in2it

A system for measurement of B-haemoglobin A1c
manufactured by BIO-RAD

Report from an evaluation organised by SKUP

Evaluated at the request of Bio-Rad

SKUP/2010/78

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This report was written by SKUP, June 2010.
The main author was Esther A Jensen, SKUP in Denmark

The organisation of SKUP

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

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

SKUP offers manufacturers and suppliers evaluations of equipment for primary healthcare and also of devices for self-monitoring. Provided the equipment 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. A *complete evaluation* requires one part performed by experienced laboratory personnel as well as one part performed by the intended users.

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

SKUP reports are published at www.skup.nu and www.skup.dk

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

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

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

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A detailed list of previous SKUP evaluations is included in the attachments.
Attachments with raw data are included only in the copy to Bio-Rad.

1. Summary

Background
Bio-Rad turned to SKUP for an evaluation of in2it HbA1c in 2009. The testing was performed under optimal conditions in the Department of Clinical Biochemistry, Odense University Hospital and Hillerød Hospital. The end-users were represented by the two primary care centres Gribskov Lægecenter, Vejby and Noer-Hansen and Søndergård, Hillerød, both sending samples to Hillerød. The comparison method was Tosoh G8 in Odense and Tosoh G7 in Hillerød.
In2it has existed for several years; however it was improved during 2008.

The aim of the evaluation

- Determination of the imprecision with 100 venous and 40 capillary patient samples in a hospital laboratory
- Determination of the imprecision with 40 patient samples at two primary care centres. The duplicate measurement consisted of one capillary sample and on venous sample
- Comparison with the established Tosoh method for HbA1c. Determination of trueness and accuracy
- Evaluation of user-friendliness
- Investigation of possible interference of carbamide (urea) and haemolysis

Materials and methods
Four in2it instruments, four cartridge lots, and samples from 180 patients were tested.

Results
The quality goals, a total error of less than ±10% and a repeatability CV of less than 4,0% were fulfilled in the hospital laboratory evaluation and in one of the two primary care centres for venous and capillary samples. An imprecision CV of 3,1% was achieved with venous samples in the hospital and with venous and capillary samples in one primary care centre, while the CV for capillary samples in the hospital laboratory was 4,0%. In the other primary care centre only 89,5% of the samples fulfilled a deviation less than ±10% mainly because of an imprecision CV of 5,2 %. Additional testing revealed that the high imprecision probably was due to low level of buffer in the cartridges caused by leakage loss near the expiry date. The leakage could not be detected visually. An indicator of leakage might prevent this. The user friendliness was satisfying; however, it was mentioned that the instrument did make too much noise when running, and that the test cartridges consume space in the refrigerator. Interference test for haemolysis demonstrated that low grade of haemolysis does not interfere with the test.

Conclusion
In the hospital laboratory: in2it fulfilled the quality goals for imprecision (<4 CV%) and total error of <±10% with both capillary and venous samples.
In the primary care centres: in2it fulfilled the goals for imprecision (<4 CV%) for the combination of one capillary and one venous samples and total error of <±10% in one centre. In the other primary care centre the imprecision CV was 5,2% and only 89,5% of the samples fulfilled a deviation less than ±10%.
The user friendliness was satisfying; however, there were unfavourable comments on too much noise, when the instrument was rotating the test cartridge.

Comments from Bio-Rad
A letter with comments from Bio-Rad, with a reply from SKUP, is attached to the report.

2. Quality goals

To qualify for an overall good assessment in a SKUP evaluation, the measuring system must show satisfactory analytical quality as well as satisfactory user-friendliness.
There are no generally recognised analytical quality goals for HbA1c-determinations. Various ways of setting goals for analytical quality are presented below.

2.1. Analytical quality goals

2.1.1. *Analytical quality goals based on biological variation*

Abbreviations:
CV_a is the analytical imprecision expressed as the coefficient of variation in percent (CV%).
CV_{bw} is the intra-individual biological variation, biological variation within healthy individuals.
CV_{bb} is the inter-individual biological variation, biological variation between healthy individuals.

Setting quality goals on the basis of biological variation is an acknowledged method (1). It is recommended that analytical imprecision should be less than or equal to half the intra-individual biological variation (CV_{bw}). In terms of HbA1c it has been observed, that CV_{bw} for diabetic patients is 4,2 — 9,8%. According to this the imprecision must be less than 2 — 5 CV%.

Ricos C et al (2) state the biological variation as CV_{bw} =1,9%, CV_{bb} = 4,0%, desirable CV_a = 1,0%, desirable bias = 1,1% and desirable total error = 2,7%. Ricos C et al provide a number of references, the most recent of which being Rohlfing C et al (3), who state the biological variation as being CV_{bw} =1,7%, CV_{bb} = 4,0%

The optimal quality goal for bias has been computed using the expression
$\leq 1/4\sqrt{CV_{bb}^2 + CV_{bw}^2}$
with which Ricos initial values permits a systematic deviation (bias) of 1,1%.

Permitted total error is a function of permitted imprecision and bias.
The Total Error (TE) should be $\leq \pm$ [$\mid$ bias $\mid$ + 1,65 x CV]

Taking Ricos' initial values, the quality goal for total error is 2,7%.

In principle, quality goals based on variation do not consider the clinical demands.

2.1.2. *Analytical quality goals based on recommendations from professionals/experts*

According to the American Diabetes Association (ADA) analytical variation (CV_a) for HbA1c should be less than 5% (4, 5).

The National Glycohemoglobin Standardization Program (NGSP) in the USA recommends that between-day CV must be less than 4%, and that 95% of the results must be within ±1,0 HbA1c-percent for the purpose of methodological comparison with a reference laboratory.

In a joint statement of December 2002, the three Norwegian Societies Endocrinological Association (NEF), Clinical Chemistry and Clinical Physiology recommended that suppliers of HbA1c methods should give evidence of a day-to-day variation less than 3%.

The Laboratory Committee under the Professional Committee in Denmark recommends that the analytical imprecision (CV_a) of measuring HbA1c in general practice should be less than 4%, and that the bias should not exceed 4%. For the HbA1c-instruments in hospital the CV_a as well as bias should be less than 3% (6).

In Sweden all HbA1c-results are standardised to the level obtained using the HPLC-method Mono S. That means, that all values are about one HbA1c-% lower than the DCCT standardised values. EQUALIS Expert Group on Protein Analyses and Swedac have laid down a national quality goal, whereby the inter-laboratory spread, i.e. reproducibility regardless of method, must be less than 3,0 CV% and a single measurement from a laboratory taking part in EQUALIS' quality assurance program for HbA1c may deviate a maximum of ±0,4 HbA1c% from the assigned value. The value is assigned by five expert laboratories all measuring HbA1c with the HPLC-system using a Mono S column.

