qLabs ElectroMeter Q-3 Plus Owren (dry)

A system for measurement of P—Prothrombin time (INR)
manufactured by Micropoint Bioscience, Inc.

Report from the evaluation SKUP/2021/123

organised by SKUP at the request of Micropoint Bioscience, Inc.

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Attachments with raw data are included only in the copy to Micropoint Bioscience, Inc.

1. Summary

Background
The qLabs Q-3 Plus PT (INR) Owren (dry) system is an in vitro diagnostic device for quantitative measurement of Prothrombin Time International Normalized Ratio (PT (INR)). The product is intended for professional use. The sample material is fresh capillary blood. The system is produced by Micropoint Bioscience, Inc. The system was launched into the Scandinavian market September 2019. The SKUP evaluation was carried out late September 2020 to early February 2021 at the request of Micropoint Bioscience, Inc. in USA.

The aim of the evaluation
The aim of the evaluation was to assess the analytical quality and user-friendliness of qLabs Q-3 Plus PT (INR) Owren (dry), when used under real-life conditions by intended users in primary health care.

Materials and methods
In four primary health care centres (PHCCs), fresh capillary blood samples from a total of 186 patients, all stable on vitamin-K-antagonist treatment, were measured on qLabs Q-3 Plus PT (INR) Owren (dry) (modified Owren method). Citrate plasma samples from the same patients were analysed on a comparison method (Equalis calibrated Owren's method with Owren's PT reagent from Medirox AB on Sysmex CS5100, Siemens Healthineers). 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) ≤5,0 % and for accuracy that ≥95 % of the results should be within ±20,0 % of the results from 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
At PT (INR) level <2,5 the CV achieved in the different PHCCs varied between 4,1 and 5,7 %, and at PT (INR) level ≥2,5 the CV varied between 3,6 and 5,1 %. When the results from all PHCCs were merged per level, the CV achieved at PT (INR) level <2,5 was 4,9 % and at PT (INR) level ≥2,5 it was 4,5 %. An average bias of 0,2 INR was shown between qLabs Q-3 Plus PT (INR) Owren (dry) and the comparison method. For accuracy, 90 % of the results were within the allowable deviation limits. Of the 178 results included, seven deviated more than 25 % from the results of the comparison method, which corresponds to 4 %. The user-friendliness was rated as satisfactory for all topics but the instrument itself, which was rated as intermediate.

Conclusion
The quality goal for repeatability was fulfilled. The quality goal for accuracy was not fulfilled. The quality goal for user-friendliness was not fulfilled.

Comments from Micropoint Bioscience, Inc.
A letter with comments from Micropoint Bioscience, Inc. is attached to the report.

*This summary is also published in Danish, Norwegian and Swedish at www.skup.org.***Feil! Hyperkoblingsreferansen er ugyldig.**

2. Abbreviations and Acronyms

APS	Antiphospholipid syndrome
BLS	Biomedical Laboratory Scientist
C-NPU	Committee on Nomenclature, Properties and Units
CI	Confidence Interval
CLSI	Clinical and Laboratory Standards Institute
CV	Coefficient of Variation
DEKS	Danish Institute of External Quality Assurance for Laboratories in Health Care
EQA	External Quality Assessment
Equalis	External quality assessment in laboratory medicine in Sweden
ISO	International Organization for Standardization
IRP	International Reference Preparation
Noklus	Norwegian Organization for Quality Improvement of Laboratory Examinations
PHCC	Primary health care centre
PT (INR)	Prothrombin Time International Normalized Ratio
RBT	Rabbit Brain Thromboplastin
SKUP	Scandinavian evaluation of laboratory equipment for primary health care
Swedac	Swedish board for accreditation and conformity assessment
WHO	World Health Organization

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 strips from separate and time-spread productions. Some evaluation codes are followed by an asterisk (*), indicating an evaluation with a more specific objective. The asterisk is explained on the front page of these protocols and reports.

3.2. Background for the evaluation

The qLabs Q-3 Plus PT (INR) Owren (dry) system is an in vitro diagnostic device for the quantitative measurement of Prothrombin Time International Normalized Ratio (PT (INR)). The product is intended for professional use. The sample material is fresh capillary blood. The qLabs Q-3 Plus PT (INR) Owren (dry) system is an upgraded version of the Q-2 Plus system, which was evaluated by SKUP in 2017. The system is produced by Micropoint Bioscience, Inc., and was launched into the Scandinavian market September 2019. The SKUP evaluation was carried out late September 2020 to early February 2021 at the request of Micropoint Bioscience in USA.

3.3. The aim of the evaluation

The aim of the evaluation was to assess the analytical quality and user-friendliness of qLabs Q-3 Plus PT (INR) Owren (dry) when used under real-life conditions by intended users in primary health care.

3.4. The model for the evaluation of qLabs Q-3 Plus PT (INR) Owren (dry)

SKUP evaluations for quantitative methods are based upon the fundamental guidelines in a book concerning evaluations of laboratory equipment in primary health care [1]. SKUP's model for PT (INR) evaluations (figure 1) focus on point-of-care device performance among the intended users in primary health care. Four primary health care centres (PHCCs) participated in the evaluation and the evaluation document the quality of the system under real-life conditions.

The evaluation of qLabs Q-3 Plus PT (INR) Owren (dry) for measurement of PT (INR) in fresh capillary whole blood samples included:

- Examination of the analytical quality (precision and accuracy) in the hands of intended users
- Evaluation of the user-friendliness of qLabs Q-3 Plus PT (INR) Owren (dry) 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.

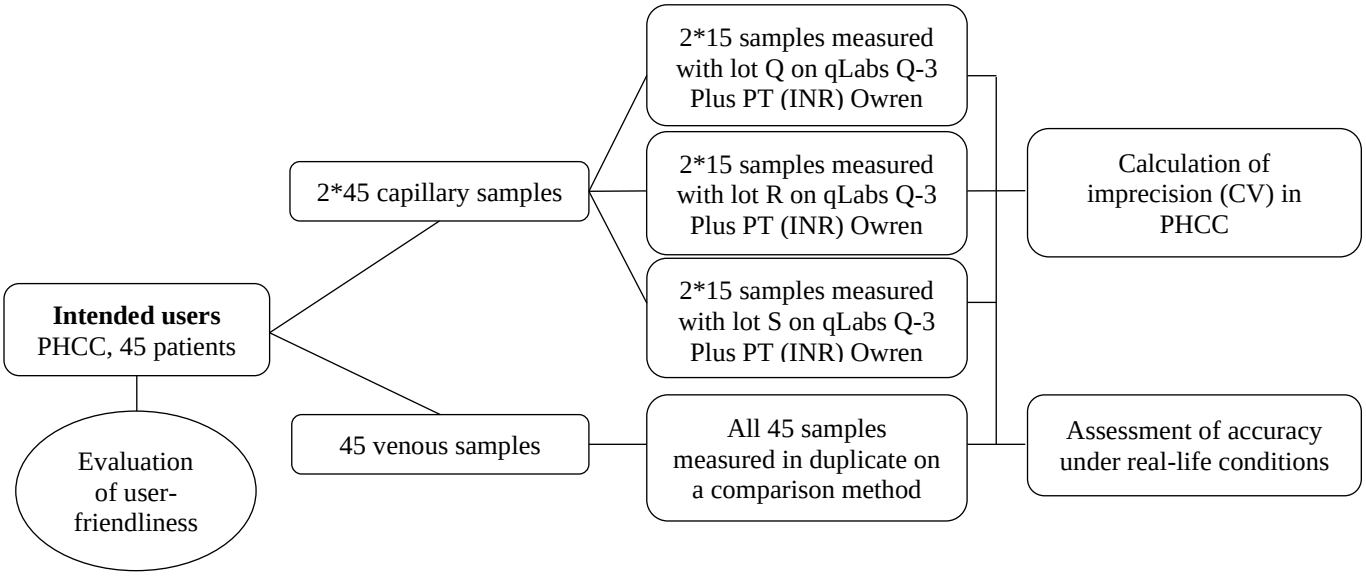

Figure 1. Flowchart illustrating the model for the evaluation of qLabs Q-3 Plus PT (INR) Owren (dry) in capillary samples. The same procedure was performed in four different PHCCs. Note, more patients were recruited if any results were <1,5 or >4,5 INR, since these results were not included in the calculations (see 4.3.1.).

