



QualiTest

Equipment Test EasyLab with EasyPack

(Fresenius Kabi Deutschland GmbH)

Cartridge-based analysis system for measurement of acid-base, blood gas and electrolyte status of blood for POC (Point of Care) diagnosis

Editorial

POC (Point of Care) diagnosis is becoming increasingly important because it allows measurement of parameters formerly exclusively reserved for determination by the central hospital laboratory. Modern cartridge technology makes it possible to use measurement sensors as disposable items relatively economically. The advantages are described by the German Federal Medical Council (BÄK) as follows [3]: analysis takes place without preparation (directly in the plasma) of the whole blood, operation of the equipment requires no qualification in medical technology and experience in laboratory medicine and – most importantly – direct therapeutic consequences can be drawn from the test. In short: easy operation, no equipment maintenance and therefore a time- and cost-saving alternative.

The central laboratory is also not involved when patient data has to be entered directly in the diagnostic system. Take for instance, the patient's body temperature: this has to be entered in the analyzer next to the hospital bed in order to determine the current coagulation or blood gas status of the patient. Either the equipment temperature is set (coagulation) or the equipment converts the patient data recorded at 37 °C to the body temperature of the patient (partial pressure of oxygen and of carbon dioxide). "POC diagnosis is not the conduction of tests at decentralized lab units with possibly smaller analysis systems than in a central laboratory" [3], but rather a cartridge-based analysis system for patient diagnosis. A new device of this type has therefore been tested once again. RZ

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Code

Particularly high demands have to be made on medical diagnostic systems as far as safety and functionality of the equipment are concerned on the one hand and accuracy and reliability of the results obtained in this manner on the other.

These are decisive criteria influencing the diagnostic and therapeutic action that is taken by the doctor for the benefit of his/her patients.

The requirements can only be fulfilled if the finished equipment is subjected to continuous objective internal and external quality control.

For the sake of economy, the cost of implementation of the equipment, of continuous maintenance and quality control in relation to the expected diagnostics and possible treatment should also be favorable.

Deliberate acceptance of deficiencies in quality to the detriment of the patient represents a limit in the competition between manufacturers.

Maximum transparency with regard to the type of test conducted, the declaration of a 'gold standard', the selected examiners as well as the published results is a prerequisite for successful external quality control by a test lab.

For the sake of fairness, each publication has to include a statement by the manufacturer or seller concerned provided this is requested, if the test lab was previously instructed to carry out an evaluation.

The test lab can only pursue its activities successfully if the operator, employees and examining experts on the one hand and the customer on the other are able to identify with this code.

Physioklin

Cartridge-based Analysis System for Measurement of Acid-Base, Blood Gas and Electrolyte Status of Blood

**EasyLab with EasyPack (Fresenius Kabi Deutschland GmbH)
(Equipment Test February 2007)**

Objective

With which degree of accuracy (inaccuracy, deviation between target and measured value) and precision (imprecision, spread of multiple measurements of a sample) can the analysis system EasyLab (Fresenius Kabi Deutschland GmbH) (see Fig. 1)

- measure the acid-base including blood gas status with pH value, partial pressure of CO₂ (pCO₂, mmHg), partial pressure of O₂ (pO₂, mmHg) as well as hematocrit (Hct, %) of a blood sample and hence calculate a base excess (BE, mmol/l), as well as the
- electrolyte status with plasma concentrations of sodium, potassium and ionized calcium.

Requirements

The requirements to be met by an analysis system for measurement of the acid-base, blood gas and electrolyte status applicable here are based on – with modification – the guidelines of the German Federal Medical Council for Quality Assurance of Quantitative Medical Laboratory Tests (RiliBÄK) from 2001 [1] with official modifications dated 2003 [2]. The accuracy is expressed therein as (systematic) maximum allowable inaccuracy (mai) on the one hand and as maximum allowable (random) deviation of an individual value (madiv) on the other:

	mai	madiv
pH	0.02	0.06
pCO ₂	5.5%	12.5%
pO ₂ (< 125 mmHg)	5 mmHg	15 mmHg
Hct	3%	9%
BE at ±0 (mmol/l)	2.5*	6.5*
Sodium	2.5%	6.1%
Potassium	4%	9%
Calcium (> 1 mmol/l)	5%	15%