2.1.3. *Analytical quality goal based on "state-of-the-art"*

Three different studies (7-9) show that analytical imprecision (CV_a) for HbA1c measurement ought to be <3%.

2.1.4. *Quality goals derived from expectations among patients and doctors*

General practitioners in Norway have been asked which analytical quality they need (10).
The median of a wanted within-laboratory analytical imprecision was 2,2% CV. However, in reality they noticed such small changes in HbA1c concentrations that they assumed there was no imprecision. A majority of the doctors also expected a smaller between-laboratories CV than the measured 3,2%.
Diabetes patients in Norway have also been asked which analytical quality they expect (10). What change in HbA1c from 9,4 HbA1c% is necessary for a patient to be certain that the change indicates a true (real) improvement or deterioration of their diabetes, i.e. the so-called critical difference (CD). From the answers, the expected analytical imprecision can be calculated, considering the known biological variation, assuming the bias component to be zero and the statistical significance set to 5%. By doing so, the patient-derived quality specification for imprecision (CV) was determined to about 3%.

2.1.5. *Other expectations from general practitioners*

It is a demand from the Danish general practitioners, that the percentage of 'tests wasted' caused by technical errors should not exceed 2%.

2.2. Evaluation of user-friendliness

The evaluation of user-friendliness was done by asking each of the evaluators to fill in questionnaires regarding user-friendliness.

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

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

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

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

2.3. SKUP’s quality goal in this evaluation

Based on the discussion about alternative quality goals above, SKUP has decided to assess the results from the evaluation of in2it against the following quality goals:

CV_a (within-series imprecision).....	<4%
Bias (systematic deviation from the Comparison Method) ..	<±4%
Total Error (allowable deviation).....	<±10%
Fraction of technical errors	<2%

The numerical values of the analytical quality goals are based on results standardised according to DCCT.

3. Materials and methods

3.1. Definition of HbA1c

HbA1c was earlier defined as the chromatographic fraction of haemoglobin believed to be glycated to A1c of the total amount of haemoglobin. The measurement results have therefore been procedure specific and varied with the chromatographic system used. However, other components have been reported to be measured also (11).
The Diabetes Control and Complications Trial (DCCT) (12) and the UK Prospective Diabetes Study (UKPDS) (13), demonstrated the clinical impact of lowering the glucose level for Diabetes type 1 and Type 2, respectably. For both studies HbA1c measurements was specified according to the *National Glycohemoglobin Standardization Program* (*NGSP*).

In the international hierarchy of methods a reference measurement procedures, if such exist, has the highest rank. For measurement of HbA1c a reference measurement procedure has been approved (14). Results from this procedure have been compared with the earlier systems for standardization of HbA1c measurements, that is the NGSP (USA), the Mono S procedure (Sweden), and the JDS/JSCC standardisation (Japan) (8) and the linear relations between the standardisation procedures are known (11,15).

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and International Union of Pure and Applied Chemistry (IUPAC) joint Committee on Nomenclature, Properties and Units (C-NPU) describes quantities, or measureands, for clinical laboratory tests. The quantities being measured by HbA1c-tests are described in table 1 both for the procedure specific measurements (NPU03835) and for the measurement traceable to the reference measurement procedure (NPU 27300).

Table 1. Name and codes for HbA1c tests according to C-NPU

NPU code	Descriptive name	Unit
NPU03835*	Hb(Fe; B)—Haemoglobin A1c(Fe); substance fraction = ?	unit 1 but often given in %
NPU27300	Hb beta chain(B)—N-(1-deoxyfructos-1-yl)Hb beta chain; substance fraction = ?	mmol/mol

* NPU03835 is used in Denmark for HbA1c (DCCT) for values in fraction. For HbA1c (DCCT) values given in percent the code RHB00001 is used.

In this report HbA1c (DCCT) % ~ NPU03835. The definition of HbA1c (IFCC) mmol/mol ~NPU27300 is 'the fraction of all haemoglobin-beta-chains that have glycated N-terminal valine'.

Odense has reported HbA1c results that are traceable to the reference measurement procedure since autumn 2009 and Hillerød since May 2010.

3.1.1. *Differences in Scandinavia:*

In Sweden the HbA1c results are traceable to the Mono S method. The results are given in the unit Mono S %. However, Sweden is going to use the IFCC standardisation from September 1st 2010. In Norway the results are traceable to the NGSP (DCCT) standardisation. In Denmark,

most laboratories give three results for each measurement of HbA1c: the HbA1c (DCCT) %, the HbA1c (IFCC) mmol/mol and the eAG (**e**stimated **A**verage **G**lucose) mmol/L ~ NPU27412. The Danish Society for Clinical Biochemistry (DSKB) has written the Danish recommendations (16). Correlation between HbA1c(DCCT)%, HbA1c(IFCC) mmol/mol, HbA1c(Mono S)%, and eAG mmol/l is shown in table 2. Column 1,2 and 4 are from DSKB (16).

Table 2. Conversion table for between differently standardised HbA1c values

HbA_{1c}(DCCT) (%)	HbA_{1c}(IFCC) (mmol/mol)	HbA_{1c} Mono S* (%)	eAG (mmol/l)
4,0	20	3,0	3,8
5,0	31	4,0	5,4
6,0	42	5,1	7,0
6,5	**48**	**5,6**	**7,7**
7,0	**53**	**6,1**	**8,5**
7,5	58	6,7	9,3
8,0	64	7,2	10,1
9,0	75	8,2	11,7
10,0	86	9,3	13,3

*calculated, Mono S = DCCT/0,956 - 1,182. ADA and the UK Prospective Diabetes Study recommend to treat new diabetics at the level HbA1c 7,0 (DCCT)% (13) whereas the European Association for the Study of Diabetes (EASD) recommend, that the HbA1c goal for treatment of the diabetics is 6,5 % (DCCT) or less.

SKUP has written the documents ”Appendix 1, Standardisation of HbA1c” and ”Appendix 2, The Comparison Method” (17). These documents describe how HbA1c results are standardised according to different international standardisation system. Results can be recalculated and compared between the systems, e.g. HbA1c NGSP (DCCT) = 0,956 x HbA1c (Mono S) + 1,182

3.1.2. *Comparison TOSOH and Mono S, Malmø*

3 samples (low, medium and high) were sent from Odense to Malmø five times and to Hillerød three times during the evaluation. The samples were measured in duplicates on in2it and TOSOH in Odense, Hillerød, and Malmø. These samples were analysed in all locations within four days from sampling time.