4. Quality goals

4.1. Analytical quality

To SKUPs' knowledge, there is no international standard for evaluation of point of care test instruments for PT (INR) in primary health care. Recently Clinical and Laboratory Standards Institute (CLSI) published a guideline to ensure reliable results for point of care testing of coagulation intended for producers and laboratories [2]. The analytical quality goals for the determination of PT (INR) are a repeatability (coefficient of variation, CV) of ≤7 % for producer studies and ≤10 % for laboratory validation, and for accuracy that at least 95 % of the individual PT (INR) results shall be within ±0,4 INR of the average measured values of the reference measurement procedure at PT (INR) level <2,0 or within ±20 % at PT (INR) level 2,0 – 4,5.

The International Organization for Standardization (ISO) 17593:2007 standard [3] gives requirements for accuracy for self-testing systems of oral anticoagulant therapy. There is no performance criterion for imprecision in the standard. In SKUP's opinion, the quality goals for accuracy in the standard, ±30 % for 90 % of the PT (INR) results in the therapeutic range 2 – 4,5 INR, is too tolerant.

Setting quality goals based on biological variation is an acknowledged method [4,5]. It is recommended that analytical imprecision (repeatability, CV) should be less than, or equal to, half the intra-individual biological variation. For systems used for monitoring, the analytical performance should aim at low imprecision compared to the within-subject biological variation. According to Kjeldsen *et al.* [6], the "in-treatment within-subject biological variation" of PT (INR) is 10,1 %. Van den Besselaar *et al*. [7] recommend a CV ≤4,5 %, while Lassen *et al.* [8] recommend a CV ≤4,7 %.

A committee appointed by the National Ministry of Health in Denmark has specified the requirements of analytical quality for PT (INR) for instruments used in primary health care [9] with an imprecision ≤5 % and a bias ≤6 %. For PT (INR) measurements in primary health care in Norway, Trydal *et al.* [10] recommend a CV ≤5 % in the therapeutic range and a minimum of 95 % of the results within ±20 % compared with the hospital method. In Sweden, External quality assessment in laboratory medicine in Sweden (Equalis) advisory group for coagulation has set up a quality goal for accuracy of ±12 % from a consensus value for external quality assessment (EQA) of PT (INR) for the Owren method [11].

SKUP recommends that PT (INR) devices used in primary health care should achieve a repeatability CV of ≤5,0 %. SKUP has not set a separate goal for bias, but a bias of 5 % is used to calculate a quality goal for allowable deviation according to the model below. In all method evaluations and comparisons, the imprecision of the comparison method must also be taken into account. SKUP allows an imprecision of the comparison method up to 3 %. In addition, SKUP has estimated the contribution of inter-laboratory-variation to 3 % and the contribution of a probable matrix effect to 5 % to account for sample specific errors when comparing two methods with different method principles.

$$\text{Allowable deviation} = |\pm\text{bias}| + 1{,}65 \times \sqrt{CV^2_{\text{test method}} + CV^2_{\text{comparison method}} + CV^2_{\text{between lab}} + CV^2_{\text{matrix}}}$$

$$= 5 + 1{,}65 \times \sqrt{25+9+9+25} = \pm 18{,}6\ \% \approx \pm 20\ \%$$

4.2. User-friendliness

The evaluation of user-friendliness was carried out by asking the evaluating persons in the PHCCs to fill in a questionnaire, see section 6.4.

Technical errors

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

4.3. Principles for the assessments

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

4.3.1. Assessment of the analytical quality

The analytical results were assessed according to pre-set quality goals. Results from the comparison method <1,5 INR and >4,5 INR are shown in difference plots and discussed, but are not included in any of the calculations as the reliability of INR values below 1,5 and above 4,5 is unknown [12].

Precision

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

Table 1. The rating of precision

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

Bias

SKUP does not set separate quality goals for bias. The confidence interval (CI) of the measured bias is used for deciding if a difference between the evaluated method and the comparison method is statistically significant (two-tailed test, 5 % significance level). The bias will also be discussed in connection with the accuracy.

Bias with three lots of test strips
Separate lot calculations are not performed. The results achieved with the three lots are included in the assessment of accuracy in the difference plot. If distinct differences between the lots appear, this will be pointed out and discussed.

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

4.3.2. Assessment of the user-friendliness

The user-friendliness is assessed according to the answers and comments given in the questionnaire (see section 6.4). 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. Possible technical errors include errors regarding reading of data matrix, errors in detection of the cuvettes and electronic errors. User errors are not included in the calculation.

4.4. SKUP's quality goals in this evaluation

As agreed upon when the protocol was drawn up, the results from the evaluation of qLabs Q-3 Plus PT (INR) Owren (dry) are assessed against the following quality goals:

Repeatability (CV)..... ≤5,0 %

Allowable deviation of the individual result
from the comparison method result*..……..... ≤±20,0 %

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

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

*If more than 1 % of the results deviate more than ±25,0 %, this is pointed out and discussed.

5. Materials and methods

5.1. Definition of the measurand

The measurement systems intend to measure the ratio of the tissue factor induced coagulation time in a sample to the normal coagulation time in plasma expressed as INR. For the evaluated system the sample material is fresh capillary whole blood and for the comparison method the sample material is venous sodium citrate plasma. The results are traceable to World Health Organization (WHO) international reference standard rTF/16 and are expressed without unit. The Committee on Nomenclature, Properties and Units (C-NPU) systematically describes clinical laboratory measurands in a database [13]. The NPU codes related to the measurand in this evaluation are NPU60231 for the evaluated method and NPU01685 for the comparison method (Owren method). In this report the term PT (INR) will be used for the measurand.

5.2. The evaluated measurement system qLabs Q-3 Plus PT (INR) Owren (dry)

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

qLabs Q-3 Plus PT (INR) test system consist of qLabs® ElectroMeter Q-3 Plus (figure 2) and qLabs® PT (INR) Owren (Dry) test strip. The system is designed to provide quantitative measurements of PT (INR) in fresh whole blood capillary samples. The product is intended for professional healthcare providers in the management of patients treated with warfarin, an oral vitamin K antagonist.

Figure 2. qLabs ElectroMeter Q-3 Plus.

The qLabs PT (INR) Owren (Dry) test strip in this evaluation is a modification of the original qLabs PT (INR) test strips. The reagent coated on the modified test strip contains fibrinogen and factor V. Thus, the modified qLabs PT (INR) test strip is only sensitive to the coagulation factors II, VII and X, and less sensitive to deficiency of fibrinogen than original qLabs PT (INR) test strip.

The qLabs ElectroMeter Q-3 Plus automatically detects the insertion of a qLabs PT (INR) test strip and heats the test strip to a pre-set operating temperature. After a drop of blood is applied to the test strip, the capillary channels carry the blood to a reaction zone, where the blood is mixed with pre-printed recombinant human thromboplastin reagent. The reaction zone contains a pair of metallic electrodes, to which a constant voltage is applied. As the coagulation of the blood proceeds, the current monitored across the two electrodes changes. The qLabs ElectroMeter Q-3 Plus detects the change of the current, which is directly proportional to the coagulation events in the reaction zone, and thereby determines the PT (INR).