It remains incomprehensible why the German Federal Medical Council (BÄK) makes no specifications for the decisive, although calculated base excess value, since treatment of metabolic acidosis is based on BE rather than pH [7, 8]. The

specifications made here (*) are applicable for the unfavorable case (error addition for pH and pCO₂ readings) with 2.5 or 6.5 mmol/l, while for a favorable case (error subtraction for pH and pCO₂) a BE variation for the maximum allowable deviation of an individual value (madiv) of only 2.5 mmol/l is obtained.

The assessment of the tested equipment is to be based on the data provided by RiliBÄK, despite the fact that some of these are not entirely comprehensible.

Material

The tests were conducted in February 2007 in the Hemodiagnosics Test Lab at the Institute of Physiology and Pathophysiology of the University of Mainz (Germany).



Fig. 1 EasyLab instrument with EasyPack cartridge (Fresenius Kabi, Bad Homburg, Germany).

Equipment and cartridges

A total of 9 EasyLab instruments (see Fig. 1) with various equipment number endings (032, 033, 054, 059, 065, 070, 074, 100, 101) were tested in continuous alternation.

6 EasyPack α cartridges were tested, this cartridge type being designed for maximum 30 measurements within 24 h. 3 EasyLab instruments were tested in parallel and the whole procedure was then repeated for the next 3 cartridges.

Each cartridge was charged with 3 capillary samples (150 μ l) per blood sample. Since a total of 4 blood samples are used consecutively, each cartridge could be tested with 12 samples in this manner. The total number of all capillary samples was therefore 72 for all 6 cartridges and 3 instruments. The maximum number of 30 measurements per cartridge was not made in order to test as many cartridges as possible.

8 EasyPack β cartridges were further tested, this cartridge type being designed for maximum 15 measurements within 48 h. 4 EasyLab instruments were tested in parallel and the whole procedure was then repeated.

Each cartridge was charged with 5 syringe samples (150 μ l) of a blood sample, with only 4 different blood samples being used consecutively. Each cartridge was tested with only 5 samples in this manner. The total number of all syringe samples was therefore 40 for all 8 cartridges and 4 consecutively used instruments. The maximum number of 15 measurements per cartridge was again not made in order to test as many cartridges as possible.

6 EasyPack α cartridges (72 samples) as well as 8 EasyPack β cartridges (40 samples) were therefore tested in the end.

Directions regarding the – very simple – operation of the instruments were provided by Fresenius Kabi (Bad Homburg, Germany) staff.

Daily quality control using the quality control material Eurotrol GAS-ISE was carried out before commencing measurement (Level 1: 13-1-B 650; Level 2: 13-2-B 649; Level 3: 13-3-B 422).

Test material

Equilibrated fresh blood from the median cubital vein of healthy subjects, heparinized with approx 100 μ l (dead space of a 20 ml syringe) of Heparin-Natrium (heparin-sodium) Braun 25,000 IU/5 ml, i.e. a dose of approx. 25 IU per ml of blood. Transfer of the blood samples from tonometer (see below) to the instruments either took place by means of a disposable syringe (1000 μ l) or a glass capillary (200 μ l volumes). Maximum storage period of blood was limited to 6 h on ice (4 °C).

Method

Definition of target values (accuracy)

Target pH values are the values measured with a pH electrode at the beginning and the end of the test period (max 30 min), using Radiometer BMS 2 Mk 2. Calibration was carried out using precision buffer solution types S 1500 and S 1510 (phosphate buffer pH 6.841 and 7.383 at 37 °C in ampoules). This procedure was selected since the measurements with several instruments require at least 25 min, leading to a however almost immeasurable reduction of the pH value in the tonometer (see below).

