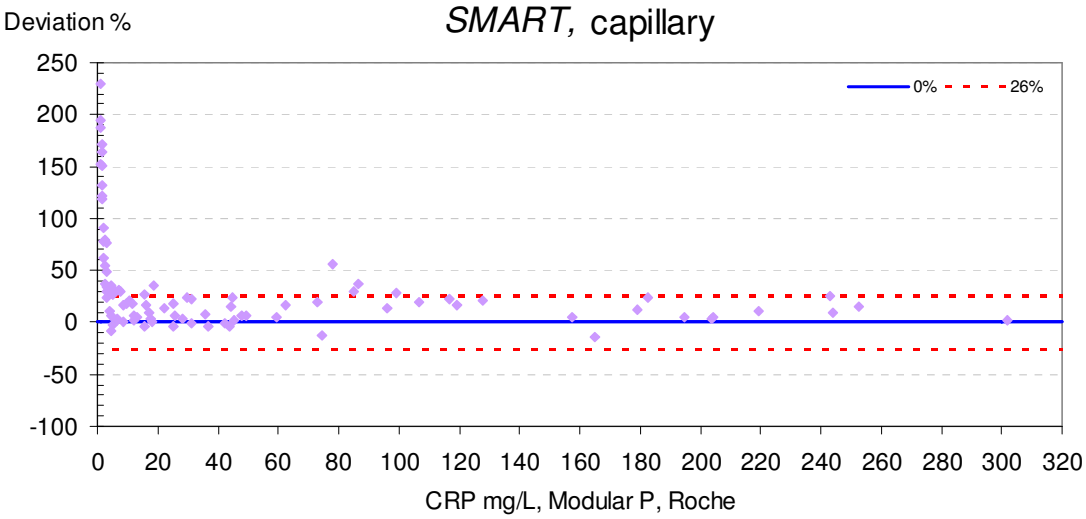


Figure 6. Accuracy of CRP in capillary whole blood samples with the *smart* CRP system under standardised and optimal measuring condition. The x-axis represents the mean value of the duplicate results with the comparison method. The y-axis shows the deviation in percent between the first measurements on the *smart* CRP system and the mean value of the duplicate results with the comparison method. The comparison method had a bias of -3,2 to 4,3%. The figure is not adjusted for this bias.

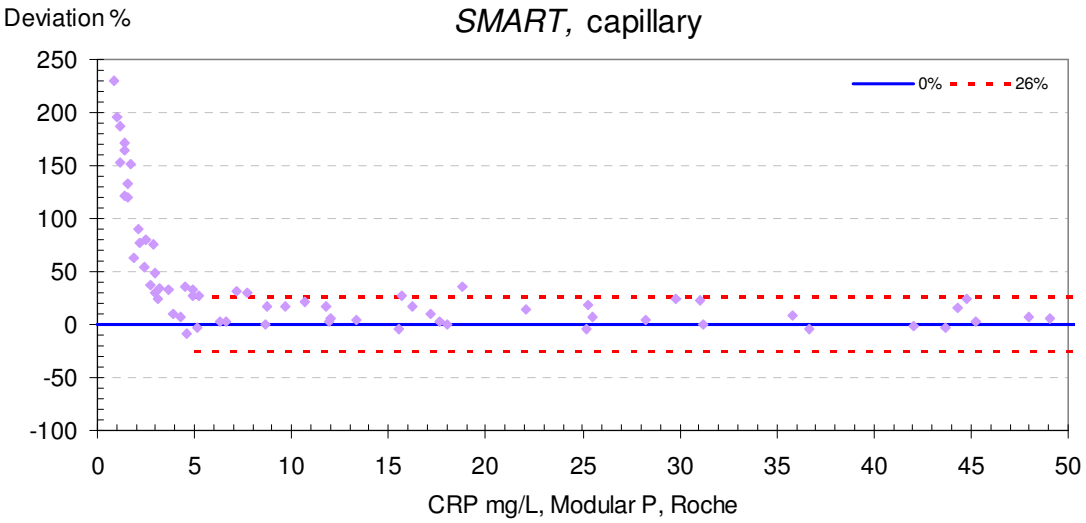


Figure 7. Same as Figure 6, but only for concentration of CRP ≤50 mg/L.

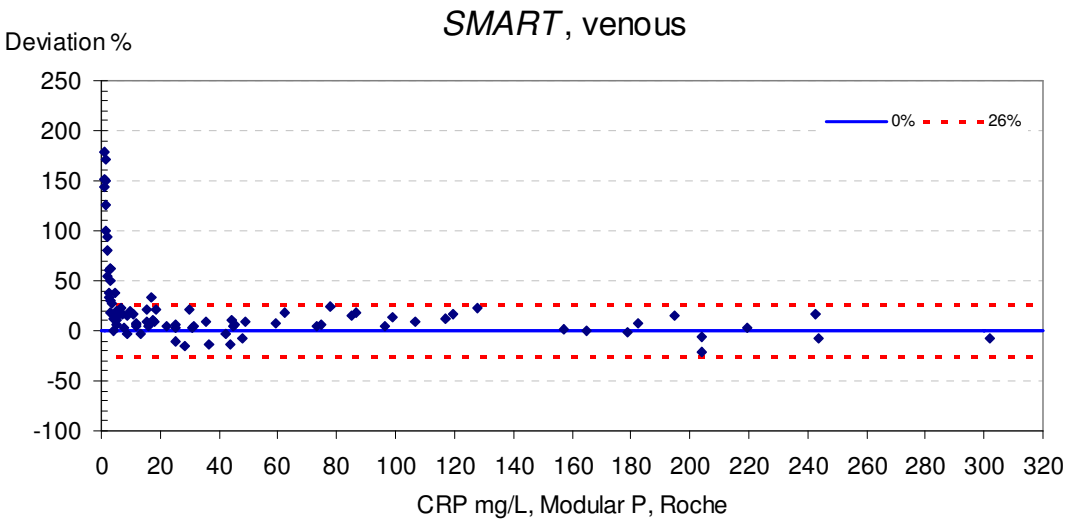


Figure 8. Accuracy in venous whole blood samples under standardised and optimal measuring condition. The x-axis represents the mean value of the duplicate results with the comparison method. The y-axis shows the deviation between the first measurements on the *smart* CRP system and the mean value of the duplicate results with the comparison method.