To ensure reliability for each test, the qLabs PT-INR Owren (Dry) test performs an "On-Board" internal quality control test which consists of multiple independent tests on meter, test strip and sampling for test. These multiple tests include checks for ambient temperature out of range, meter malfunction due to defect electrical components, defect test strip and insufficient sample addition. If any one of the above internal checks fails an error code is displayed and the patient test is aborted.

A strip code printed on the pouch of every test strip contains information about calibration and type of test. The same information is contained in a USB chip that has to be inserted into the reader before performing the test.

The manufacturer produces the qLabs PT-INR Liquid Control Kit, QS-1-CL Pro, with Level 1 in the normal range and Level 2 in the therapeutic range. The PT (INR) values of qLabs PT-INR Liquid Controls are specified per control lot.

Conditions (such as Lupus) that produce anti-phospholipid antibodies may interfere with the ability of blood to clot through the normal means. The qLabs test strip contains heparin neutralizing reagent which renders the qLabs test insensitive to the presence of up to 1,0 kIE/L (U/mL) of heparin in sample.

For technical details about the qLabs Q-3 Plus PT (INR) Owren (dry), see table 2. For more information about the qLabs Q-3 Plus PT (INR) Owren (dry) 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 qLabs Q-3 Plus PT (INR) Owren (dry)	
Sample material	Fresh capillary blood
Sample volume	10 µL
Measuring time	30 – 100 seconds
Measuring range	0,5 – 8,0 INR
Haematocrit	30 – 55 %
Storage capacity	500 results
Electrical power supply	100 – 240 V

5.3. The selected comparison method

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

5.3.1. The selected comparison method in this evaluation

The selected comparison method in this evaluation was the routine method for PT(INR) in the laboratory of clinical chemistry at the University hospital, Linköping, Sweden, hereafter called "the comparison method". The method is accredited according to ISO 15189 (2012) by the Swedish board for accreditation and conformity assessment (Swedac).

Instrument:	Sysmex CS5100
Reagent:	Owren's PT, Medirox AB
Principle:	Owren's method, rabbit brain thromboplastin (RBT) and adsorbed bovine plasma
Traceability:	WHO's manual tilt tube technique and the reference thromboplastin WHO IRP 67/40 (international reference preparation), through RBT 90 [14-16]
Calibrators:	Two-point calibration with Equalis INR-calibrators

Internal analytical quality control
Internal analytical quality control samples, two levels (Multi control, normal and abnormal, Medirox AB), was measured daily on the comparison method.

External analytical quality control
The hospital laboratory participates in Equalis EQA scheme for PT (INR) (Owren method) with two levels in ten rounds per year. The assigned value for PT (INR) is based on the consensus value from 110 participants (2020).

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 venous citrated samples from the patients.

Trueness
The Norwegian and Swedish hospital laboratories use PT (INR) calibrators from Equalis. In Denmark, the hospital laboratories use PT (INR) calibrators from Danish Institute of External Quality Assurance for Laboratories in Health Care (DEKS). The calibrating systems from Equalis and DEKS are different with respect to the production of the materials as well as to the way the PT (INR) target values are assigned.

- PT (INR) calibrators from Equalis were analysed as samples on the comparison method on two occasions (halfway through and in the end) of the evaluation. The calibrator material is a pool of citrated anti-coagulated freeze-dried plasma of human origin (Swedish donors). The certified values are traceable to an internationally agreed reference measurement procedure (WHO's manual tilt tube technique) and the reference thromboplastin WHO IRP 67/40, through RBT/90 [14-16]. The procedures used to assign values are described in several publications and documents [17-19].

- PT (INR) calibrators from DEKS were analysed as samples on the comparison method on three occasions (at the start, in the middle, and in the end) of the evaluation to get a link to the Danish PT (INR) level. The calibration materials from DEKS are freshly frozen pooled citrate-plasmas, which serve as national reference plasmas in Denmark. The DEKS calibration is a three point's calibration with a normal, therapeutic and high PT (INR). The assigned values come from three Nordic expert laboratories.

The trueness of the comparison method was also verified with EQA results.

5.4. The evaluation

5.4.1. Planning of the evaluation

Inquiry about an evaluation
Micropoint Biocience, Inc. via Cédric Sire, Sales and Marketing Director in Europe, applied to SKUP in March 2019 for an evaluation of qLabs Q-3 Plus PT (INR) Owren (dry).

Protocol, arrangements and contract
In January 2020, the protocol for the evaluation was approved, and Micropoint Bioscience, Inc. and SKUP signed a contract for the evaluation. Biomedical laboratory scientists (BLSs) at the laboratory of clinical chemistry at the University hospital, Linköping, Sweden were assigned to do the practical work with the comparison method. Four PHCCs; Mjölby vårdcentral, Vadstena vårdcentral, Skänninge vårdcentral and Kungsgatans vårdcentral from Östergötland county agreed to represent the intended users in this evaluation.

Training
Maria Medbrant and Karolin Eriksson from LumiraDx, the local supplier, demonstrated qLabs Q-3 Plus PT (INR) Owren (dry) for the PHCCs. The training in the PHCCs reflected the training usually given to the end-users. Micropoint Bioscience, Inc. and LumiraDx were not allowed to contact or supervise the evaluators during the evaluation period.

5.4.2. Evaluation sites and persons involved

The practical work was carried out during September 2020 to February 2021[1]. The laboratory of clinical chemistry at the University hospital in Linköping was responsible for the comparison method and has approximately 90 employees.

Five BLSs participated in the evaluation from PHCC1, from PHCC2 one BLS, one biologist and one chemist participated, from PHCC3 two BLSs and one biologist participated and from PHCC4 three BLSs participated. Some of these persons occasionally performed sampling and analysis in some of the other PHCCs, as they were substitutes from time to time. All PHCCs take both venous and capillary samples in routine.

[1]Delayed start-up due to strained health care at the beginning of the Covid-19 pandemic.

5.4.3. The evaluation procedure for intended users

Internal analytical quality control

Internal analytical quality control samples for qLabs Q-3 Plus PT (INR) Owren (dry) (qLabs PT-INR liquid controls, Micropoint Bioscience, Inc.) was measured each evaluation day on qLabs Q-3 Plus PT (INR) Owren (dry); one level per day alternating between the two levels. The reproducibility (CV) as achieved with the quality control material was calculated.

Recruitment of patients

Patients, age 18 years or older, coming into the PHCCs for PT (INR) measurements were asked if they were willing to donate two capillary and one venous blood samples for the evaluation. All participants were stable on vitamin-K-antagonist treatment. Patients with known antiphospholipid syndrome (APS) were not recruited. Participation was voluntary and verbal consent was considered sufficient based on national regulations.

Handling of the samples and measurements

Fresh capillary blood samples were used for measurement with the qLabs Q-3 Plus PT (INR) Owren (dry) system. All measurements were performed in duplicate, i.e., two separate fingersticks. The puncture site was disinfected with alcohol pads and the area dried completely before sampling.

For the capillary sampling, disposable lancing devices (Safety-Lanzette, Sarstedt) with penetrating depth 1,6 mm and blade width 1,5 mm were used. The first drop of capillary blood was wiped off, then a big drop of blood was allowed to form before using a capillary (microcap, 20 µL) to transfer blood to the test strip. The sample was measured immediately on qLabs Q-3 Plus PT (INR) Owren (dry) and in accordance with the instructions from the manufacturer. The complete sampling and measurement procedure were repeated immediately for the second measurement on the qLabs Q-3 Plus PT (INR) Owren (dry). In case of error codes, the test was repeated if possible until a result was obtained. Three lot numbers of test strips were used at each site during the course of the evaluation.