3.2. The in2it device

3.2.1. *Description of in2it*

The in2it System (Bio-Rad) is a small point-of-care system intended for use by health care personnel in primary health care, hospital clinics, etc. In2it can be used either as a basic system where the user manually records the results, or as a an system where accessories enable automatic printing of results, barcode reading for patient ID, operator ID, and full connectivity to a PC (not part of this evaluation).

The in2it System for HbA1c consists of three parts: The in2it™ Analyzer, the in2it™ HbA1c Test Cartridges and an in2it™ System Check Cartridge used to check the Analyzer. Along with the test cartridges the company also supplies the blood collection devices which they refer to as Blood Keys.

Figure 1. Picture of in2it Analyzer and the in2it Test Cartridge with the blood key.

3.2.2. *Analyzing a patient sample*

A short version of the procedure for analyzing capillary blood on the instrument is shown below in figure 2. The illustrations and explanations are found at the Bio-Rad web-page. Venous samples can be analyzed as well.

Figure 2: Analyzing a patient sample

- Capillary blood is drawn from a fingertip and 10 µl is collected with the blood key
- The blood key is aligned correctly with, and placed in the Test Cartridge until you hear a distinct click and the blood key is locked firmly in place. The handle on the blood key is easily broken off and the Test Cartridge is placed in the Analyzer
- After closing the Analyzer the procedure is automatic and the result is displayed on-screen after 10 minutes

3.2.3. *Measuring principle*

The in2it System uses boronate affinity chromatography to separate the glycated haemoglobin fraction from the non-glycated haemoglobin fraction. Turning the round Test Cartridge in the Analyzer leads to fluid movement between the chambers in the cartridge due to gravity.
In2it reports results between 4,0 to 14 HbA1c%. Results below 4,0 are given as <4,0 and results above 14 as >14,0.

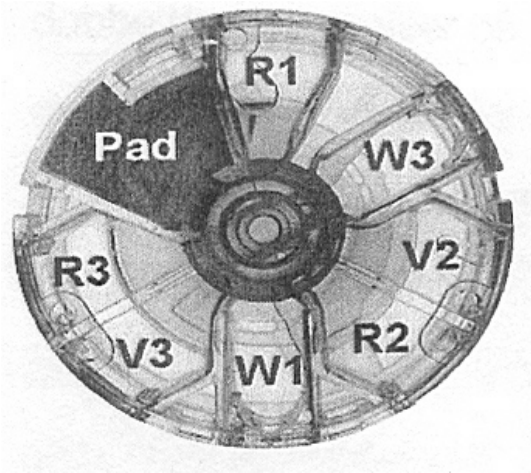

Figure 3. The Test Cartridge

- The sample is added to R1 where it is mixed with the sample buffer
- The sample buffer contains surfactant to lyse the erythrocytes, and boronate attached beads which bind the glycated haemoglobin
- Gravity pushes the sample through to the centre holding back the HbA1c-boronate complex

and washing the non-glycated haemoglobin through to W1 where it is photometrically measured at 440 nm
- The wash solution in R2 now runs through the centre
- The elution buffer in R3 containing sorbitol is now released and HbA1c is eluted to W3 where it is also measured at 440nm

The HbA1c percentage is calculated using the following algorithm:

$$\text{HbA1c (\%)} = M\left([A_{\text{glycated fraction}} \times 100]/[A_{\text{glycated fraction}} + A_{\text{non-glycated fraction}}]\right) + C$$

Here, M and C represent the slope and intercept factors used to correct the crude value.

Technical data from the manufacturer are shown in table 3. More facts about the system are shown in attachment 1.

Table 3. Technical data from the manufacturer

Technical data for in2it	
Working temperature	+18 to +27 °C at 30-70% humidity
Sample	capillary blood, EDTA blood
Sample volume	10µL
Units	either % or mmol/mol
Measuring time	10 minutes
Measuring range	4,0 — 14,0 HbA1c % (DCCT)
Memory	200 patient results
Power supply	AC or four AA lithium batteries
Operating time with battery	about 20 tests
Dimension	width 13 cm; depth 12 cm; height 10 cm
Weight	0,840 kg

3.2.4. *Product information, in2it*

in2it instruments	4 units: No IB-008444, IB-008527, IB-008076, IB-008537
Test Cartridges	40 boxes of 902072t-32 expiry date 2010-01-05 40 boxes of 902072t-34, expiry date 2010-01-27 40 boxes of 902072t-35, expiry date 2010-02-05 40 boxes of 902072t-36, expiry date 2010-02-13 Lot no 29824, 30176, 30321, 30448
Blood Keys	149U21 expiry date 2010-03-10 3 units, lot 149U23 expiry date 2010-04-08
System Check Cartridge	Batch 074023, expiry date 2009-09-05 Lot no 27840
Instructions for use	4 units
in2it Printer Kit	3 units, lot no. 092S07
in2it Barcode Scanner Kit	2 units, lot 081x18, 2 units, lot 081x19
in2it Keypad Kit	4 units, lot 080z18
in2it System Software Kit	1 unit lot 082V14, 3 lot nr 082V15
G5Controls	A1C Control Level 1 Kit Batch 075M26, expiry date 2010-02-09 A1C Control Level 2 Kit Batch 075M26, expiry date 2010-02-09 10 boxes of in2it Control. One box contains 2 bottles of control – one at each of two levels. Each bottle of control contains 0,5 mL blood. A bottle of control can be kept for 3 month at -70°C, and 7 days refrigerated (2-8°C) when opened. 1 Lot 313D32, expiry date 2010-02-09. Target HbA1c (DCCT%) = 5,5% for in2it 2 Lot 313F32, expiry 2010-02-09 Target HbA1c (DCCT%) = 10,0% for in2it
Allowable difference	Between instruments, a maximum difference of 0,5 units of HbA1c % (DCCT) is allowed by Bio-Rad.

3.2.5. *Manufacturer of in2it*
Bio-Rad
Internet: www.bio-rad.com
Representative of the Bio-Rad in this evaluation: Jan Barrack, Director of R&D, Quality and regulatory
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3.2.6. *Suppliers of in2it in the Scandinavian countries*

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3.3. The designated comparison method

In the absence of a reference method, a fully specified comparison method is used for the evaluation of a field method.