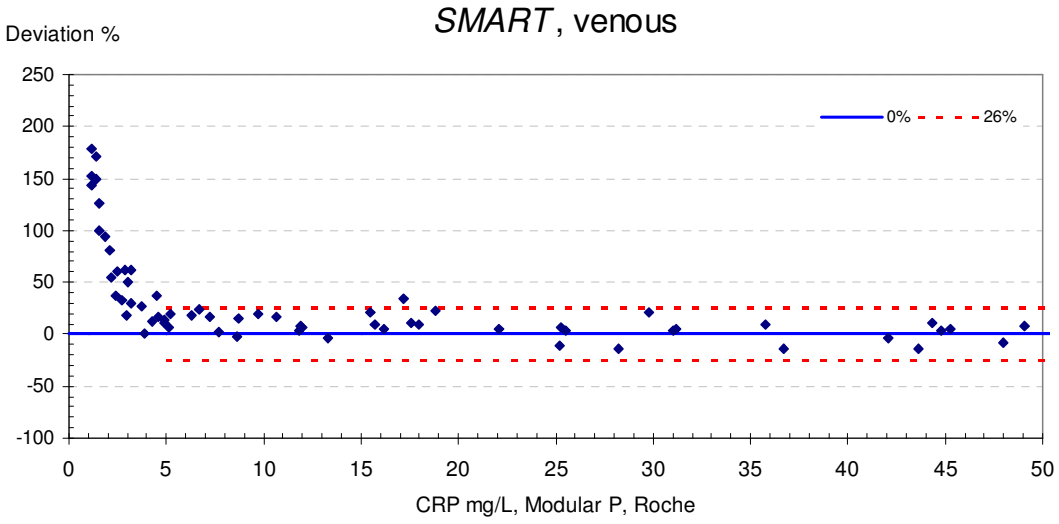


Figure 9. A closer look at some of the results in Figure 8.

Discussion: The venous whole blood samples in the range 4,5 to 36 mg/L have a CV% in duplicates of 5% while the capillary whole blood samples have a CV% of 10%. The capillary results fulfil the goals for Total Error ≤26% from 8 mg/L, while the venous whole blood results fulfil the goals for Total Error from a concentration of 3 mg/L.

5.3.8. *Interference from haematocrit*

Interference from haematocrit was not part of the protocol; however SKUP in Denmark decided to include a haematocrit measurement from all samples. This was done because hospitalised patients with very high CRP concentrations in a university hospital might have low haematocrit. Among the patients in primary care these patients are rare; however the amount of them in the hospital evaluation could theoretically ruin an evaluation and give a false impression of an instrument if it was sensitive to low or high haematocrit concentrations.

In the following the haematocrit issue is elucidated. Especially it is investigated if a deviation of more than 26% was caused by an abnormal haematocrit in the sample.

A possible interference from haematocrit was checked by plotting the haematocrit-values on the X-axis and the deviations from the Comparison Method on the Y-axis in a diagram.

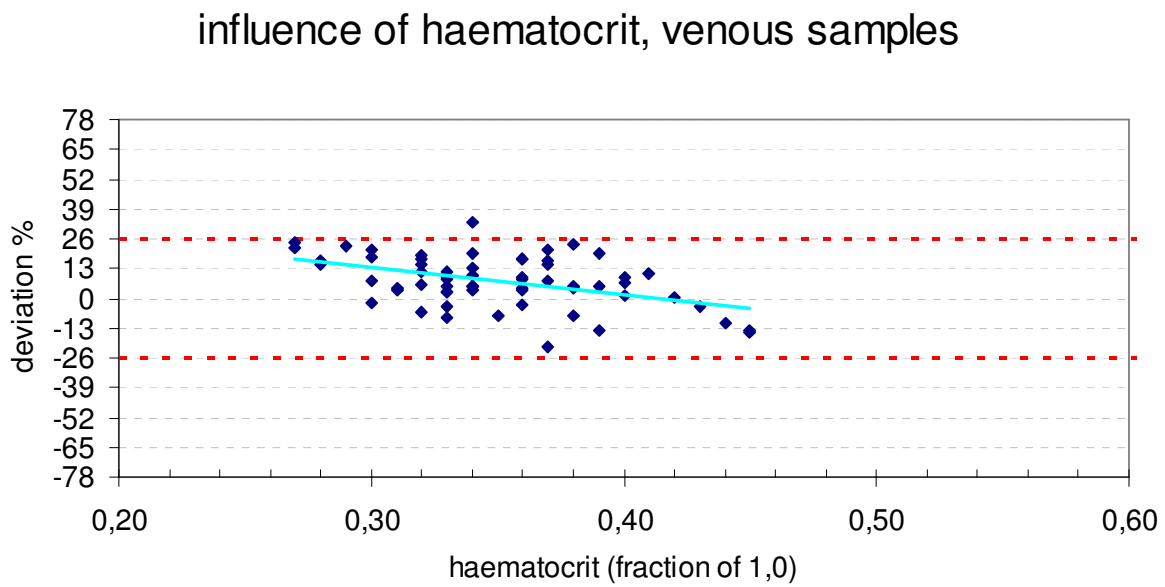


Figure 10. Difference plot. Haematocrit (fraction) and deviation of CRP, venous samples. The diagram shows the deviation of the venous CRP results as a function of haematocrit in the samples with a CRP ≥5 CRP mg/L in the comparison method. X-axis = haematocrit in the sample. Y-axis = ((the first CRP result– mean of the duplicate results with the comparison method,)/ mean of the duplicate results with the comparison method) x 100. Stippled red lines represent the tolerance limits ±26%, n=61

Discussion

It is said in the information about the instrument that all the capillary samples should have a haematocrit of 0,40 and that haematocrit is not supposed to be of importance for the venous samples. If the haematocrit is known the smart instrument can adjust for it. Figure 10 demonstrates that haematocrit (EVF) values between 0,27 to 0,45 do seem to influence the results of the venous samples; however the influence is not enough to exceed the allowed deviation of 26%.