Samples for the comparison method were obtained from venous puncture and collected into 2,7 mL BD Vacutainer tubes with sodium citrate (3,2 %). The tubes were inverted 10 times to ensure thorough mixing and kept at room temperature until transported to the hospital laboratory later the same day or the day after. In the laboratory the samples were centrifuged at 10 minutes at 2500 g. The citrate plasma samples were measured in duplicate for PT (INR) on the comparison method within 48 hours after sampling.

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 180 patient samples measured in duplicate by intended users. At the end of the evaluation, a total of 186 patients were enrolled.
PHCC1 recruited 50 patients (SKUP ID 101 – 150), PHCC2 recruited 45 patients (SKUP ID 201 – 245), PHCC3 recruited 46 patients (SKUP ID 301 – 346), and PHCC4 recruited 45 patients (SKUP ID 401 – 445). The results from the comparison method covered the PT (INR) interval 1,06 – 4,71. The evaluation was carried out using three lot numbers of test strips, and each PHCC was alternating between the lot numbers. An account of the number of samples not included in the calculations, is given below.

Missing results

- On three occasions there were no results from an internal quality control the same day as analysis of patient samples. The results from the patient samples these days were still included in the calculations.
- ID 304 had only a single result on qLabs Q-3 Plus PT (INR) Owren (dry). The single value was included in the calculation of bias and the assessment of accuracy.

Omitted results

- ID 109, 110 and 111 were omitted since that qLabs Q-3 Plus PT (INR) Owren (dry) instrument was wrong calibrated, the instrument was replaced.
- ID 123 and ID 328 had mean results of the comparison method <1,5 INR. The results from these IDs were not included in any calculations but the accuracies are shown in the difference plots for information only.
- ID 112 had a mean result of the comparison method >4,5 INR. The results from this ID were not included in any calculations but the accuracy is shown in the difference plots for information only.

Excluded results (statistical outliers)

Statistical outliers in SKUP evaluations are detected by the criterion promoted by Burnett [20].

- ID 323 and ID 403; the results from the comparison method were classified as outliers according to Burnett's model in the calculation of repeatability. When using highly precise methods, differences are more easily pointed out as statistically outliers. The removal of these IDs did not affect the final result of the evaluation. The results were not included in the calculation of bias and the assessment of accuracy, but the results from qLabs Q-3 Plus PT (INR) Owren (dry) were included in the calculation of repeatability.

Recorded error codes, technical errors and failed measurements

There was one error code E004 of insufficient amount of sample. There were six reports on failed calculation of the PT (INR) value, whereof five showed error code E007.20. There were 11 error code E010, concerning timing of application of sample, some of them were reported by the PHCCs to have appeared although the sample was applied within the given time of 120 seconds. There was one error code, E018, concerning the test strip being placed incorrectly and one error code, E034, was not explained in the manual. Finally, it was one report on a defect test strip,

which did not absorb the blood. This adds up to 21 error reports, six of them were considered preanalytical (E004, E018, two of the E007.20 due to applied air bubble and due to very cold hands of the patient, one of the E010 where the test strip application field was not placed correct, and the defect test strip). The rest of them were considered as technical errors. There were 372 original samples (2*186) and 15 technical errors. This amounts to 4,0 % technical errors. In addition, a software bug in the instruments first delivered to the sites caused problems. The bug was quickly fixed and the PHCCs received updated instruments. This is not included as a technical error. The SKUP recommendation of a fraction of ≤2 % tests wasted due to technical errors was not 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 (Multi control, normal and abnormal, Medirox AB), two levels, were within the allowable control limits (data not shown).

6.2.2. The precision of the comparison method

Duplicate measurements of each citrate plasma patient sample were performed on the comparison method. The results were checked to meet the imposed condition for using formula 1 in attachment 5. There were no systematic differences pointed out between the paired measurements (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 two 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 PT (INR) measured in citrate plasma samples.

Level	n*	Excluded results (statistical outliers)	Mean value PT (INR)	CV (90% CI), %
<2,5	87	0	2,2	0,4 (0,4 – 0,5)
≥2,5	93	2**	2,9	0,5 (0,4 – 0,5)

*The given number of results (n) were counted before the exclusion of statistical outliers. Mean and CV were calculated after the exclusion of statistical outliers. An account of the number of samples is given in section 6.1.
**ID 323 and ID 403 were statistical outliers according to Burnett's model [20] in the calculation of repeatability and therefore excluded.

Discussion

The CV for the comparison method was 0,4 % for PT (INR) level <2,5 and 0,5 % for PT (INR) level ≥2,5.

6.2.3. The trueness of the comparison method

To demonstrate the trueness of the comparison method, calibrators from Equalis (table 4) and DEKS (table 5) were analysed on the comparison method. The trueness was confirmed with EQA results in the evaluation period. The calibrators from Equalis were analysed as samples on two different occasions: halfway through and at the end of the evaluation. The calibrators from DEKS

were analysed on three different occasions: at start-up, halfway through and at the end of the evaluation.

Table 4. Equalis PT (INR) calibrators measured on the comparison method.

Material	Assigned value PT (INR) (uncertainty)	Date	n	Mean value PT (INR) Sysmex CS5100
Equalis INR calibrator Low Lot 37	**1,07** (0,98 – 1,16)	20-10-22	5	1,07
		20-12-17	5	1,07
Equalis INR calibrator High Lot 38	**3,01** (2,75 – 3,27)	20-10-22	5	3,07
		20-12-17	5	3,06
Equalis INR control Lot 39	**2,42** (2,21 – 2,63)	20-10-22	5	2,49
		20-12-17	5	2,47

Table 5. DEKS PT (INR) calibrators measured on the comparison method.

Material	Assigned value PT (INR) (uncertainty)	Date	n	Mean value PT (INR) Sysmex CS5100
DEKS INR calibrator Normal Lot 13-05	**1,00** (0,98 – 1,03)	20-09-24	5	0,99
		20-10-22	5	0,98
		20-12-17	5	0,98
DEKS INR calibrator Therapeutic Lot 04-18	**2,35** (2,30 – 2,40)	20-09-24	5	2,42
		20-10-22	5	2,44
		20-12-17	5	2,43
DEKS INR calibrator High Lot 14-08	**3,50** (3,40 – 3,60)	20-09-24	5	3,41
		20-10-22	5	3,45
		20-12-17	5	3,45

Equalis EQA program for PT (INR) in hospital laboratories comprise ten rounds per year, with two levels per round. The robust mean value from 110 participants (2020) is used as consensus. The quality goal is a result within ±12 % of the consensus value. The laboratory participated in all five rounds during the evaluation period, showing results within -4,5 – 3,5 %.

Discussion

The results from the comparison method matched the assigned Equalis calibrator values, see table 4. The results from the comparison method matched the assigned DEKS calibrator values at levels normal and high, but the results were slightly high at the therapeutic level at all three occasions, see table 5. The trueness of the comparison method was verified with EQA results, being within the quality goal for every external quality control analysed. The comparison method gave results in accordance with other hospital laboratories using PT (INR) calibrators from Equalis.

6.3. Analytical quality of qLabs Q-3 Plus PT (INR) Owren (dry) achieved by intended users

The results below reflect the analytical quality of qLabs Q-3 Plus PT (INR) Owren (dry) under real-life conditions in the hands of intended users in PHCCs.

6.3.1. Internal analytical quality control

All results from the internal analytical quality control (qLabs PT-INR liquid controls, Micropoint Bioscience, Inc.), two levels, were within the allowable control limits (data not shown). The reproducibility (CV) achieved with the internal analytical quality control lot 3052K1202 was 1,8 % (n=42) for level 1 and 2,0 % (n=41) for level 2. The CVs for the other two control lots used (3052K1203 and 3052L1101) are not presented due to few results, n<8, and thus high degree of uncertainty. The daily control was analysed on the same lot of test strip (Q, R, S) used for patient samples during that day. Raw data is attached for the requesting company only, see attachment 7.