3.3.1. *Tosoh G8 and G7 - the designated comparison methods in this evaluation*

The comparison method in this evaluation is the HPLC method on Tosoh G8 for HbA1c in Odense and Tosoh G7 in Hillerød. Tosoh G7 and Tosoh G8 have the same principle for measurement.
Most hospital laboratories in Denmark use the HPLC-method from Tosoh Corporation which is a High Pressure Liquid Chromatography (HPLC) method. Haemoglobin separation of the various fractions is achieved by a cation exchange nonporous polymer column and elution is performed by a step-wise gradient using three citric acid buffers with different salt concentrations and pH. The fractions are measured at absorbance 415 nm. Each fraction produces a peak in the chromatogram. The result is calculated from the area of the HbA1c peak divided with the total area of all haemoglobin peaks and is placed in the calibration function algorithm.
Example from one Tosoh:
HbA1c = 1,2914 x (HbA1c/all Hb) + 0,1999.
SA1c (area of stable A1c fraction) = 72,52 AU (area of all haemoglobin fractions) = 1605,61
HbA1c = 1,2914 x (72,52/1605,61) * 100 + 0,1999 = 5,6 %

3.3.2. *Product information, the comparison method, Odense*

Instrument	Tosoh G8
Traceability:	IFCC% (calibrators from DEKS (Danish Institute of External Quality Assurance for Laboratories in Health Care) in 3 levels with assigned IFCC values also converted to DCCT values (18).
External quality Assurance:	1) EUROTROL every 14 days 2) Labquality 4-5 times a year.
Internal quality control:	Bio-Rad level 1 and Bio-Rad level 2, analysed every 2 hours
Allowable difference	Between instruments, a maximum difference of 0,3 units of HbA1c % (DCCT) is allowed

3.3.3. *Product information, the comparison method, Hillerød*

Instrument	Three Tosoh G7 instruments. Below called Tosoh 1/2/3.
Traceability:	IFCC% (DEKS calibrators in 3 levels with assigned IFCC values also converted to DCCT values)
Calibration	Tosoh instrument1, instrument 2 and instrument 3: 2nd June 2008 Tosoh 2: calibration 2nd February 2009 Tosoh 1+2+3: 28th May 2009

	The following calibrators were used at all calibrations: DEKS, low calibrator: lot 2009.1191, expiry 2017-08 DEKS, high calibrator: lot 2009.1193, expiry 2017-08 The medium calibrator: lot 2009.1192, expiry 2017-08 was not used for calibration but for internal control every day
External quality Assurance:	Labquality 4-5 times a year
Internal quality control:	DEKS calibrator each day. Until 28th May 2009 DEKS calibrator, target 8,00% (DCCT%) lot 2006.2712, exp. 2016-10 From 28th May 2009 DEKS calibrator, target 8,11% (DCCT%) lot 2007.1432, exp. 2017-08 Bio-Rad 1, lot 33751, expiry 30th November 2010 (5,4-6,0 DCCT%) Bio-Rad 2, lot 33752, expiry 30th November 2010 (9,4-10,0 DCCT%)
Allowable difference	Between instruments, a maximum difference of 0,4 HbA1c % (DCCT) is allowed.

3.3.4. *Verification of the Comparison methods*

The bias and the imprecision for the Tosohs in the biochemical departments of Odense and Hillerød were calculated before, under and after the evaluation. The deviation from other Tosoh instruments in Labquality had been <±1% (12 month before the evaluation) in both laboratories and the imprecision had been <2% (12 month before the evaluation) in both laboratories, see tables and figures of external quality assurance in chapter 5.
The Tosoh HbA1c method group had a negative bias <2% in the Labquality external quality assurance programs.
The target concentracions in the survey originate from the European Reference Laboratory for Glycohemoglobinthat have used two different HPLC methods for the targets. The targets are measured according to IFCC and have an assigned DCCT concentration.
Odense is supervising the Labquality external quality assurance program for HbA1c in Denmark.

3.4. Planning of the evaluation

Background for the evaluation
Bio-Rad applied to SKUP for an evaluation of in2it after implementing various improvements of the system during 2008. The major changes compared to older versions of in2it are:

- The measuring time: prolonged from 7 minutes to 10 minutes
- Improvement of the gel
- Better mixing
- Improved venting to aid buffer flow around the cartridge
- Improved stability

Inquiry about an evaluation
Early in 2009 Tomas Nielsen, Instruments and applications Specialist, Clinical Diagnostic group, Nordic region, Bio-Rad, asked SKUP to do an evaluation of in2it HbA1c.

Meetings, contract and protocol
Meeting in Odense 5th of February 2009: Participants: Jan Barrack, Director of R&D, Quality and Regulatory, Bio-Rad Laboratories Deeside, Rebecca Howard, Tomas Nielsen, Bio-Rad, Esther Jensen, Nina Brøgger, SKUP.
The testing was demonstrated by Bio-Rad. Nina tested capillary, venous and control samples. It was assured that the 4 instruments were measuring the same concentrations in the same samples. The protocol was discussed during the meeting.

A new version of the protocol was written. This protocol was accepted by Bio-Rad and SKUP and the contract was signed on the 30th March 2009 by Jan Barrack, Bio-Rad Laboratories Deeside and Åsa Spängs, Sales Manager CDG, Nordic Region, Bio-Rad Laboratories AB, Sweden.

Tomas Nielsen visited Odense on the 2nd April and installed new software in the instruments.

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

The primary care evaluation took place in centres sending samples to Hillerød Hospital. Laboratory consultant Inge Lykke Pedersen was contact person to the primary care centres.
Primary Care Centre 1 (GP1): Gribskov Lægecenter, Lundehuset, Tisvildevej 28, 3210 Vejby. At this primary care centre there are six general practitioners, two secretaries, two nurses and a laboratory technician. The laboratory technician managed the samples. Normally the HbA1c samples were sent to Hillerød Hospital for analysing.
Primary Care Centre 2 (GP2): Noer-Hansen and Søndergaard, Slangerupgade 16D, 3400 Hillerød. At this primary care centre there are two general practitioners, two nurses and a secretary. The laboratory work was performed by the two nurses. Normally the HbA1c samples were sent to Hillerød Hospital for analysing.

The evaluation should have taken place only in Odense; however it was delayed because the in2it reagents arrived just before SKUP moved from Odense to Hillerød. Stine B Weber, SKUP, had to

finalize the hospital testing in Hillerød. The statistical calculations were made by Esther Jensen, who also wrote most of the report.

Table 4. Evaluation sites and persons involved

Place	Person	Title	Task
Hillerød Hospital	Esther A Jensen	Physician	Author of report
OUH	Nina Brøgger	Technologist	Hospital testing
OUH	Palle Fruekilde	Pharmacologist MSc.	Responsible for comparison method
OUH	Gitte Åkerlund	Technologist	Responsible for comparison method
Hillerød Hospital	Stine B. Weber	Biochemist, MSc	Hospital testing
Hillerød Hospital	Steen Ingemann Hansen	Biochemist, MSc	Responsible for comparison method
Hillerød Hospital	Grete Schrøder	Technologist	Responsible for comparison method
Hillerød Hospital	Inge Lykke Pedersen	Technologist	Primary care testing
General practice	Gribskov Lægecenter, Vejby, Helle Gonzales	Technologist	Primary care testing
General practice	Noer-Hansen and Søndergård, Hillerød Ann-Dorte Christensen Lena Hansen	Nurses	Primary care testing

3.4.2. *Blood sampling devices*

The capillary punctures were made with the sampling tool the technologists were accustomed to. In Odense and Hillerød venous blood was drawn into EDTA tubes (K2).