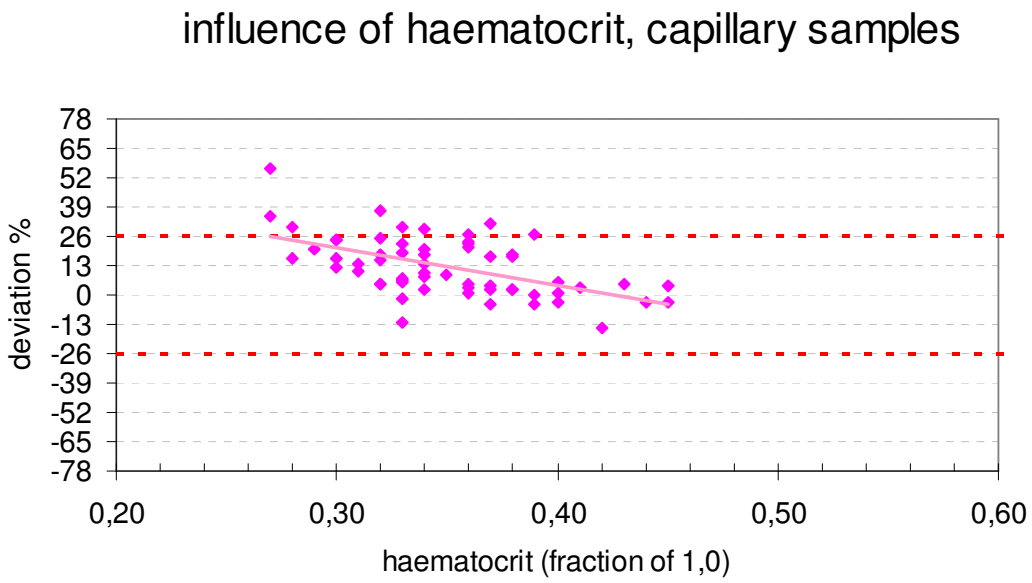


Figure 11. Difference plot. Haematocrit (fraction) and deviation of CRP, capillary samples. The diagram shows the deviations of the capillary CRP results as a function of haematocrit in the samples with a CRP ≥5 CRP mg/L in the comparison method. X-axis = haematocrit in the sample. Y-axis = ((the first CRP result – mean of the duplicate results with the comparison method,)/ mean of the duplicate results with the comparison method) x 100. Stippled red lines represent the tolerance limits ±26%, n=61

Discussion
The comparison laboratory method only gives CRP results of ≥5,0 mg/L. All results lower is given as <5,0 mg/L. Therefore only CRP results of ≥5,0 mg/L are taken in consideration. The *smart* instrument treats all samples as if they had a haematocrit of 0,40 unless the operator feeds the *smart* instrument with another Haematocrit. The haematocrit seems to be of importance for the capillary whole blood samples and not for the corresponding venous whole blood samples. Figure 11 demonstrates the capillary results from the same patients whose corresponding venous results are seen in figure 10.
This indicates that it is the sampling that is of importance for the results.

5.3.9. *Interference from haematocrit in outpatients and hospitalised*
The mean Haematocrit of the patients in the three groups with low, medium and high CRP was 0,387 for the low CRP, 0,368 for the CRP's between 4,5 to 35,8 mg/L and 0,333 for the group with a CRP > 36,7 mg/L.
The mean haematocrit of the 27 outpatients with a CRP >3,0 mg/L was 0,385 while the mean haematocrit of the 45 hospitalised patients with a CRP >3,0 mg/L was 0,335.
A possible interference from haematocrit was checked by plotting the haematocrit-values on the X-axis and the deviations from the Comparison Method on the Y-axis in a diagram. In case of a deviation >26% it is investigated if the deviation was caused by an abnormal haematocrit in the sample or one lot number.

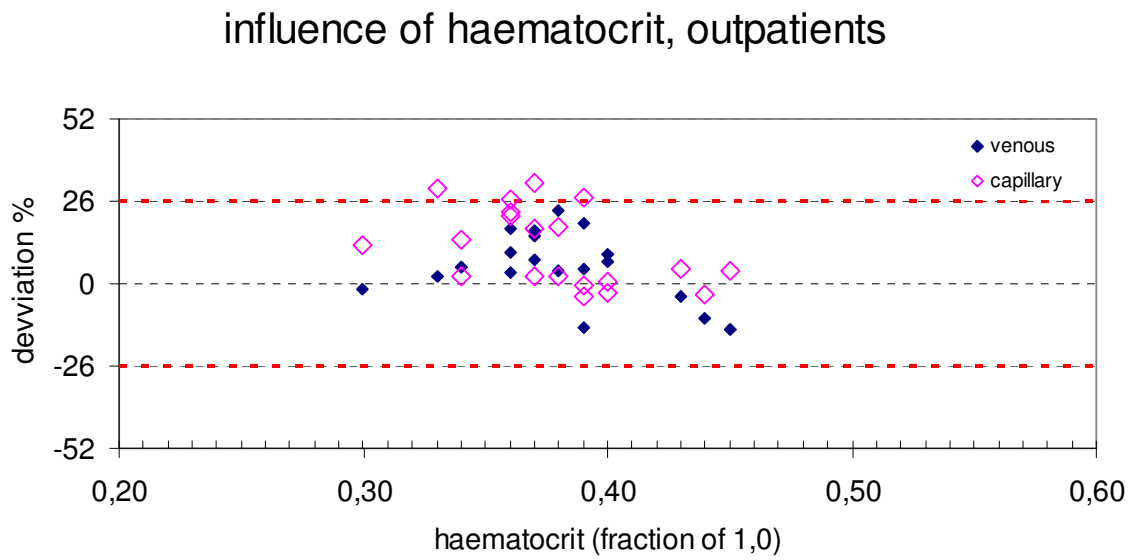


Figure 12. Difference plot. Haematocrit (fraction) and deviation of CRP, capillary and venous samples from the outpatients. The diagram shows the deviations of the CRP results as a function of haematocrit in the samples with a CRP ≥5 CRP mg/L in the comparison method. X-axis = haematocrit in the sample. Y-axis = ((the first CRP result– mean of the duplicate results with the comparison method,)/ mean of the duplicate results with the comparison method) x 100. Stippled red lines represent the tolerance limits ±26%.