6.3.2. The precision of qLabs Q-3 Plus PT (INR) Owren (dry)

Duplicate measurements of fresh capillary blood samples from each patient were performed on qLabs Q-3 Plus PT (INR) Owren (dry). The results were checked visually to meet the imposed condition for using formula 1 in attachment 5.

The precision is presented as repeatability (CV). The CV with a 90 % CI is shown in table 7. The results were sorted and divided into two levels according to the mean of the results of qLabs Q-3 Plus PT (INR) Owren (dry). Raw data is attached for the requesting company only, see attachment 8.

Table 7. Repeatability (CV) of qLabs Q-3 Plus PT (INR) Owren (dry) for PT (INR) measured in capillary blood samples. Results achieved by intended users.

Place	PT (INR) level qLabs Q-3 Plus PT (INR) Owren (dry)	n*	Excluded results (statistical outliers)	Mean value PT (INR)	CV (90% CI), %
PHCC 1	<2,5	17	0	2,2	5,7 (4,4-8,0)
	≥2,5	28	0	3,0	3,6 (2,9-4,6)
PHCC 2	<2,5	13	0	2,3	4,1 (3,1-6,1)
	≥2,5	32	0	3,0	5,0 (4,2-6,3)
PHCC 3	<2,5	15	0	2,3	4,6 (3,5-6,7)
	≥2,5	29	0	2,9	5,1 (4,2-6,5)
PHCC 4	<2,5	11	0	2,2	5,3 (3,9-8,4)
	≥2,5	34	0	3,1	4,0 (3,3-5,0)
PHCC All	<2,5	56	0	2,2	4,9 (4,3-5,9)
	≥2,5	123	0	3,0	4,5 (4,1-5,0)

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

Discussion
The CV achieved by intended users in the different PHCCs varied between 4,1 and 5,7 % at PT (INR) level <2,5, and between 3,6 and 5,1 % at PT (INR) level ≥2,5.

PHCCs 2 and 3 had lower, but not statistically significant lower, CV than the quality goal at PT (INR) level <2,5. PHCCs 1 and 4 had higher, but not statistically higher, CV than the quality goal at PT (INR level <2,5. PHCCs 1 and 4 had statistically significantly lower CV than the quality goal at PT (INR) level ≥2,5. At the same level, PHCC 2 had lower, but not statistically significant lower, CV than the quality goal and PHCC 3 had higher, but not statistically higher, CV than the quality goal. Since the results, per level, had overlapping CIs, the results from all PHCCs were merged into CV All. Then the CV was lower than the quality goal for both levels, but only statistically significant lower for PT (INR) level ≥2,5.

Conclusion
When the PHCCs results were merged per level to CV All, the quality goal for repeatability was fulfilled.

6.3.3. The bias of QLabs Q-3 Plus PT (INR) Owren (dry)

The mean deviation (bias) of qLabs Q-3 Plus PT (INR) Owren (dry) results from the comparison method was calculated. The bias is presented with a 95 % CI in table 8. The results were sorted and divided into two 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 8. Bias of qLabs Q-3 Plus PT (INR) Owren (dry) for PT (INR) measured in capillary blood samples. Results achieved by intended users.

Place	PT (INR) level Comparison method	n*	Excluded results (statistical outliers)	Mean value PT (INR) Comparison method	Mean value PT (INR) qLabs Q-3 Plus PT (INR) Owren (dry)	Bias (95 % CI) PT (INR)	Bias, %
PHCC 1	<2,5	23	0	2,1	2,3	0,14 (0,05 — 0,22)	6,4
	≥2,5	21	0	3,0	3,1	0,09 (-0,01 — 0,19)	3,2
PHCC 2	<2,5	26	0	2,2	2,5	0,29 (0,21 — 0,36)	13,0
	≥2,5	19	0	2,9	3,3	0,39 (0,24 — 0,53)	13,3
PHCC 3	<2,5	21	0	2,2	2,4	0,17 (0,08 — 0,26)	7,6
	≥2,5	23	0	2,9	3,0	0,10 (-0,01 — 0,22)	3,6
PHCC 4	<2,5	17	0	2,2	2,4	0,23 (0,13 — 0,34)	10,8
	≥2,5	27	0	2,9	3,2	0,23 (0,13 — 0,33)	7,8

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

Discussion
qLabs Q-3 Plus PT (INR) Owren (dry) gave systematically higher results than the comparison method. The bias was statistically significant for all PHCCs at PT (INR) level <2,5 and for two of the PHCCs at PT (INR) level ≥2,5. The bias shown in PHCC 2 was higher than in the other PHCCs. The average bias was 0,21 INR for level <2,5 and 0,20 INR for level ≥2,5 in the four PHCCs.

6.3.4. The accuracy of qLabs Q-3 Plus PT (INR) Owren (dry)

To evaluate the accuracy of PT (INR) results on qLabs Q-3 Plus PT (INR) Owren (dry), the agreement between qLabs Q-3 Plus PT (INR) Owren (dry) and the comparison method is illustrated in difference plots (figure 3). The limits for the allowable deviation according to the quality goal (±20,0 %) are shown with sloped stippled lines. All the first measurements from qLabs Q-3 Plus PT (INR) Owren (dry) are included in the plot. The plot illustrates both random and systematic errors, reflecting the total measuring error in the qLabs Q-3 Plus PT (INR) Owren (dry) results. Raw data is attached for the requesting company only, see attachment 6 and 8.

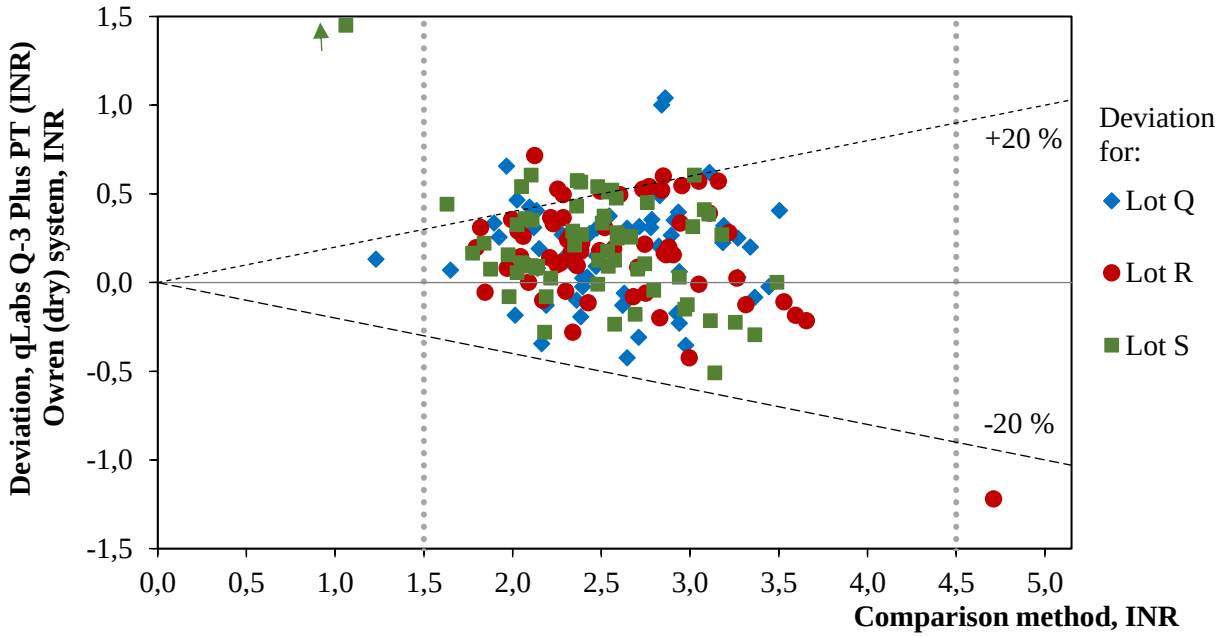

Figure 3a. Accuracy of PT (INR) results on qLabs Q-3 Plus PT (INR) Owren (dry) achieved by intended users presented per lot number. The x-axis represents the mean PT (INR) result of the comparison method. The y-axis represents the PT (INR) deviation of the first capillary measurement on qLabs Q-3 Plus PT (INR) Owren (dry) from the mean result of the corresponding sample of the comparison method. The different lot numbers are illustrated with the symbols ♦ (Lot Q), ● (Lot R), and ■ (Lot S). Sloped stippled lines represent the allowable deviation limits of ±20,0 %. The vertical stippled lines at INR 1,5 and 4,5 illustrates the cut off values for calculations. The arrow marks one result outside the plot; ID 206. Number of results totally (n) = 181. Number of results included in the calculation of accuracy (n) = 178. An account of the number of samples is given in section 6.1.