Target values of the partial pressures pO_2 and pCO_2 are set by equilibration with defined gases, provided at a flow of 60 ml/min by a gas mixing system using ultrapure gases (Linde) via microprocessor controlled valves (Precision Gas Mixer Corning 192). Accuracy was verified with gravimetrically produced test gases and found to be 0.35 mmHg or 0.05% for the respective gas. Calculation of the target value takes into account later moistening with a pH_2O of 47 mmHg (37 °C) as well as current barometric pressure (pB) at laboratory altitude (mercury barometer, Lambrecht, Göttingen, Germany).

Example: $pCO_2 = 40$ mmHg with $pB = 760$ mmHg and fractional CO_2 concentration = 0.0561 (5.61 %), so

$$(760 - 47) \times 0.0561 = 40.0 \text{ mmHg.}$$

Equilibration of the blood samples is carried out in an IL-tonometer 237 (Instrumentation Laboratory) at 37 °C with water saturated gases.

Blood from subjects is only used if a normal base excess **BE** of 0 ± 1 mmol/l can be demonstrated after equilibration to pCO_2 40 mmHg with complete oxygenation; other BE values from -5 to $+5$ mmol/l are adjusted by addition of defined amounts of HCl or $NaHCO_3$ afterwards. BE target values are then calculated from the pH, pCO_2 , cHb (g/dl) and sO_2 (%) target values.

cHb is calculated from the hematocrit reading measured by the instrument (Hct, %) (see below) as follows:

$$cHb \text{ (g/dl)} = 0.336 \times \text{Hct (\%)}$$

A variation of the cHb or the Hct is achieved by withdrawal or addition of plasma to the centrifuged blood sample. The sO_2 (%) is calculated from the measured pO_2 (mmHg) by the formula in the instrument.

The target hematocrit value is determined according to the microhematocrit method by centrifugation, with reading optimization by means of a laboratory magnifying glass.

The target values of the electrolyte status, i.e. the concentrations of sodium (cNa^+ , mmol/l), potassium (cK^+ , mmol/l) and ionized calcium (cCa^{2+} , mmol/l) were determined using Ionometer 3 (Fresenius Medical Care, Bad Homburg) [5] (see Fig. 2). The required blood volume is 300 μ l. A variation of electrolyte concentration is obtained automatically with the BE setting. Electrolyte increase was additionally achieved using 1 molar NaCl, KCl and $CaCl_2$ solution.

Definition of multiple measurements (precision)

Each blood sample was also measured several times per instrument in order to be able to make an assessment of the precision of multiple measurements. The target values of pO_2 , pCO_2 and Hct or cHb remain absolutely constant in the process, while those of pH and therefore also BE decrease minimally due to lactic acid formation by the erythrocytes during equilibration. This is equally applicable for the target and actual values, with subsequently no influence on accuracy and minor influence of precision.

Results

Results of a total of 112 individual measurements with 9 EasyLab instruments and 14 EasyPack cartridges are represented in Figs. 3–5, with

- the actual values determined using EasyLab compared to the target values,
- representation of the line of identity for comparison,
- the linear regression line shown between actual (Y) and target (X) value and, when deviating from the line of identity, also quoted numerically.

Since no systematic differences whatever between all 9 instruments and 14 cartridges could be demonstrated, results for all instruments and cartridges are represented with the same symbols. Since different results were obtained for the different modes of application, syringe or capillary in individual cases, two different symbols are used here.

The linear regression lines correspond to the lines of identity for all 4 represented readings (R^2 in all cases > 0.988), with a minimal deviation in the lower region only observed for hematocrit. The linear equation here is: $Y = 0.9299 X + 3.881$ (R^2 only 0.7837). This results in a systematic overestimation of Hct at e.g. 40% of 1.0%, an almost negligible deviation.

Obviously erroneous readings (outliers) of the 112 readings in total were eliminated and not represented, namely 3 pH values, 2 pCO_2 values, 10 pO_2 values and 2 Hct values, corresponding to a rate of less than 10% of all readings even for the least favorable case (pO_2).