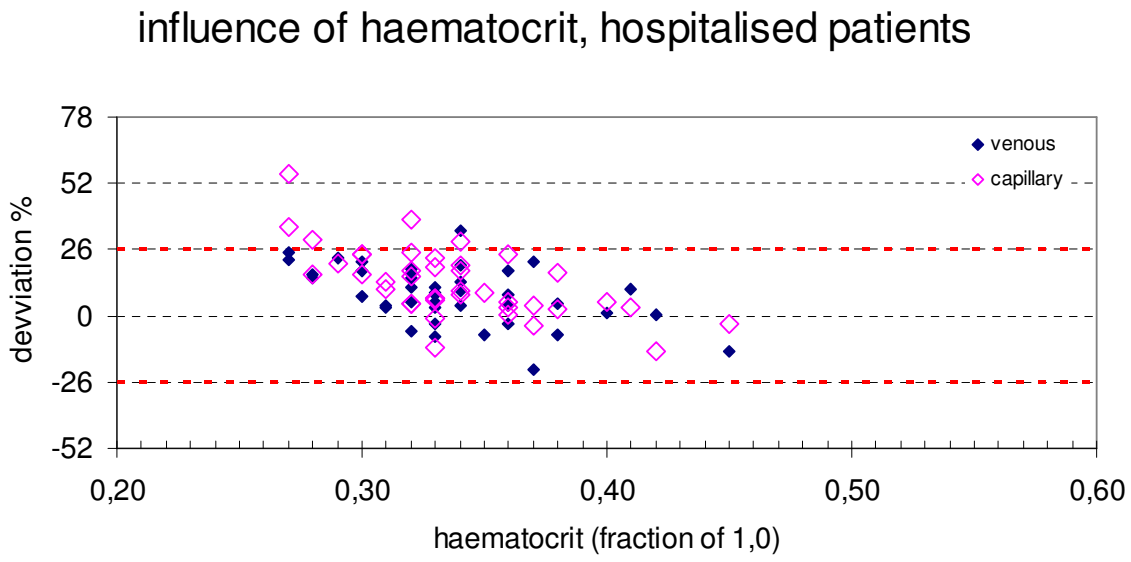


Figure 13. Difference plot. Same as figure 12 except the patients were hospitalised.

Discussion: It is seen that the hospitalised patients have a low haematocrit compared to the outpatients. However; the haematocrit of the patients do not seem to influence on the systematic deviation from the comparison method in capillary samples.

Both the venous and capillary results origin from whole blood samples from the same patients. The lot used for one patient were used in both the capillary and the venous duplicate samples. Thus there is no good reason for the higher deviation in the capillary samples except that it could have some connection to the sampling or to other preanalytical matters.

It was not part of the evaluation to adjust for the haematocrit and recalculate the CRP's because the general practitioners do not normally have a haematocrit value.

5.3.10. *Men and women with CRP >5,0 mg/L*

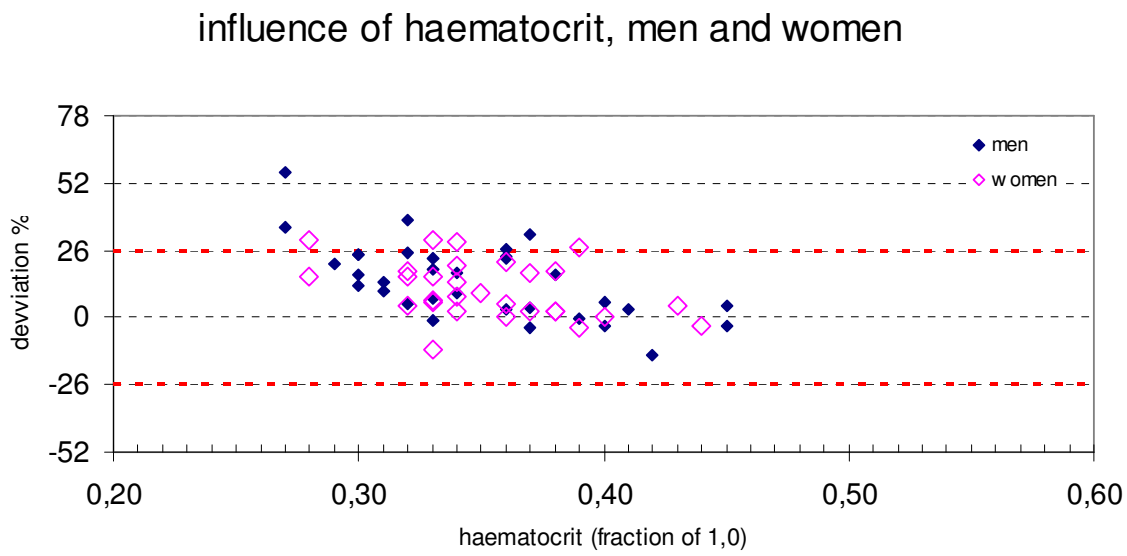


Figure 14. Difference plot. Haematocrit (fraction) and deviation of CRP, capillary samples for men and women. The diagram shows the deviations of the CRP results as a function of haematocrit in the samples with a CRP ≥5 CRP mg/L in the comparison method. X-axis = haematocrit in the sample. Y-axis = ((the first CRP result– mean of the duplicate results with the comparison method,)/ mean of the duplicate results with the comparison method) x 100. Stippled red lines represent the tolerance limits ±26%.

Separate reference intervals for haematocrit are given for men (0,40-0,52) and women (0,35-0,47).
Figure 14 demonstrates that the gender have no influence of the deviation of the CRP concentrations from the comparison method.

5.3.11. *Influence of lot numbers, repeatability and bias*

Some results were hard to explain in the evaluation and it appeared that part of it could depend on the lot numbers used. Therefore imprecision and bias were calculated for the lot numbers used in the hospital laboratory.

Table 19. Repeatability and bias of *smart* in the hospital laboratory with two lots of tests for concentrations >5,0mg/L in the comparison method

		mean CRP-concentration	Capillary samples		Venous samples	
lot	**n**	**mg/L**	**CV%**	**Bias% (95% CI)**	**CV%**	**Bias% (95% CI)**
657055	20	48,4	6,8	7,1 (+2,3 — +11,9)	5,8	3,6 (-1,2 — +8,3)
757051-1	41	74,7	8,1	13,3 (+9,2 — +17,2)	5,0	7,7 (+4,5 — +10,8)
in total	61	66,1	7,7	11,3 (+8,0 — +14,4)	5,3	6,6 (+3,9 — +9,2)

Comments

The results in table 19 demonstrate the repeatability with lot 657055 and lot 757051-1. There was overlap of the confidence intervals and thus there were no difference in repeatability (data not shown) for the two lots.

The bias results show positive bias for the capillary samples in both lot numbers whereas only lot 757051-1 has a positive bias for the venous samples. In the in hospital laboratory evaluation there is significantly higher bias in the 41 results with lot 757051-1 in capillary samples, than in the 20 results with lot 657055 in venous samples because there is no overlap in the confidence intervals.