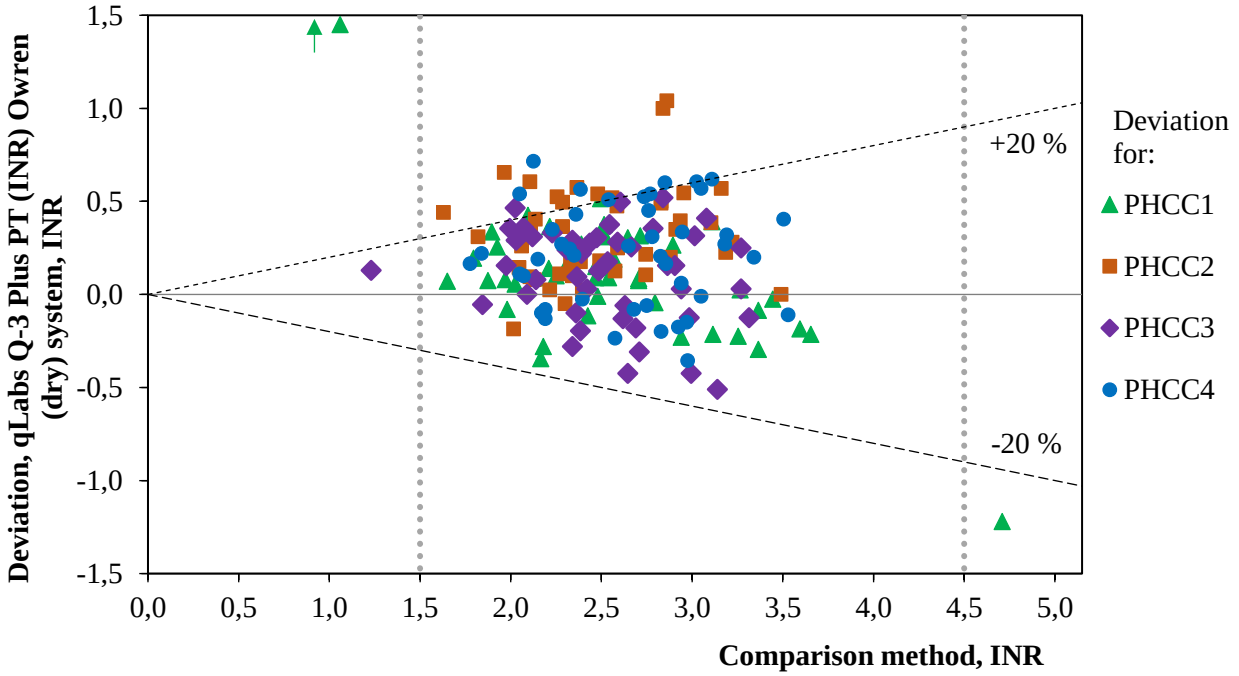

Figure 3b. Accuracy of PT (INR) results on qLabs Q-3 Plus PT (INR) Owren (dry) achieved by intended users presented per PHCC. The x-axis represents the mean PT (INR) result of the comparison method. The y-axis represents the PT (INR) deviation of the first capillary measurement on qLabs Q-3 Plus PT (INR) Owren (dry) from the mean result of the corresponding sample of the comparison method. The different PHCCs are illustrated with the symbols ▲ (PHCC1), ■ (PHCC2), ♦ (PHCC3), and ● (PHCC4). Sloped stippled lines represent the allowable deviation limits of ±20,0 %. The vertical stippled lines at INR 1,5 and 4,5 illustrates the cut off values for calculations. The arrow marks one result outside the plot; ID 206. Number of results totally (n) = 181. Number of results included in the calculation of accuracy (n) = 178. An account of the number of samples is given in section 6.1.

Discussion

As shown in figure 3a and b, the PT (INR) results from qLabs Q-3 Plus PT (INR) Owren (dry) tend to be higher than the results from the comparison method, for all three lot numbers as well as PHCCs 2 and 4, which is consistent with the calculated bias. Samples where the results from the comparison method are <1,5 INR (2 results) as well as >4,5 INR (1 result) are included in the plots but excluded from all calculations (see section 4.3.1.). One of these results (ID 328) is consistent between the methods, while one showed considerably lower result (ID 112, –26 %) and one showed considerable higher result (ID 123, 137 %) with qLabs Q-3 Plus PT (INR) Owren (dry) than the comparison method.

160 of 178 results were inside the limits for allowable deviation of ±20,0 % corresponding to 90 % within the limits. Of the 178 results, seven deviated >25 %, which corresponds to 4 %; all were higher than the comparison method and the large deviations were not lot dependent. Five of these results originated from PHCC 2, which is consistent with the bias being the highest from this site. In two of the four PHCCs, more than 95% of the results were within the allowable deviation limits. The quality goal for individual results within the limits ±20,0 % is ≥95 %.

Conclusion

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

6.4. Evaluation of user-friendliness

6.4.1. Questionnaire to the evaluators

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

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

The questionnaire is divided into four 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; five BLSs.
PHCC2; one BLS, one biologist and one chemist.
PHCC3; two BLSs and one biologist.
PHCC4; three BLSs.

Table A. Rating of operation facilities

Topic	Rating	Rating	Rating	Rating	Option
To prepare the test / instrument	**S,S,I[1],S**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
To prepare the sample	**S,S,I[2],S**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Application of specimen	**I[3],S,I[3],I[3]**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Specimen volume	**S,I[4],I[4],I[4]**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Number of procedure step	**S,I[5],S,S**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Instrument / test design	**S,S,I[6],S**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Reading of the test result	**E,E,E,E**	**Easy**	Intermediate	Difficult	No opinion
Sources of errors	**S,S,I[7],S**	**Satisfactory**	**Intermediate**	Unsatisfactory	No opinion
Cleaning / Maintenance	**S,S,S,S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
Hygiene, when using the test	**S,S,S,S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
Size and weight of package	**S,S,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	**I**	No precautions	**Sorted waste**	Special precautions	
Intended users	**S**	**Health care personnel or patients**	Laboratory experience	Biomedical laboratory scientists	
Total rating by SKUP			**Intermediate**		

[1]A bit unclear what to do when. Would have been helpful with a signal (like flashing light) to indicate the procedure.
[2]No comment given by the evaluating site.
[3]Two of the PHCCs thought it was difficult to use a microcap capillary (although they were used to them) in the application of the patient sample, e.g., bubbles easily appeared. Three of the PHCCs thought the method to apply capillary samples directly from a hanging drop was too difficult.
[4]It is needed a quite large volume. The right amount of blood was difficult to achieve even though using microcap capillaries.
[5]It was a lot of scanning steps.
[6]It was difficult to get the test strip out of the package. It was a lot of waste.
[7]It was difficult to understand the error messages while sitting with a patient during analysis.