3.5. Evaluation procedure in the hospital laboratory

The Hospital evaluation was performed in the Department of Clinical Biochemistry, Odense University Hospital. The comparison method in Odense is Tosoh G8. Samples at three levels were sent to Malmø five times and to Hillerød three times to compare the two Danish laboratories measuring HbA1c (DCCT) with Mono S in Sweden.
The duplicates in the comparison method were measured on two Tosoh instruments to achieve the mean-comparison result. In the field method all samples from one patient were measured on the same in2it instrument and only one lot of test cartridges was used.

3.5.1. *The aim of the evaluation*

The evaluation in the hospital laboratory deals with:

- Determination of the imprecision with 100 venous and 40 capillary patient samples in a hospital laboratory
- Comparison with the established Tosoh method for HbA1c. Determination of trueness and accuracy
- Evaluation of user-friendliness
- Investigation of possible interference of carbamide (urea) and haemolysis

3.5.2. *Training*

The supplier was responsible for the training on the in2it. Training was given by Bio-Rad to Nina Brøgger, Odense and to Inge Lykke Pedersen and Stine B Weber, Hillerød Hospital.

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

All data, specimen collection, days of analyses, lot numbers on test cartridges and controls, results, etc. were reported. The lot numbers were used box by box at random; the first lot was used for 9 patients, the second for 45 patients, the third for 19, and the fourth lot for the last 27 patients.

3.5.4. *Internal quality control*

The System Check Cartridge and a Bio-Rad control were run in duplicate every day samples were tested on the in2it instrument. Every second day the high Bio-Rad control was analysed and every second day the low Bio-Rad control was analysed.

3.5.5. *Recruitment of the patients*

- 40 random out-patients with diabetes agreed to participate in the hospital evaluation and have two skin penetrations for capillary-testing on in2it as well as two measurements using venous EDTA blood.
- 11 patients in the haemodialysis department were asked to participate before and after dialysis (venous EDTA blood).
- 49 EDTA samples from the routine HbA1c section were included. A maximum of five samples were to have a concentration less than 4,0% or higher than 14,0% HbA1c.

A total of 100 venous blood samples and 40 capillary samples were analysed in duplicates.

3.5.6. *Handling of specimens and measurements*

Blood samples were collected from diabetic patients that had their HbA1c measured in the out-patient clinic.

The 40 outpatients had capillary tests performed in duplicate. Duplicate measurements were performed, that is two skin perforations in two separate fingers, on in2it. Following they had a total of three EDTA tubes taken in one venous puncture. The first sample was analysed in routine. The second sample was immediately analysed in duplicate on the same in2it instrument as the capillary samples: A volume of 10 µl EDTA was applied into the test cartridge twice by the use of the blood key. The sample in the third tube was analysed on another Tosoh than the first comparison sample (the routine sample). In total, four measurements were carried out on in2it per patient.

Four measurements were also performed on in2it for the 11 patients in the haemodialysis department. Before and after haemodialysis a duplicate measurement on the in2it was performed (venous EDTA blood). Two measurements were performed on two Tosoh instruments, one drawn before, and one after dialysis. The patients had urea measured before and after dialysis as well.

Two venous measurements were performed on in2it for the last 49 individuals. The duplicate measurement on the in2it was performed on the same venous EDTA blood tube.

The samples were measured within 24 hours from the sampling time on both Tosoh and in2it. After analysing on the comparison method, the EDTA whole blood was centrifuged and the degree of haemolysis was determined in four categories visually by colour.

All results were registered by the evaluator doing the practical work. If an instrument showed an error while analysing a sample, a new measurement was made on the same instrument. The errors were reported. All results were signed by the person doing the practical work. Data was recorded in Excel.

Samples from the routine production were analysed on Tosoh and in2it and sent to Malmø five times and Hillerød three times before, during and after the evaluation.

3.5.7. *Evaluation of user-friendliness*

Nina Brøgger evaluated the user friendliness immediately after testing had ended. She used the evaluation form with the four categories; manual, time factors, Quality Assurance and operation facilities.

3.6. Evaluation procedure in Primary Care

40 diabetic patients in each of two primary care centres were asked to participate in the evaluation.

3.6.1. *Evaluation procedure in the primary health care*

40 diabetic patients in each of two primary care centres, having their HbA1c measured routinely, agreed to participate in the evaluation. Each patient had one capillary sample and one venous EDTA sample measured on in2it. All results were registered as in 3.5.6.

The samples from the 40 patients were measured on one instrument and using four lot numbers in each primary care centre.

GP1 did the measurements during 49 days.
GP2 did the measurements during 210 days.

3.6.2. *The aim of the evaluation*

- Determination of the imprecision with 40 patient samples at two primary care centres. The duplicate measurement was changed from two capillary samples to one capillary sample and on venous sample
- Determination of the imprecision with 40 capillary patient samples at two primary care centres
- Comparison with the established Tosoh method for HbA1c. Determination of trueness and accuracy
- Evaluation of user-friendliness

3.6.3. *Training*

The supplier was responsible for training on in2it. Training was given by Bio-Rad to the staff in the two primary care centres. When the evaluation began, the evaluators had to handle in2it on their own, without any supervision or correction from the manufacturer/supplier. If there were questions they were addressed to SKUP.

3.6.4. *Evaluation procedure in the primary care centres*

All data, specimen collection, days of analyses, lot numbers on test cartridges and controls, results etc. were reported.

3.6.5. *Internal quality control*

Two Bio-Rad controls were used every day in primary care centre 1.
The System Check Cartridge and one Bio-Rad control were run in primary care centre 2.

3.6.6. *Recruitment of the patients*

40 individuals with diabetes agreed to participate in the evaluation in each primary care centre.

3.6.7. *Handling of specimens and measurements in the primary health care centres*
Blood from a finger prick was first filled into the blood key and applied to the test cartridge. Then the patients had two EDTA tubes taken in one venous puncture. One EDTA sample was used for testing on the in2it instrument. The second sample was sent to Hillerød by ordinary sample transport in room temperature. In the Department of Clinical Biochemistry HbA1c was analysed in routine. Then each sample was measured again in another Tosoh instrument.
The samples were measured within 48 hours on both Tosohs and on the in2it in Hillerød.