The analysing was performed by an experienced Biomedical Laboratory Scientist working in the Odense University Hospital.

5.3.12. *Deviation for the two lots, mean of duplicates*

The two lots of tests used in the hospital evaluation are shown in the figure 15 and 16.

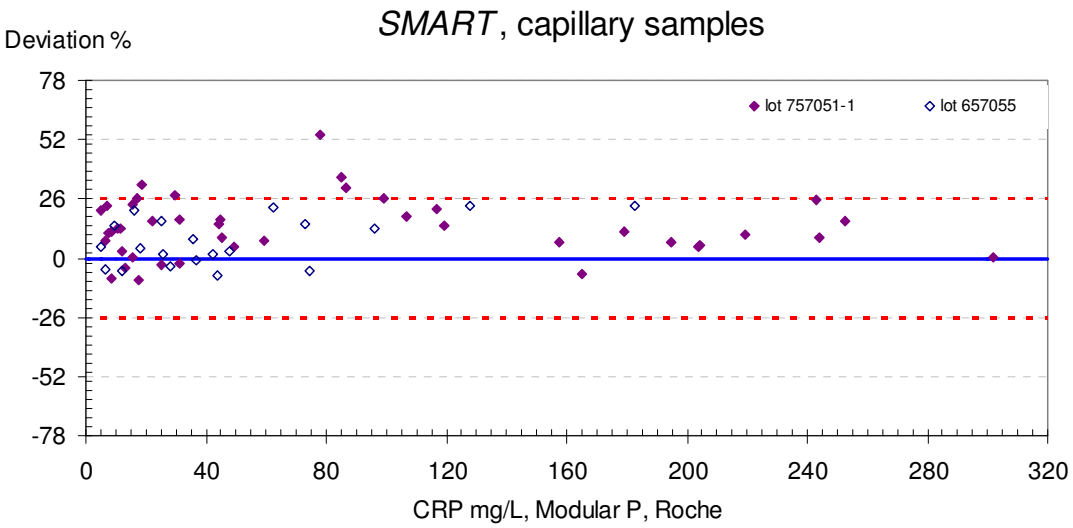


Figure 15. Accuracy of CRP in capillary whole blood samples with the *smart* CRP system under standardised and optimal measuring condition. The x-axis represents the mean value of the duplicate results with the comparison method. The y-axis shows the deviation in percent between the mean measurements on the *smart* CRP system and the mean value of the duplicate results with the comparison method in the CRP interval 5,0 – 300 mg/L, n = 61

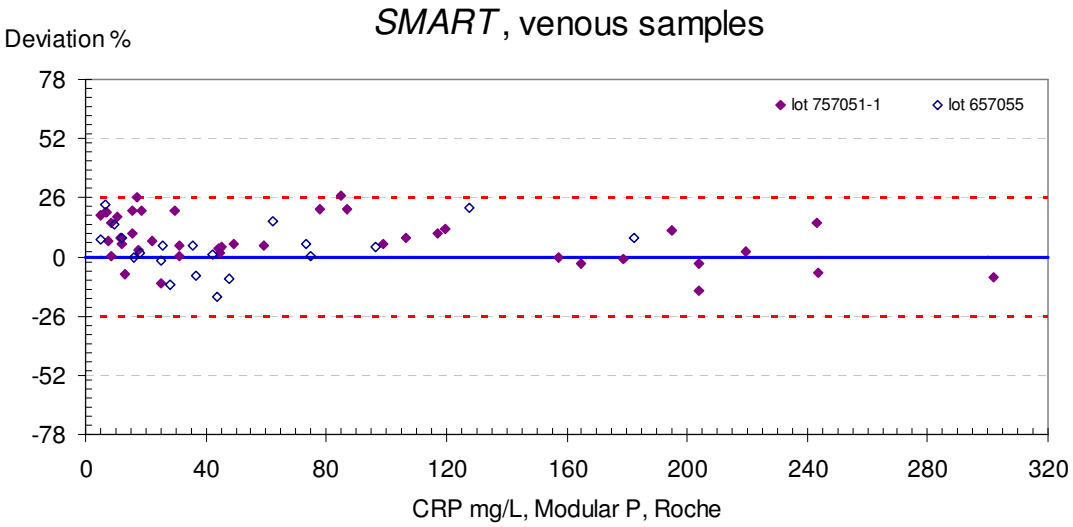


Figure 16. Accuracy of CRP in venous whole blood samples with the *smart* CRP system under standardised and optimal measuring condition. The x-axis represents the mean value of the duplicate results with the comparison method. The y-axis shows the deviation in percent between the mean measurements on the *smart* CRP system and the mean value of the duplicate results with the comparison method in the CRP interval 5,0 – 300 mg/L, n = 61

Comments
Figure 15 and 16 demonstrates the deviation of the two lots of tests. A systematic deviation of one lot does not explain the difference in the same lot between the whole blood measurements in capillary and venous blood.
The comparison method had a bias of -3,2 to 4,3%. This can not explain the deviation either, because the results originate from the same patients.
The lot 657055 was used for the first measurements. However this can not explain the deviation, again because the results originate from the same patients.

5.4. Evaluation of user-friendliness

5.4.1. *Evaluation of the user-friendliness by laboratory-educated staff in a hospital laboratory*

Table 20. Assessment of the information in the manual / insert

Information in manual / insert about:	0 point	1 point	2 point
Well-presented, easy-to-grasp	Unsatisfactory	Less satisfactory	Satisfactory
Specimen collection	Unsatisfactory	Less satisfactory	Satisfactory
Preparations / Pre-analytic/test procedure	Unsatisfactory	Less satisfactory	Satisfactory
Measurement / reading	Unsatisfactory	Less satisfactory	Satisfactory
Measurement principle	Unsatisfactory	Less satisfactory	Satisfactory
Sources of error	Unsatisfactory	Less satisfactory	Satisfactory
Fault-tracing/Troubleshooting	Unsatisfactory	Less satisfactory	Satisfactory
Index	Unsatisfactory	Less satisfactory	Satisfactory
Readability / clarity of presentation	Unsatisfactory	Less satisfactory	Satisfactory
Insert available in Danish, Norwegian, Swedish	Unsatisfactory*	Less satisfactory*	Satisfactory
Rating for information in manual			Satisfactory

* The manual is only available in Swedish and English. The instrument is not yet available in Scandinavia