Additional positive comments (Table A): The instrument was easy to use. Good to have readily prepared reagents and internal quality controls and that they could be stored at room temperature. Easy to use the test strips. Good that it was stated on the display whether an internal quality control was approved or not. The station could be used both to charge the reader as well as print results, which was perceived practical.

Additional negative comments (Table A): It would be good to have a signal when enough sample has been applied. It would have been good if the instrument could read the lot number on the test strip instead of scanning. It would have been convenient to have the test strips in an airtight jar instead of single packed. The On button was a bit tricky to handle, many times it had to be pressed hard and several times before the reader started. The Bluetooth connection was interrupted on several occasions. There is no application for venous samples coming in anti-coagulated tubes from other sites (such as elderly care homes).

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

Topic	Rating	Rating	Rating	Rating	Option
Table of contents / Index	**S,S,S,S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
Preparations / Pre-analytic procedure	**S,N,S,S**	**Satisfactory**	Intermediate	Unsatisfactory	**No opinion**
Specimen collection	**S,N,I[1],S**	**Satisfactory**	**Intermediate**	Unsatisfactory	**No opinion**
Measurement procedure	**S,N,S,S**	**Satisfactory**	Intermediate	Unsatisfactory	**No opinion**
Reading of result	**S,N,S,S**	**Satisfactory**	Intermediate	Unsatisfactory	**No opinion**
Description of the sources of error	**S,S,S,S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
Help for troubleshooting	**S,N,S,S**	**Satisfactory**	Intermediate	Unsatisfactory	**No opinion**
Readability / Clarity of presentation	**S,S,S,S**	**Satisfactory**	Intermediate	Unsatisfactory	No opinion
General impression	**S,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]It says the finger pricking should be in the middle finger or the ring finger but in another section, it is a picture showing pricking in the index finger, which is confusing.

Additional positive comments: One PHCC thought the manual was easy to read and easy to find in.

Additional negative comments: The confusion of which finger to prick was mentioned by another PHCC as well. In addition, they addressed the error code E010, which could appear although the sample was applied in time. They were not satisfied with the explanation and correction of this error code. Furthermore, they would have liked contact information to the local supplier in the manual.

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**		

Additional positive comments: When the internal quality control is analysed not only the result is shown on the display, but also if the control passed or not.

6.4.2. Assessment of the user-friendliness

Assessment of the operation facilities (table A)

The operation facilities were in total assessed as intermediate since three out of four PHCCs rated both the application of sample as well as the volume of the sample as intermediate, this because it was considered difficult to apply the sample with capillaries (air bubbles) or from hanging drop as well as to apply the right amount of sample. In addition, the SKUP recommendation of an incident of ≤2 % technical errors was not achieved. In total 4 % of the measurements had to be repeated due to errors.

Assessment of the information in the manual (table B)
The manual was assessed as satisfactory with the positive comment that it was easy to read and to find in.

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 with the positive comment that the result of internal quality control analysis is addressed as approved or not approved on the display.

Conclusion
The user-friendliness of the operation facilities was rated as intermediate. The manual, the time factors and the analytical quality controls were rated as satisfactory. To achieve the overall rating "satisfactory", the tested equipment must reach a total rating of "satisfactory" in all four subareas of characteristics. The quality goal for user-friendliness of qLabs Q-3 Plus PT (INR) Owren (dry) was not fulfilled.

7. References

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Attachments

1. The organisation of SKUP
2. Facts about qLabs Q-3 Plus PT (INR) Owren (dry)
3. Information about manufacturer, retailers and marketing
4. Product specifications for this evaluation, qLabs Q-3 Plus PT (INR) Owren (dry)
5. Statistical expressions and calculations
6. Raw data PT (INR), results from the comparison method
7. Raw data PT (INR), internal analytical quality control results, qLabs Q-3 Plus PT (INR) Owren (dry), intended users
8. Raw data PT (INR), qLabs Q-3 Plus PT (INR) Owren (dry) results, intended users
9. Comments from Micropoint Bioscience, Inc.

Attachments with raw data are included only in the copy to Micropoint Bioscience, Inc.

The organisation of SKUP

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

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

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

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

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

SKUP reports are published at www.skup.org.

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

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

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

Facts about QLabs Q-3 Plus PT (INR) Owren (dry)

This form is filled in by Micropoint Bioscience, Inc.

Table 1. Basic facts

Name of the measurement system	qLabs® ElectroMeter Q-3 Plus Owren
Dimensions and weight	Width: 70 mm Depth: 26 mm Height: 148 mm Weight: 203 g
Components of the measurement system	ElectroMeter, single use test strips and optional liquid controls
Measurand	PT (INR)
Sample material	Fresh capillary whole blood
Sample volume	10 µL
Measuring principle	Electrical impedance
Traceability	To the WHO tilt tube standard
Calibration	Happens automatically with barcode scanning of test strip pouches
Measuring range	0.5 – 8.0 INR
Haematocrit range	30 – 55 %
Measurement time	Varies from 30 seconds to 100 seconds depending on status of anticoagulation of sample
Operating conditions	Temperature 10ºC – 35ºC. Relative humidity 10 % – 90 %.
Electrical power supply	Battery: Built-in lithium-ion polymer Battery Charger: Enter: 100 – 240 VAC/50 – 60 Hz Output: 5 VDC Input Power: 29 VA
Recommended regular maintenance	External cleaning and disinfection between patients
Package contents	qLabs ElectroMeter, power adaptor, User's Manual, Quick Start Guide, Lancet Needles, Carrying Case, USB Cable
Necessary equipment not included in the package	Test strips are sold separately. Liquid control solutions are sold separately.

Table 2. Post analytical traceability

Is input of patient identification possible?	Yes, a patient identification can be entered via the onboard barcode scanner or manually typed via the touch screen
Is input of operator identification possible?	Yes, an operator identification or password can be scanned or entered manually via the touch screen
Can the instrument be connected to a bar-code reader?	Barcode scanner is integrated as part of the meter
Can the instrument be connected to a printer?	Yes, the meter can be connected to specific printer – eStation II via Bluetooth, or be connected to PC for printing via USB port and cable
What can be printed?	Once connected to eStation II, test result can be printed. Once uploaded to a PC, all data can be printed.
Can the instrument be connected to a PC?	Yes
Can the instrument communicate with LIS (Laboratory Information System)? If yes, is the communication bidirectional?	Communication to LIS is possible and communication is bidirectional
What is the storage capacity of the instrument and what is stored in the instrument?	Stores up to 2000 patient records and 500 raw data
Is it possible to trace/search for measurement results?	Yes, past results can be reviewed from meter memory

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

Name of the reagent/test strips/test cassettes	qLabs® PT-INR Owren (Dry) Test Strips
Stability in unopened sealed pouch	18 months
Stability in opened pouch	10 minutes
Package contents	24 test strips with individual pouch package, 1 multi-language insert, 1 code chip

Table 4. Quality control

Electronic self check	Yes
Recommended control materials and volume	qLabs PT-INR liquid controls and volume of one drop per test
Stability in unopened sealed vial	12 months
Stability in opened vial	15 days, if capped tightly at 18-30°C
Package contents	Two vials of Level 1 and two vials of Level 2

Information about manufacturer, retailers and marketing

This form is filled in by Micropoint Bioscience, Inc and LumiraDx AB.

Table 1. Marketing information

Manufacturer	Micropoint Bioscience, Inc.
Retailers in Scandinavia	Denmark: LumiraDx A/S Norway: LumiraDx AS Sweden: LumiraDx AB
In which countries is the system marketed	Globally* ☐ Scandinavia ☒ Europe ☐
Date for start of marketing the system in Scandinavia	2019-09-01
Date for CE-marking	2018-04-26
In which Scandinavian languages is the manual available	Swedish, Norwegian and Danish

*The system is also available with test strips based on the Quick method, these are marketed globally.