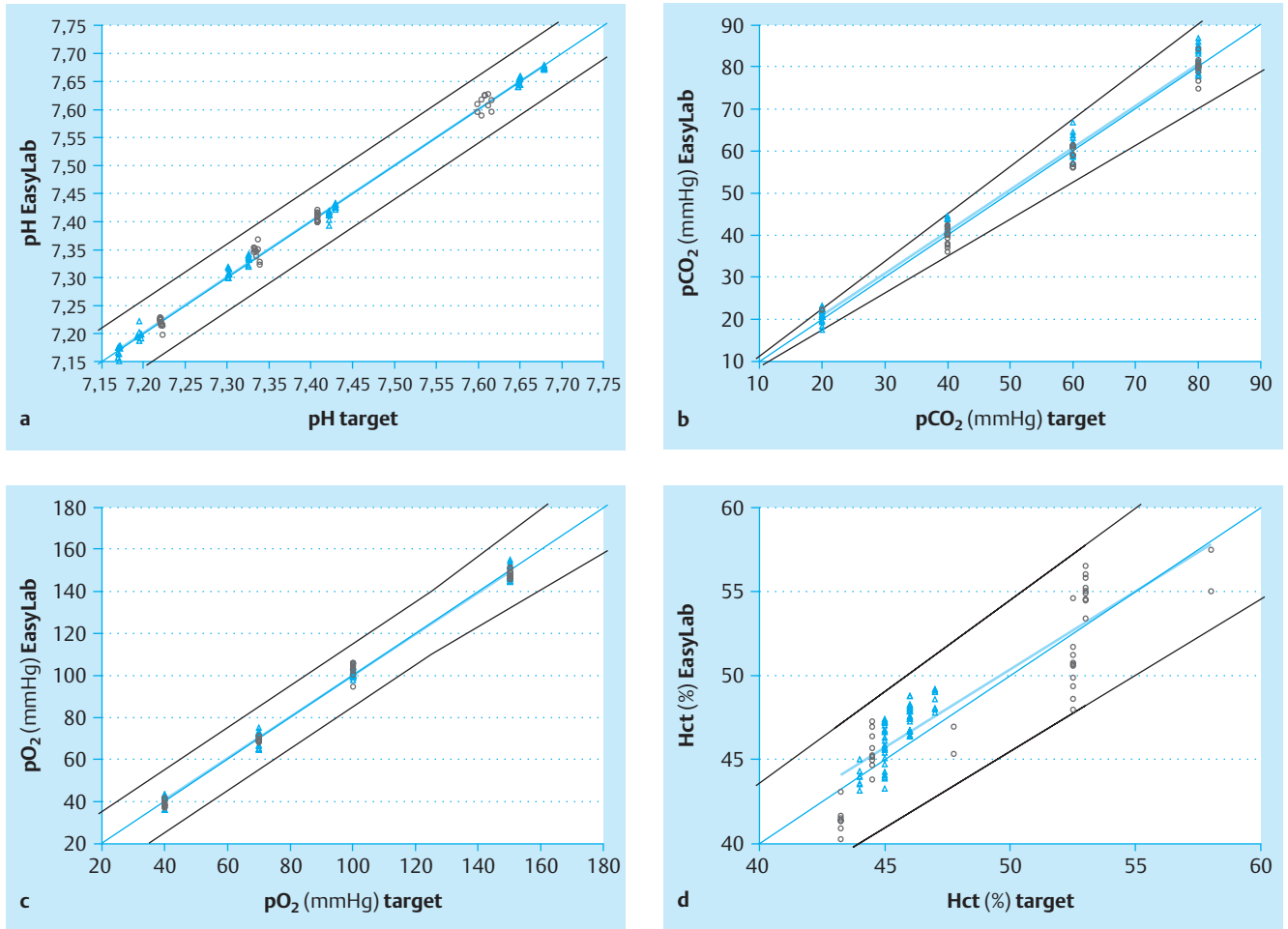


Fig. 2 Ionometer 3 (Fresenius Medical Care, Bad Homburg, Germany).