Table 21. Assessment of Time factors

Time factors	0 point	1 point	2 point
Preparations / Pre-analytical time	>10 min	6 to 10 min.	≤6 min.
Analytical time	>20 min	10 to 20 min.	≤10 min.
Requirements to training	days	>2 hours	0 — 2 hours
Stability of test kit, unopened, (no/package)	≤3 months	>3 — 5 months	>6 months
Storage conditions of test kit, unopened	–20 °C	2 — 8 °C	15 — 30 °C
Rating of time factors			Satisfactory

Table 22. Assessment of Quality control possibilities

Quality Control	0 point	1 point	2 point
Internal quality control	Unsatisfactory	Less satisfactory	Satisfactory
External quality control	Unsatisfactory	Less satisfactory	Satisfactory
Stability of quality control material	≤3 months	>3 — 5 months	>6 months
Storage conditions of control material	-20^{0}C	2 — 8°C	15 — 30°C
Interpretation of the quality control	Unsatisfactory	Less satisfactory	Satisfactory
Rating of quality control			Satisfactory

Table 23. Assessment of Operation facilities

Operation facility	0 point	1 point	2 point
To prepare the test / instrument	Unsatisfactory	Less satisfactory	Satisfactory
To prepare the sample *	Unsatisfactory	Less satisfactory	Satisfactory
Application of specimen	Unsatisfactory	Less satisfactory	Satisfactory
Specimen volume	Unsatisfactory	Less satisfactory	Satisfactory
Number of procedure steps	Unsatisfactory	Less satisfactory	Satisfactory
Interpretation of the test	Very difficult	Difficult	Easy
Sources of errors	Unsatisfactory	Less satisfactory	Satisfactory
Cleaning/maintenance	Unsatisfactory	Less satisfactory	Satisfactory
Hygiene, when using the test	Unsatisfactory	Less satisfactory	Satisfactory
Environmental requirements, waste handling	Poison	Special handling	No special handling
Educational requirements	Lab. technologist	Training course	GP staff
Size and weight of package	Unsatisfactory	Less satisfactory	Satisfactory
Rating of operation			Satisfactory

* Comments: The pipette for sampling is difficult to wipe if blood is on the outer surface.
The cuvette with buffer can be difficult to open

The user-friendliness was rated as satisfactory in the hospital; however, there were remarks to the preparation of the sample. The user-friendliness has only been rated by laboratory educated personal.

6. References

1. National Institute for Biological Standards and Control. Template version: 18 February 2003. Page 1-3, 85/506

2. http://www.westgard.com/biodatabase1.htm visited **visited 1 Aug.** 2008

3. Macy EM, Hayes TE, Tracy RP. Variability in the measurements of C- reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. Clin Chem 1997; 43: 52-58

4. Clark GH, Fraser CG. Biological variation of acute phase proteins. Ann Clin Biochem 1993; 30: 373-376

5. Kvalitetskrav og kvalitetsvurdering for hyppigt udførte klinisk biokemiske og klinisk mikrobiologiske analyser i almen praksis. Konsensus dokument udarbejdet af Laboratorieudvalget under Sygesikringens og PLOs Faglige Udvalg vedr. Almen Praksis i samarbejde med DEKS og Dansk Selskab for Klinisk Biokemi's Videnskabelige Udvalg. Nov 2003. Eller SKUP i Danmarks hjemmeside www.SKUP.dk: Kvalitetskrav til analyser i almen praksis

6. *smart* user manual English. 14.03.07 (vers. A01/0307)

7. http://www.eurolyser.com/_new/products_poc_testparam_crphscrp-en.html. aug 2008

8. Metode validering, Modular P, Roche. Dept BFG, Odense University Hospital

9. International vocabulary of metrology – Basic and general concepts and associated terms, VIM, 3rd edition, JCGM 200:2008.

10. Burnett RW. Accurate estimation of standard deviations for quantitative methods used in clinical chemistry. Clin Chem 1975; 21:1935-8.

7. Attachments

Attachment A Evaluations under the direction of SKUP

Summaries and complete reports from the evaluations are found at www.skup.nu or www.skup.dk

SKUP evaluations from number 51 and further

Evaluation no.	Component	Instrument/testkit	Producer
SKUP/2010/89*	Glucose	FreeStyle Lite	Abbott Laboratories
SKUP/2010/88	HbA1c	*Confidential*	
SKUP/2010/82*	Glucose, protein, blood, leukocytes, nitrite	Medi-Test URYXXON Stick 10 urine test strip and URYXXON Relax urine analyser	Macherey-Nagel GmBH & Co. KG
SKUP/2010/81*	Glucose	mylife PURA	Bionime Corporation
SKUP/2010/80	PT (INR)	INRatio2	Alere Inc.
SKUP/2010/79*	Glucose, protein, blood, leukocytes, nitrite	CombiScreen 5SYS Plus urine test strip and CombiScan 100 urine analyser	Analyticon Biotechnologies AG
SKUP/2010/78	HbA1c	In2it	Bio-Rad
SKUP/2009/76*	HbA1c	*Confidential*	
SKUP/2009/75	Glucose	Contour	Bayer HealthCare
SKUP/2009/74	Glucose[1]	Accu-Chec Mobile	Roche Diagnostics
SKUP/2010/73	Leukocytes	HemoCue WBC	HemoCue AB
SKUP/2008/72	Glucose[1]	*Confidential*	
SKUP/2009/71	Glucose[1]	GlucoMen LX	A. Menarini Diagnostics
SKUP/2008/69*	Strep A	Diaquick Strep A test	Dialab GmbH
SKUP/2010/67	Allergens	*Confidential*	
SKUP/2008/66	Glucose[1]	DANA DiabeCare IISG	SOOIL Developement co. Ltd
SKUP/2008/65	HbA1c	Afinion HbA1c	Axis-Shield PoC AS
SKUP/2007/64	Glucose[1]	FreeStyle Lite	Abbott Laboratories
SKUP/2007/63	Glucose[1]	*Confidential*	
SKUP/2007/62*	Strep A	QuikRead	Orion Diagnostica Oy
SKUP/2008/61	CRP	i-CHROMA	BodiTech Med. Inc.

*A report code followed by an asterisk, indicates evaluations at special request from the supplier, or evaluations that are not complete according to SKUP guidelines, e.g. the part performed by the intended users was not included in the protocol.