Product specifications for this evaluation, qLabs Q-3 Plus PT (INR) Owren (dry)

qLabs Q-3 Plus PT (INR) Owren (dry) instrument serial numbers

Serial number*	Used by	Used for SKUP ID
033800K0600125	PHCC1	101 – 108
033800K0600058**	PHCC1	109 – 111
033800K0100039	PHCC1	112 – 150
033800K0300309	PHCC2	201 – 236
033800K0400024***	PHCC2	237 – 239
033800L0500072	PHCC2	240 – 245
033800K1200498	PHCC3	301 – 326
033800L0500074	PHCC3	327 – 346
033800K0400024	PHCC4	401 – 445

*Due to malfunction of software the instruments could not be charged once they were discharged, therefore most PHCCs had to change instrument to one with an updated software.
**This instrument was not calibrated to the right INR level, the results from these SKUP IDs were removed from all calculations.
***Inherited instrument from PHCC4, but it was discharged quickly.

qLabs Q-3 Plus PT (INR) Owren (dry) test strips

Lot no	Code chip number	Alias	Expiry date	Used by
3050K1203	BBPQ	Lot Q	2021-06-09	PHCC1–4
3050K1206	BBPR	Lot R	2021-06-22	PHCC1–4
3050K1207	BBPS	Lot S	2021-06-23	PHCC1–4

Internal analytical quality control

Lot no	Code chip number	Expiry date	Control	Allowable range	Used by
3052K1202	BBMN	2020-12-11	Level 1	0,6 – 1,2	PHCC1–4
			Level 2	2,0 – 3,2	
3052K1203	BBMX	2020-12-23	Level 1	0,7 – 1,3	PHCC2, PHCC3
			Level 2	2,0 – 3,2	
3052L1101	BBWH	2021-11-19	Level 1	0,7 – 1,3	PHCC3
			Level 2	2,0 – 3,4	

Statistical expressions and calculations

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

Statistical terms and expressions

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

Precision

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

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

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

Trueness

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

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

Accuracy

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

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

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

Statistical calculations

Statistical outliers

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

Calculation of imprecision

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

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

d = difference between two paired measurements (formula 1)
n = number of differences

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

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

m = mean of paired measurements (formula 2)

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

Calculation of bias

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

Assessment of accuracy

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

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

Raw data PT (INR), results from the comparison method

Shown to the requesting company only.

Raw data PT (INR), internal analytical quality control results, qLabs Q-3 Plus PT (INR) Owren (dry), intended users

Shown to the requesting company only.

Raw data PT (INR), qLabs Q-3 Plus PT (INR) Owren (dry) results, intended users

Shown to the requesting company only.

Comments from Micropoint Bioscience, Inc

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April 21st, 2021

Comment on SKUP Evaluation Report on qLabs system

Dear Ladies and Gentlemen,

Thank you for the evaluation report on qLabs Owren (Dry) system and appreciate the opportunity to review and comment on this report. Micropoint Bioscience (MBI) would like to thank the SKUP team for conducting this evaluation between a whole blood POCT system qLabs and a plasma-dilution laboratory method.

In general, we are satisfied with the majority of the outcomes of this evaluation, however, we would like to share MBI's feedback regarding specific points:

Repeatability
We were pleased that the evaluation proved that the quality goal for repeatability was fulfilled. The overall CV achieved at PT (INR) level <2,5 was 4,9 % and at PT (INR) level ≥2,5 it was 4,5 % which correspond to SKUP criteria.

Accuracy
For accuracy, according to the SKUP report, 90% of the results were within the ≤±20,0 % allowable deviation limit. The report concludes that 2 out of 162 results appear to be outside ±30% of the therapeutic range 2-4,5 INR (ISO standard criterion), corresponding to >98,8% of the results falling within ±30% deviation limits of a laboratory reference method. While this does not fulfill the SKUP quality goal, it does meet the ISO 17593:2007 *Clinical laboratory testing and in vitro diagnostic test systems In-vitro monitoring systems for anticoagulant therapy self-testing*.

It is noteworthy that, of the 178 results, 7 results equivalents to 4,0% deviated from the > 25% upper limit, rather than a combination of the >+25% and <-25% limits, suggesting a unidirectional bias against a comparison method. Furthermore, one of the four test sites showed significantly higher bias cases than the other three PHCCs: out of the total 18 results that are outside of the +20,0 % upper deviation limits in four PHCCs, 10 results (55,6%) were from this PHCC.

Lastly, qLabs Owren (Dry) system was determined to have an 8,5% overall systematic deviation higher than Sysmex comparison method in this evaluation. Thus, re-calibration of the qLabs results may correct this systematic deviation. Indeed, based on our theoretical calculations of making a re-calibration aiming to reduce this systematic deviation, 96,1% of the re-calculated qLabs results fall within the ≤±20,0 % allowable deviation limits, and no deviation exceeds the ≤±25,0 % limits. This shows that adjusted calibration of new lots potentially can fulfill the SKUP accuracy goal. As a result, we have taken immediate actions to implement this re-calibration which facilitates reducing this deviation.

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User-friendliness

We were pleased that user-friendliness was rated as satisfactory for manual/quick guide, time factors and quality control. It was unexpected that the qLabs instrument operation was rated as intermediate in user-friendliness. A majority of the user-friendliness topic were rated as satisfactory, but application of sample as well as the volume of the sample were rated as intermediate.

The comments concerning capillary sampling and sample volume are not issues that MBI receives frequently. According to our experience, when the patient is properly prepared (e.g., warm hands), the sample volume at 10 µL is generally easy to obtain and apply. Users are trained to apply the fingerstick blood sample on strips directly and do not use microcap capillary to aid sample collection and application. It is therefore advisable that the microcap capillary should not be used in the future for easy pre-analytical. The qLabs system has been used by many professional and self-test users in numerous countries for the last 10 years

Also, some individual comments were recorded in evaluation sites.

1) One site felt it would be helpful if qLabs instrument can indicate the test procedure with a signal. We unexpected this as qLabs system is a POCT device and easy to operate. The screen interface can indicate every step with a displaying text.
2) One site felt qLabs instrument had a lot of scanning steps. qLabs instrument can scan Operator ID, Sample ID and strip code. The scanning is designed to reduce manual input and avoid typing error.
3) One site felt it was difficult to get the strip out of the package, and it was a lot of waste on material usage. Actually, qLabs strips use individual pouch package for every single strip, because we received a lot of feedbacks from users in many countries that individual package is preferred over a bottle package used by our main competitor. This design can provide better protection and avoid the rest strips being exposed to the ambient humidity before use.

There are 4,0 % tests wasted due to technical errors, which failed to achieve SKUP's recommendation of ≤2 %. The 10 (E010 error) of 15 technical errors are most likely caused by the sample addition being very close to the 120 second countdown limit, causing the sample to reach reaction zone outside of the time limit. Recently we had received similar feedback on E010 error and accordingly made a software change which added an additional 15 seconds countdown when the reaction zone fails to detect the incoming sample within 120 seconds limit. This change can eliminate this error risk and reduce the qLabs technical error and tests wasted down to 1,3%. We thank SKUP for this feedback and assure that this software update has already been implemented.

MICROPOINT is pleased with the results of this study. We think that the qLabs Owren (Dry) system with the new software and new calibration of strip will be safe and reliable to be used for managing patients under anticoagulant therapy.

Best Regards
Micropoint Bioscience, Inc.

Cédric SIRE
Global Sales and Marketing Director

Shawn Wang
Director of Programme