All results were registered by the evaluator doing the practical work. If an instrument showed an error while analysing a sample, a new measurement was not performed. The errors were reported. All results were signed by the person doing the practical work. Data was recorded in a form produced by Nina Brøgger.

One instrument and four lots of test cartridges were used in each primary care centre.

3.6.8. *Evaluation of user-friendliness*
The evaluators filled in the user friendliness form after completing the testing. They were also questioned orally about their opinion on the four categories manual, time factors, quality assurance and operating facilities.

4. Statistical expressions and calculations

The definitions in this section come from the ISO/IEC Guide 99; International Vocabulary of Metrology, VIM (19).
The definitions in this section: International Vocabulary of Metrology, VIM (19).

4.1. Statistical terms and expressions

4.1.1. *Precision*

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

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

Repeatability is the agreement between the results of consecutive measurements of the same component carried out under identical measuring conditions (within the measuring series). Reproducibility is the agreement between the results of discontinuous measurements of the same component carried out under changing measuring conditions over time. The reproducibility includes the repeatability.

To be able to interpret an assessment of precision, the precision conditions must be defined. The "specified conditions" can be, for example, repeatability, intermediate precision, or reproducibility conditions of measurement. The precision conditions in this evaluation are close to the defined *repeatability* and *reproducibility* conditions, and the imprecision is expressed as repeatability CV and reproducibility CV. The imprecision is summarised in tables.

4.1.2. *Accuracy*

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

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

4.1.3. *Trueness (bias)*

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

Trueness is measured as bias (systematic errors). Bias is a systematic deviation from the reference method. Trueness is descriptive in general terms (good, poor), whereas bias is the

estimate, reported in the same unit as the analytical result or in %. The bias at concentration levels (high, medium, low) is summarised in tables.

4.2. Statistical calculations

4.2.1. *Statistical outliers*

All the results are checked for outliers according to Burnett (20), with repeated truncations. The model takes into consideration the number of observations together with the statistical significance level for the test. The significance level is often set to 5%, therefore also in this evaluation. Where the results are classified according to different concentration levels, the outlier-testing is done at each level separately. Statistical outliers are excluded from the calculations. Possible outliers will be commented on under each table.

4.2.2. *Calculations of imprecision*

The imprecision is calculated with the following formula:

$SD = \sqrt{\frac{\sum d^2}{2n}}$, d = difference between duplicate measurements, n = number of differences

The imprecision may also be calculated with the following formula:

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

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

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

4.2.3. *Calculation of trueness*

To measure the trueness of the results on the in2it, the average bias at three concentration levels is calculated based on the results obtained under standardised and optimal measuring conditions.

4.2.4. *Calculation of accuracy*

To evaluate the accuracy of the results on the in2it, the agreement between in2it and the comparison method is illustrated in difference plots. In the plots the x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at in2it with three lots and the mean value of the duplicate results at the comparison method.

5. Results and discussion

The samples from the patients were measured on four in2it instruments and four lot numbers of test cartridges were used. It was not a part of the evaluation to investigate if the instruments were in agreement with each other. The supplier guaranteed that the lot numbers gave corresponding results, a difference of 0,4 HbA1c% was accepted.
At the familiarisation the same control samples were run on all instruments and on all lot numbers as well as the System Check Cartridge.

5.1. Number of samples

Table 5. Number of tests cartridges used

Evaluation site	Number of test cartridges used
Hospital laboratory	
To get familiar with test	54
Venous samples	200
Capillary samples	80
Control samples	80
Interference	22
Additional testing	46
Primary care	
To get familiar with test	80
Primary Care 1 samples	80
Control samples	22
Primary Care 2 samples	80
Control samples	49

5.2. Missing or excluded results

Six samples from the hospital and three samples from the primary care centres were not measured in duplicates on the comparison method within the time limit.

5.3. Failed measurements

Hospital laboratory: One test cartridge failed because of technical difficulties with the blood key
One test cartridge had no barcode
Primary care Two test cartridges produced no results.

In total four Test Cartridges were discarded due to errors, which is less than 1%.

5.4. Analytical quality of the designated comparison methods

5.4.1. *The precision of the Odense comparison method*

Table 6. Repeatability of the Odense Tosoh G8 with venous patient samples in the hospital laboratory

Level	Comparison method interval (%, DCCT)	n	Excluded results	Tosoh G8 HbA1c mean (%, DCCT)	CV% (95% CI)
Low	5,0 — 5,7	33	0 (*2)	5,4	1,0 (0,8 — 1,3)
Medium	5,7 — 7,7	34	0 (*3)	6,5	0,6 (0,5 — 0,8)
High	7,7 — 12,7	33	0 (*1)	9,1	0,6 (0,5 — 0,8)
All	5,0 — 12,7	100	0 (*6)	7,0	0,8 (0,7 — 0,9)

* For six comparison method results there were no duplicate measurements.

The calculated CV values are practical measures of repeatability, but they also include some additional variance components. The measurements were performed in 57 days, the duplicate measurements were typically analysed within two days, and the duplicate samples were analysed on two different instruments of Tosoh G8.

5.4.2. *The trueness of all Tosoh participants in the Labquality EQA program 3044*

Table 7. Bias of all Tosoh participants in the Labquality HbA1c EQA program 3044

Survey	Quality Assurance Labquality HbA1c program 3044	Target (DCCT%)	Tosoh mean (DCCT%) n=19 to n=25	Δ HbA1c Tosoh-Target	Bias (%) Tosoh n=19 to n=25
1/09	Labquality 1 (DCCT%)	11,28	11,59	0,31	2,7
1/09	Labquality 2 (DCCT%)	6,43	6,48	0,05	0,8
2/09	Labquality 1 (DCCT%)	9,05	9,2	0,15	1,7
2/09	Labquality 2 (DCCT%)	6,2	6,24	0,04	0,6
3/09	Labquality 1 (DCCT%)	8,66	8,69	0,03	0,3
3/09	Labquality 2 (DCCT%)	6,31	6,47	0,16	2,5
4/09	Labquality 1 (DCCT%)	8,69	8,8	0,11	1,3
4/09	Labquality 2 (DCCT%)	6,35	6,51	0,16	2,5
5/09	Labquality 1 (DCCT%)	8,36	8,44	0,08	1,0
5/09	Labquality 2 (DCCT%)	6,44	6,57	0,13	2,0
1/10	Labquality 1 (DCCT%)	4,96	5,11	0,15	3,0
1/10	Labquality 2 (DCCT%)	6,44	6,68	0,24	3,7
mean					1,9

Table 7 shows that the results of the Tosoh participants have a positive bias compared to all results in the Labquality HbA1c program 3044, where two fresh samples are sent to laboratories five times a year. Every laboratory is compared to all participants, to the target, and to the group of instruments their method belongs to. 19 to 25 laboratories using Tosoh participated in the 2009

survey. The average bias of the Tosoh participants was +1,9%. The quality goal is that the bias for the individual laboratory should be less than ±3,0% (6).