[1] Including a user-evaluation among diabetes patients

Grey area – The instrument is not in the Scandinavian market any more

Evaluation no.	Component	Instrument/test kit	Producer
SKUP/2007/60	Glucose[1]	*Confidential*	
SKUP/2007/59	Glucose[1]	Ascensia BREEZE2	Bayer HealthCare
SKUP/2006/58	HbA1c	*Confidential*	
SKUP/2007/57*	PT (INR)	Simple Simon PT	Zafena AB
SKUP/2007/56*	PT (INR)	*Confidential*	
SKUP/2007/55	PT (INR)	CoaguChek XS	Roche Diagnostics
SKUP/2007/54*	Mononucleosis	*Confidential*	
SKUP/2006/53*	Strep A	*Confidential*	
SKUP/2005/52*	Strep A	Clearview Exact Strep A Dipstick	Applied Biotech, Inc.
SKUP/2005/51*	Glucose[1]	FreeStyle	Abbott Laboratories
SKUP/2006/50	Glucose[1]	Glucocard X-Meter	Arkray, Inc.
SKUP/2006/49	Glucose[1]	Precision Xtra Plus	Abbott Laboratories
SKUP/2006/48	Glucose[1]	Accu-Chek Sensor	Roche Diagnostic
SKUP/2006/47	Haematology	Chempaq XBC	Chempaq
SKUP/2005/46*	PT (INR)	*Confidential*	
SKUP/2006/45	Glucose[1]	HemoCue Monitor	HemoCue AB
SKUP/2005/44	Glucose[1]	Accu-Chek Aviva	Roche Diagnostics
SKUP/2005/43	Glucose[1]	Accu-Chek Compact Plus	Roche Diagnostics
SKUP/2005/42*	Strep A	Twister Quick-Check Strep A	ACON laboratories, Inc.
SKUP/2006/41*	HbA1c	*Confidential*	
SKUP/2005/40	Glucose[1]	OneTouch GlucoTouch	LifeScan, Johnson &
SKUP/2005/39	Glucose[1]	OneTouch Ultra	LifeScan, Johnson &

*A report code followed by an asterisk, indicates evaluations at special request from the supplier, or evaluations that are not complete according to SKUP guidelines, e.g. the part performed by the intended users was not included in the protocol.

[1] Including a user-evaluation among diabetes patients

Grey area – The instrument is not in the Scandinavian market any more

Evaluations performed in 1999 – 2004

Evaluation no.	Component	Instrument/test kit	Producer
SKUP/2004/38*	Glucose	GlucoSure Plus	Apex Biotechnology Corp.
SKUP/2004/37*	u-hCG	Quick response u-hCG	Wondsfo Biotech
SKUP/2004/36*	Strep A	Dtec Strep A testcard	UltiMed
SKUP/2004/35*	u-hCG	QuickVue u-hCG	Quidel Corporation
SKUP/2004/34*	u-hCG	RapidVue u-hCG	Quidel Corporation
SKUP/2004/33	PT (INR)	Hemochron Jr. Signature	ITC International Technidyne
SKUP/2004/32*	Strep A	QuickVue In-Line Strep A test	Quidel Corporation
SKUP/2004/31*	PT (INR)	*Confidential*	
SKUP/2004/30	Glucose[1]	Ascensia Contour	Bayer Healthcare
SKUP/2004/29	Haemoglobin	Hemo_Control	EKF-diagnostic
SKUP/2003/28*	Strep A	QuickVue In-Line Strep A test	Quidel Corporation
SKUP/2003/27*	Strep A	QuickVue Dipstick Strep A test	Quidel Corporation
SKUP/2003/26*	HbA1c	*Confidential*	
SKUP/2003/25*	HbA1c	*Confidential*	
SKUP/2003/24*	Strep A	OSOM Strep A test	GenZyme, General Diag.
SKUP/2002/23*	Haematology with CRP	ABX Micros CRP	ABX Diagnostics
SKUP/2002/22	Glucose[1]	GlucoMen Glycó	Menarini Diagnostics
SKUP/2002/21	Glucose[1]	FreeStyle	TheraSense Inc.
SKUP/2002/20	Glucose	HemoCue 201	HemoCue AB
SKUP/2002/19*	PT(INR)	Reagents and calibrators	
SKUP/2002/18	Urine–Albumin	HemoCue	HemoCue AB
SKUP/2001/17	Haemoglobin	Biotest Hb	Biotest Medizin-technik GmbH
SKUP/2001/16*	Urine test strip	Aution Sticks and PocketChem UA	Arkray Factory Inc.
SKUP/2001/15*	Glucose	GlucoSure	Apex Biotechnology Corp.
SKUP/2001/14	Glucose	Precision Xtra	Medisense
SKUP/2001/13	SR	Microsed SR-system	ELECTA-LAB
SKUP/2001/12	CRP	QuikRead CRP	Orion
SKUP/2000/11	PT(INR)	ProTime	ITC International Technidyne Corp
SKUP/2000/10	PT(INR)	AvoSure PT	Avocet Medical Inc.
SKUP/2000/9	PT(INR)	Rapidpoint Coag	
SKUP/2000/8*	PT(INR)	Thrombotest/Thrombotrack	Axis-Shield
SKUP/2000/7	PT(INR)	CoaguChek S	Roche Diagnostics
SKUP/2000/6	Haematology	Sysmex KX-21	Sysmex Medical Electronics Co
SKUP/2000/5	Glucose	Accu-Chek Plus	Roche Diagnostics
SKUP/1999/4	HbA1c	DCA 2000	Bayer
SKUP/1999/3	HbA1c	NycoCard HbA1c	Axis-Shield PoC AS
SKUP/1999/2*	Glucose	Precision QID/Precision Plus Electrode, whole blood calibration	Medisense
SKUP/1999/1	Glucose	Precision G/Precision Plus Electrode, plasma calibration	Medisense

*A report code followed by an asterisk, indicates evaluations at special request from the supplier, or evaluations that are not complete according to SKUP guidelines, e.g. the part performed by the intended users was not included in the protocol.