The linear regression line deviates insignificantly from the line of identity for the calculated value of the BE and is expressed as: $Y = 1.048 X + 0.3896$ (R^2 0.8386). This results in a minimal underestimation of the BE at e.g. – 5 mmol/l of 0.15 mmol/l, practically negligible. For a BE of e.g. + 5 mmol/l the overestimation is however already 0.62 mmol/l, a measurable deviation.

The linear regression lines are practically identical to the lines of identity ($R^2 > 0.960$) for all 3 represented readings, with a minimal deviation only observed for sodium. The linear equation here is: $Y = 0.9989 X - 0.3043$ (R^2 only 0.824). This results in a systematic underestimation of the sodium concentration at e.g. 140 mmol/l of 0.5 mmol/l, an almost negligible deviation.

No erroneous measurements (outliers) had to be eliminated from the total of 112 readings. The impression that the total number of 112 measurements is not achieved for the representation of the readings for potassium is based on the fact that many of the values lie on top of each other.



Figs. 3a–d EasyLab readings for detailed acid-base status pH, pCO₂ (mmHg), pO₂ (mmHg) and Hct (%) as function of the corresponding target value.

Discussion

For assessment of the measured and calculated values obtained from testing the EasyLab instrument with EasyPack disposable cartridges, reference is again made to the guidelines of the German Federal Medical Council for Quality Assurance of Quantitative Medical Laboratory Tests (RiliBÄK) of 2001 [1] with modifications dated 2003 [2].

The required accuracy for a total of 7 readings, expressed as maximum allowable (random) deviation of an individual value (madiv) is clearly achieved in all cases. Readings do not lie outside the marked area between the upper and lower limits for any case. This has to, however, be qualified by emphasizing that 3 pH values for the acid-base status as well as 2 pCO₂ values and 10 pO₂ values for the blood gas status were eliminated as obvious erroneous measurements (outliers). It is suspected

that the erroneous measurements could be based on the introduction of gas microbubbles, which are not recognized as such by the conductivity measurement (Hct) with only 2 erroneous measurements. Consideration of the total number of 17 erroneous measurements in relation to the total number of 784 measured values (7 measurement parameters per 112 measurements), allows this number of 2% to be designated as minimal, which may, however, definitely bother the user.

Assessment of the (systematic) maximum allowable inaccuracy (mai) according to RiliBÄK is expressed as follows: there are readings that unambiguously fulfill this requirement: the pH clearly meets the requirement concerning maximum allowable inaccuracy with a value of 0.02, similarly pO₂ with 5 mmHg, sodium with 2.5%, potassium with 4% and calcium with 5%. The target is only narrowly missed by pCO₂ (5.5%) and hematocrit (3%).

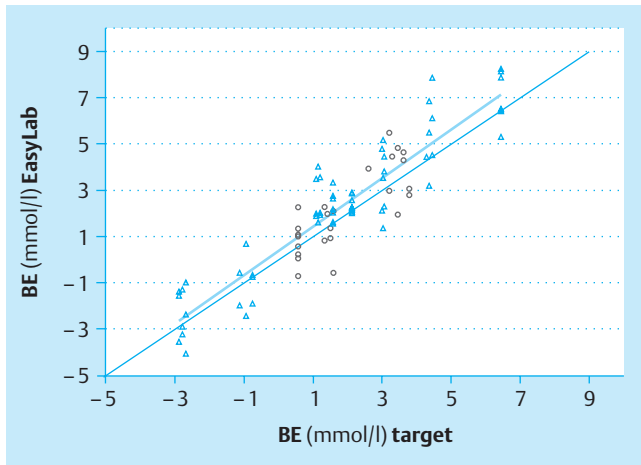


Fig. 4 The Base Excess BE (mmol/l) calculated by EasyLab from pH, pCO₂, sO₂ (derived from pO₂) and cHb (derived from Hct) as a function of the target value.