5.4.3. *External quality control for the results for the two results for the two comparison methods*
EUROTROL (lyophilised) material with DCCT and IFCC target values was run every 14 days. The goal for systematic deviation is a bias less than ±3,0% (6). Until 2009 the HbA1c was measured in % (DCCT) in Odense. However, all targets were also given in HbA1c mmol/mol (IFCC). The calculations were made in DCCT concentrations.

Part of the external quality control program also included samples with target for a diabetic and a non-diabetic individual, data not shown.
The evaluation were done in the period from April 2009 to February 2010

Table 8. The comparison methods in Odense and Hillerød, compared with the Tosoh group in Labquality HbA1c EQA program 3044

Survey	**Quality Assurance Labquality HbA1c** program 3044	**Tosoh mean (DCCT%)** n=19 to n=25	**Tosoh Odense** DCCT%	**Tosoh Hillerød** DCCT%	**Deviation Odense** %	**Deviation Hillerød** %
1/09	Labquality 1 (DCCT%)	11,59	11,5	11,6	-0,8	0,1
1/09	Labquality 2 (DCCT%)	6,48	6,5	6,5	0,3	0,8
2/09	Labquality 1 (DCCT%)	9,2	9,2	9,3	0,0	0,7
2/09	Labquality 2 (DCCT%)	6,24	6,3	6,3	1,0	1,0
3/09	Labquality 1 (DCCT%)	8,69	8,6	8,4	-1,0	-3,0
3/09	Labquality 2 (DCCT%)	6,47	6,4	6,4	-1,1	-1,1
4/09	Labquality 1 (DCCT%)	8,8	8,9	8,8	1,2	0,4
4/09	Labquality 2 (DCCT%)	6,51	6,5	6,5	-0,2	-0,2
5/09	Labquality 1 (DCCT%)	8,44	8,4	8,4	-0,5	-0,5
5/09	Labquality 2 (DCCT%)	6,57	6,6	6,6	0,5	0,5
1/10	Labquality 1 (DCCT%)	5,11	5,2	5,2	1,8	1,0
1/10	Labquality 2 (DCCT%)	6,68	6,8	6,7	1,9	-0,2
mean					+0,2	±0,0

As seen above, the comparison method in Hillerød had no bias and the comparison method in Odense had just a small bias +0,2%, compared to the Tosoh group in the Labquality results. The bias was checked in the range 5,11 to 11,59 HbA1c% (DCCT)

5.4.4. *Internal quality control with the Odense comparison method*
The imprecision with internal control samples run every two hours on all Tosohs using a self-made control with a concentration of 5,60 HbA1c% (DCCT).

Table 9. Internal quality assurance of the Tosohs in 2009 in Odense

Month	jan-09	feb-09	mar-09	apr-09	may-09	jun-09	jul-09	aug-09	sep-09	oct-09	nov-09	dec-09	all
mean Tosoh G8-1	5,69	5,68	5,67	5,7	5,72	5,68	5,69	5,76	5,69	5,65	5,63	5,78	5,70
mean Tosoh G8-2	5,64	5,68	5,75	5,7	5,73	5,7	5,72	5,72	5,68	5,69	5,61	5,67	5,69
n Tosoh G8-1	87	75	84	79	78	89	63	78	76	88	88	65	79,17
n Tosoh G8-2	84	98	72	78	77	88	61	80	114	85	74	65	81,33
CV% Tosoh G8-1	1,3	2,04	1,2	1,05	0,9	1,09	1,13	1,09	1,34	1,31	1,2	1,7	1,28
CV% Tosoh G8-2	0,99	1,01	1,4	0,96	1,04	1,41	0,91	1,08	1,15	1,07	0,95	1,3	1,11

As seen in table 9 the imprecision was less than 2% for both Tosoh G8 every month.

5.4.5. *External quality control with the Hillerød comparison method*
As demonstrated in table 8 the three Tosohs in Hillerød had 0,0% deviation in average during the five Labquality surveys in 2009 and the first survey in 2010 when compared with other Tosoh measurements. The Tosoh group had a bias of about +1,9% in the same period.

5.4.6. *Internal quality control with the Hillerød comparison method*
For the control, DEKS medium, that was run twice a day, the CV% for all Tosohs was less than 1% at the concentration 8,11% HbA1c (DCCT) and the bias was less than +2%.

Table 10. Quality control results during 2009 with the Hillerød comparison method

Month	jan-09	feb-09	mar-09	apr-09	maj-09	jun-09	jul-09	aug-09	sep-09	okt-09	nov-09	dec-09	mean
Target	**8,00**	**8,00**	**8,00**	**8,00**	**8,11**	**8,11**	**8,11**	**8,11**	**8,11**	**8,11**	**8,11**	**8,11**	
Mean Tosoh 1	8,30	8,20	8,20	8,20	8,30	8,20	8,20	8,10	8,20	8,20	8,20	8,20	8,21
Mean Tosoh 2	8,20	8,10	8,20	8,20	8,30	8,30	8,30	8,20	8,20	8,20	8,10	8,10	8,20
Mean Tosoh 3	8,30	8,10	8,10	8,10	8,20	8,20	8,20	8,10	8,20	8,10	8,20	8,30	8,18
n Tosoh 1	17	16	23	17	20	18	18	20	22	22	20	19	19,3
n Tosoh 2	15	16	21	17	19	20	21	20	23	20	20	19	19,3
n Tosoh 3	17	16	16	15	17	19	12	20	22	20	20	17	17,6
Deviation Tosoh 1	0,30	0,20	0,20	0,20	0,19	0,09	0,09	-0,01	0,09	0,09	0,09	0,09	0,14
Deviation Tosoh 2	0,20	0,10	0,20	0,20	0,19	0,19	0,19	0,09	0,09	0,09	-0,01	-0,01	0,13
Deviation Tosoh 3	0,30	0,10	0,10	0,10	0,09	0,09	0,09	-0,01	0,09	-0,01	0,09	0,19	0,10
Bias DEKS % Tosoh 1	3,75	2,50	2,50	2,50	2,34	1,11	1,11	-0,12	1,11	1,11	1,11	1,11	1,68
Bias DEKS % Tosoh 2	2,50	1,25	2,50	2,50	2,34	2,34	2,34	1,11	1,11	1,11	-0,12	-0,12	1,57
Bias DEKS % Tosoh 3	3,75	1,25	1,25	1,25	1,11	1,11	1,11	-0,12	1,11	-0,12	1,11	2,34	1,26
CV% Tosoh 1	0,9	0,8	0,6	1,1	0,7	0,6	0,6	0,6	0,7	0,4	0,5	0,6	0,68
CV% Tosoh 2	0,7	1,1	0,6	0,8	0,5	0,3	0,4	0,6	0,6	0,6	1,3	0,1	0,63
CV% Tosoh 3	0,9	0,6	0,7	0,6	0,3	0,0	0,0	0,6	0,6	0,7	1,0	0,3	0,53

Table 10 shows the results from the three Tosoh instruments in Hillerød (Tosoh 1, Tosoh 2 and Tosoh 3). Target (DCCT%) refers to the calibrator from DEKS that originates from Weycamp.