[1] Including a user-evaluation among diabetes patients

Grey area – The instrument is not in the Scandinavian market any more

Attachment B Raw data

Raw data, (blue and red illustrate two instruments)

Attachment C Control material from ILS

Controls from ILS				Lot.nr.			
Kontrol	Dato	Smart	Smart	Device	Modular	Modular	Comments
Lav	01.04.08	5.8	6.1	657055			
Høj	01.04.08	90.2	105.5	657055			
Lav	02.04.08	6.4	5.9	657055	4.8	4.9	
Høj	02.04.08	87.9	87.5	657055	77.1	77.5	
Lav	08.04.08	6.2	5.4	657055			
Høj	08.04.08	87.3	86.5	657055			
Lav	09.04.08	5.8	4.5	657055			Begge kurver ujævne
Høj	09.04.08	87.2	89.6	657055			
Lav	21.04.08	6.2	6.1	657055	4.0	4.6	
Høj	21.04.08	83.1	84.4	657055	77.5	78.0	
Lav	21.05.08	5.8	6.2	757051-1			
Høj	21.05.08	102.0	101.9	757051-1			
Lav	22.05.08	6.4	6.1	757051-1			
Høj	22.05.08	89.4	77.7	757051-1			
Lav	23.05.08	5.9	6.0	757051-1			
Høj	23.05.08	108.2	104.5	757051-1			
Lav	19.05.08	6.1	6.0	757051-1			
Høj	19.05.08	102.6	101.0	757051-1			
Lav	28.05.08	7.1	7.7	757051-1			
Høj	28.05.08	90.5	92.6	757051-1			
Lav	04.06.08	4.5	1.6	757051-1			1. best: kurve ujævn, 2. best: kurve grim.
Høj	04.06.08	86.0	91.2	757051-1			
Lav	09.06.08	5.9	6.0	757051-1			
Høj	09.06.08	93.3	89.4	757051-1			
Lav	11.06.08	6.5	6.1	757051-1			
Høj	11.06.08	95.4	97.6	757051-1			
Lav	23.06.08	6.4	6.5	757051-1			
Høj	23.06.08	97.3	92.8	757051-1			
Lav	24.06.08	5.4	6.1	757051-1			
Høj	24.06.08	96.5	96.9	757051-1			
Lav	25.06.08	6.1	6.2	757051-1			
Høj	25.06.08	96.8	92.0	757051-1			
Lav	30.06.08	5.8	5.6	757051-1			
Høj	30.06.08	91.9	112.0	757051-1			
Lav	01.07.08	6.2	5.9	757051-1	4.3	5.0	
Høj	01.07.08	91.2	95.2	757051-1	74.1	74.8	
Lav	03.07.08	6.4	6.3	757051-1	4.0	4.2	
Høj	03.07.08	91.1	93.2	757051-1	74.0	73.9	

There are two Modular P instruments in the hospital laboratory. The numbers with white background are run in one Modular P instrument, the coloured numbers in another Modular P.

Raw data internal control

Low, Medium and High Pools from patients

date	Smart	Smart	lot
01.04.2008	4,2	4	657055
02.04.2008	3,8	3,7	657055
21.04.2008	3,6	4,5	657055
19.05.08	4	3	757051-1
23.05.08	3,1	3,4	757051-1
09.06.08	4	3,5	757051-1
24.06.08	3,6	3,4	757051-1
01.07.08	3,7	2,9	757051-1
01.04.2008	14,9	15,8	657055
08.04.2008	17,5	16,9	657055
21.05.08	15,7	14,7	757051-1
28.05.08	17,4	15	757051-1
11.06.08	18,3	16,5	757051-1
25.06.08	17,8	16,6	757051-1
03.07.08	15,7	15,9	757051-1
01.04.2008	168,5	166,7	657055
09.04.2008	167,1	164,6	657055
22.05.08	166,7	160,9	757051-1
04.06.08	158,8	180,8	757051-1
23.06.08	163,3	163,5	757051-1
30.06.08	165,2	157,7	757051-1

Attachment D Technical specifications

a) Name of the analyser	*Smart* 546
Physical dimensions	*140mm (W) x 240mm(H) x 140mm (D)*
Manufacturer (with address)	Eurolyser Diagnostica GmbH Bayernstrasse 11 a 5020 Salzburg Österrike
Distributor (with address)	Danmark ILS-Laboratories Scandinavia AB Kortebovägen 6 553 11 Jönköping, Sweden
	Norge ILS-Laboratories Scandinavia AB Kortebovägen 6 553 11 Jönköping, Sweden
	Sverige ILS-Laboratories Scandinavia AB Kortebovägen 6 553 11 Jönköping

b) Analysis menu, sample materials and volume of the analysis

Component	Sample materials	Volume of the analysis
CRP	Whole blood, Serum or Plasma	5 µL

c) Analysis principles (reference to the instruction manual)

Parameter	Principle
CRP	Kinetic determination of the concentration of CRP by photometric measurement at 546 nm of antigen-antibody reaction between antibodies to human CRP bound to polystyrene particles and CRP present in the sample

d) Area of analysis

Component	Area of analysis: infection	Unit
whole blood-CRP	2,6-316	mg/L
Serum/Plasma-CRP	1,6-180	mg/L

		Point-of-care, in-vitro diagnostic for treatment monitoring

e) Time for analysis per component (precisely stated)

Component	Pre-analysis time (with an explanation)	Analysis time
CRP	*1-2 minutes*	*3 minutes*

f) Calibration

Is calibration possible?	*yes*
How often?	*The kit (32 tests) contain a calibration card with a calibration function with 10 points.* *The user can perform a one point calibration if required.*
Who does the calibration?	*The calibration function is made by the manufacturer.* *The user can perform a one point calibration*

g) Recommended maintenance

Maintenance	How often?
None	*n.a.*

h) Control materials

Is control material available (from the producer or other companies)?	*Yes, control material with two levels from the producer. It is possible to use other control materials.*

Picture of ***SMART***

Attachment E The measuring steps (from the manufacturer)

1. Preparing the system


the RFID card

⇒


open the casette

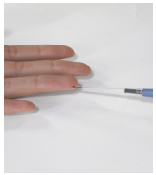
⇒


place the cuvette in the base

⇒


press symbol on screen

2. Capillary samples or EDTA whole blood


5µL blood

or


5µL from EDTA micro tube

or


5µL from EDTA tube

⇒


5µL sample to cuvette

⇒


lid on

3. Serum, Li-Heparin plasma or EDTA plasma


5µL serum/plasma

or


5 µL serum/plasma from microtube

⇒


5µL sample to cuvette

⇒


lid on

4. Before analysing with the *smart* instrument

Identity: write
Sample: Choose '*serum/plasma' or ' Whole Blood'*

EVF haematokrit: 0,40 (unless informations about EVF is given manually


apply the cuvette and press 'start'