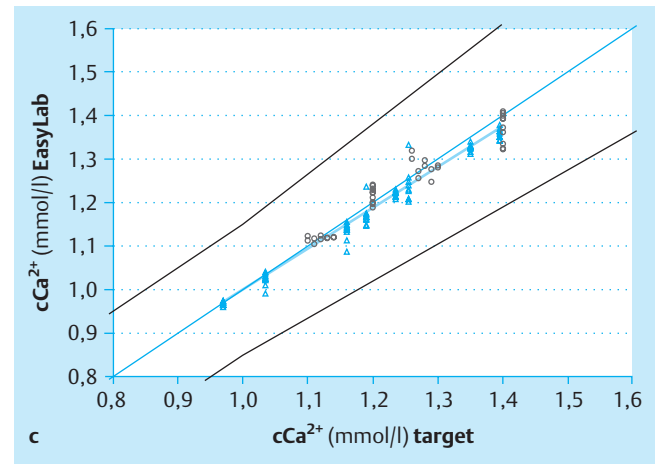
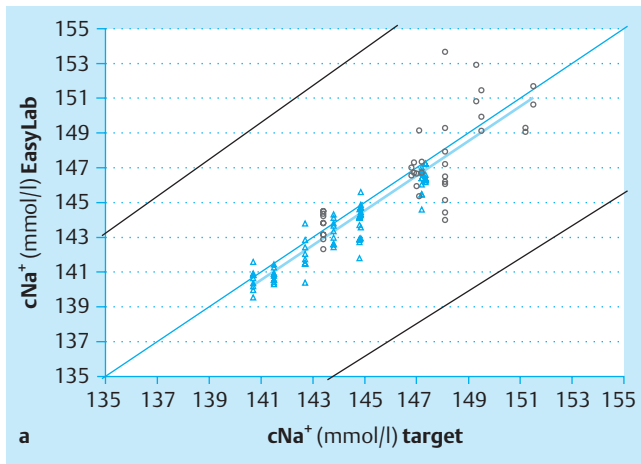
- Syringe
- △ Capillary
- Linear regression line for all readings
- Line of identity

Particularly pleasing is the fact that the lacking maximal allowable inaccuracy for the BE by RilibÄK, which is observed to be 2.5 mmol/l in the least favorable case, is just reached by the calculated BE here (not represented in Fig. 4).

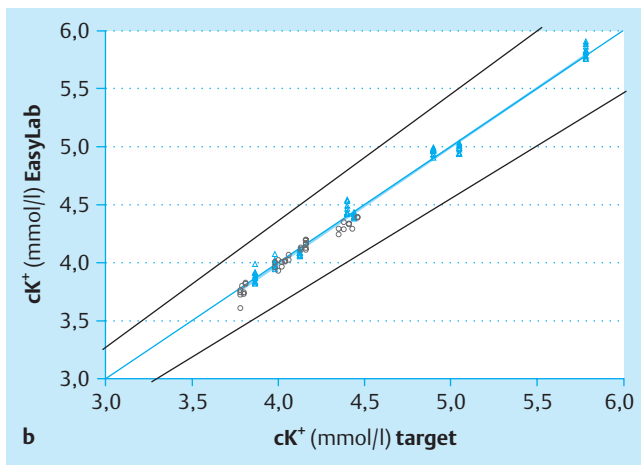
As already presented in an earlier test [10], the BE requires special consideration. It is the decisive value for acid-base status treatment, therefore justifying POC diagnosis [7, 8]. The arterial blood gas status on the other hand is frequently determined non-invasively and continuously nowadays, as arterial O₂ saturation with a pulseoxymeter and as end-expiratory pCO₂ using a capnometer.

Since a BE modification of only 6 mmol/l at the time of hospital admission predicts a 25% increase in later mortality for approx. 8,000 polytrauma patients [8, 9], strict standards have to be applied to the accuracy of BE determination, as explained above.

This is particularly applicable for clinical utilization of such equipment [6].



Figs. 5a–c EasyLab readings for the electrolyte status (mmol/l), namely plasma concentrations of sodium (cNa⁺), potassium (cK⁺) and calcium (cCa²⁺) as function of the corresponding target value.



- Syringe
- △ Capillary
- Maximum allowable upward or downward deviation of an individual value
- Line of identity
- Linear regression line for all readings

The alteration of a $p\text{CO}_2$ accuracy from an original 4% [RiliBÄK 2001] to a current 5.5% [RiliBÄK 2003] together with a pH accuracy of 0.02 leads to a BE inaccuracy of 2.5 mmol/l, which can just about be tolerated.

The tested EasyLab instrument is actually in a position to do this, while it is noticed that considerable benefits could be gained by an improvement of the inaccuracy and imprecision of the $p\text{CO}_2$ measurement. The BE would profit greatly from this.

It obviously pays off that the equation used for BE calculation used in the EasyLab instrument is the one that was published earlier, which is superior to all other equations recommended by international specialists [4]: the BE calculation alone is possible with an accuracy of distinctly under 1.0 mmol/l, irrespective of whether arterial or venous blood is used [4, 9]. This was specifically tested here, the $p\text{O}_2$ and thereby the $s\text{O}_2$ were lowered.

With regard to the acid-base – including blood gas – status the EasyLab instrument with EasyPack cartridges certainly stands up to a comparison with the GEM Premier 3000 (Instrumentation Laboratory) instrument tested here earlier [10], even though GEM 3000's impressive accuracy and precision regarding pH, $p\text{CO}_2$ and $p\text{O}_2$ readings could not yet be completely matched by the EasyLab instrument.

No problems are obviously observed for the also tested electrolyte status, when the plasma concentrations measured by Ionometer 3 (Fresenius Medical Care) are used as target values. This instrument operates with ion-selective electrodes (ISE), as is customary nowadays, directly in undiluted whole blood samples (direct ISE). The accuracy of this instrument corresponds to the flame photometry reference method and indirect ISE [5].

The requirements of the guidelines of the German Federal Medical Council for Quality Assurance of Quantitative Medical Laboratory Tests (RiliBÄK) from 2001 with modifications dated 2003 are clearly fulfilled.

The method of sample application, via syringe (insertion) or via capillary (aspiration), has practically no influence on the measurement result. This does not, however, apply to determination of sodium and hematocrit, where an increasing spread of the readings is observed for the syringe mode.

Recommendations

1. Optimization of the precision of the $p\text{CO}_2$ measurement, especially in the upper region with the consequence of further improvement of the BE calculation.
2. Optimization of the precision of the hematocrit determination via the conductivity measurement with the prospect of display and clinical utilization of the Hb concentration calculated therefrom.
3. Registration and identification of erroneous measurements with the aim of allowing quick elimination of these by the user.
4. Examination of the mode of introduction by syringe for sodium and hematocrit determination.

Evaluation

The EasyLab instrument in combination with the disposable cartridges fulfils the requirements of the guidelines of the German Federal Medical Council for Quality Assurance of Quantitative Medical Laboratory Tests (RiliBÄK) dated 2001 and 2003.

1. The accuracy for a total of 7 readings, expressed as maximum allowable (random) deviation of an individual value is clearly achieved in all cases.
2. 5 readings are clearly below the specified value of the (systematic) maximum allowable inaccuracy, the measured $p\text{CO}_2$ and hematocrit values are only just out of target range.
3. Obvious erroneous measurements (outliers) are only 2% for a total of 784 readings, which may, however, bother the user.

The EasyLab instrument can therefore be used for determination of acid-base, blood gas as well as electrolyte status for routine clinical POC diagnosis.

Examining Experts

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Conflict of Interests

Prof. Dr. med. R. Zander advises Fresenius Kabi in the development of EasyLab.

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Mode of operation of the Physioklin Test Lab

The Physioklin Test Lab was established in 2007 from the third-party funded project 'Hemodiagnosics Test Lab at the Institute of Physiology and Pathophysiology of the University of Mainz'. It finances itself by producing expert reports for equipment manufacturers. By independent function testing and quality control of hemodiagnostic equipment, its general aim is to test, improve and guarantee the quality of such equipment and to publish the corresponding results. Examining experts may only – with or without payment of a fee – work for the test lab subject to agreement to declare any possible conflict of interests. This could arise if the examining experts receive material or financial contributions from the manufacturer or seller of the equipment or method concerned.