DEKS also distributes material from BIORAD with a target. Hillerød Hospital buys both materials, but in table 10 we only report the calibrator control results The laboratory uses these as daily quality controls for HbA1c.

The differences between the Tosoh instruments have never been ≥0,4 DCCT%.

5.4.7. *Comparison of results of Tosoh, in2it and Mono S*

Three samples (low, medium and high) were sent from Odense to Malmø five times (and to Hillerød three times). The duplicate results on Tosoh in Odense, in2it in Odense, and Mono S in Malmø are shown in table 11 and visualised in the difference plot in figure 4. Unfortunately, the results from Hillerød were lost in the relocation process of SKUP.

The Mono S measurements were performed four days after the samples were drawn. Three samples had stayed at room temperature for seven days when measured in triplicates in Malmø.

Table 11. Comparison of 15 samples measured with Mono S, Tosoh and in2it

	Odense in2it		**Odense Tosoh G8**		**Malmø mono S**		
Sample/unit	**HbA1c (DCCT%)**		**HbA1c (DCCT%)**		**HbA1c (Mono S %)**		
low 1	5,3	5,7	5,1	5,3	4,11	4,09	
medium 1	8	8,2	8,3	8,3	7,19	7,15	
high 1	12,5	12,1	11,8	11,9	11,58	11,59	
low 2	5,3	5,2	5,2	5,3	4,33	4,33	
medium 2	7,1	7,6	8,1	8	7,18	7,18	
high 2	8,9	8,7	9,3	9,2	8,11	8,08	
low 3	5,6	5,1	5,2	5,2	*3,87**	*3,85**	*3,79**
medium 3	7,8	7,8	8,1	8,1	*7,13**	*7,12**	*7,08**
high 3	10,1	10	10,4	10,4	*9,74**	*9,64**	*9,78**
low 4	5,1	5,5	5	5,1	4,05	4,03	
medium 4	7,8	8,1	8,2	8,1	7,65	7,6	
high 4	11,5	11,6	11,5	11,7	12,04	12,06	
low 5	5	5,2	4,6	4,3	3,4	3,37	
medium 5	7,7	8	7,8	7,7	6,51	6,56	
high 5	10,8	11,2	10,5	10,4	9,6	9,61	

* The samples were kept at room temperature for seven days before they were analysed in triplicates in Malmø with Mono S. Fraction HbA3 was high, which indicates that a sample is old.

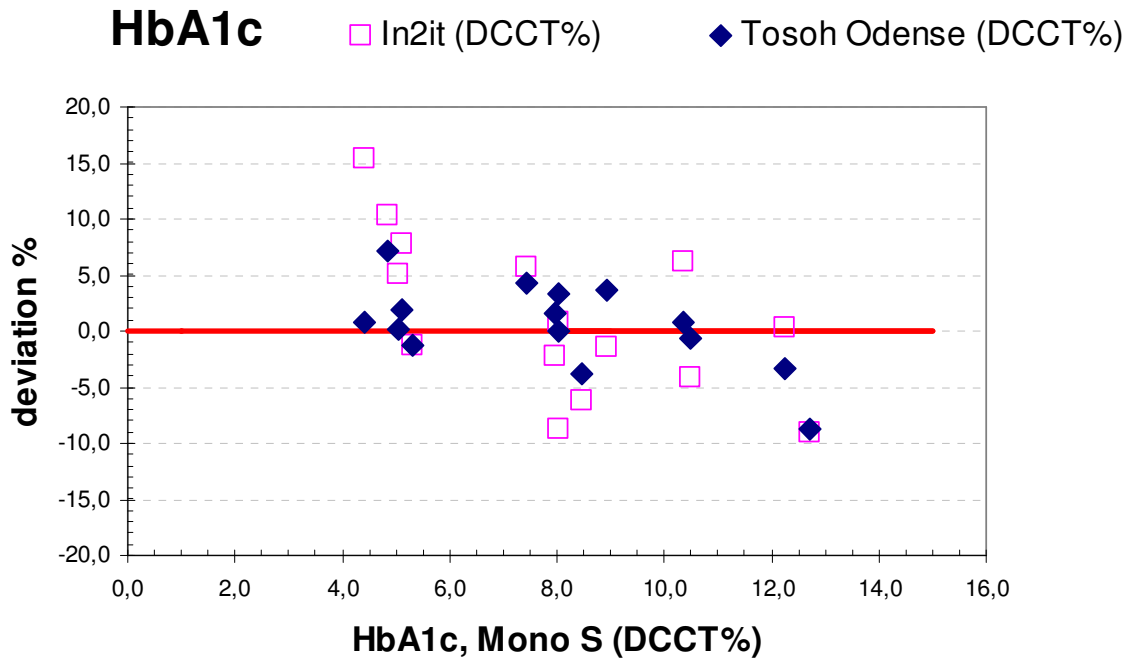

Figure 4. The X-axis shows the mean of the duplicate or triplicate Mono S measurement results expressed in DCCT%. The y-axis shows the deviation of the duplicate measurements of HbA1c Tosoh and in2it shown in percentages. The Mono S values are first recalculated to DCCT values with the equation: DCCT = 0,956 x Mono S + 1,182

As expected the Mono S values are about 1,0% lower than HbA1c (DCCT). However, when using the equation recommended by EQUALIS DCCT = 0,956 x Mono S + 1,182 it is seen that the Tosoh and the in2it are placed around deviation = 0, which means there are no significant differences between the measurement results in Malmø, Odense and in2it. The CV% for the 15 in2it results was 3,3%. For the Tosoh results the CV was 1,6% and the results were measured in two Tosoh instruments during two days. For Mono S the CV was 0,3%.

5.5. Analytical quality of in2it used in a hospital laboratory

5.5.1. *System Check*

A reusable System Check Cartridge was run daily to check that the optical and operating systems of the Analyzer were working correctly. The System Check Cartridge was analysed in the hospital laboratory, n=23, and always gave the same result: 10,0 HbA1c%.

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

Two capillary samples were taken from 40 individuals for measurements on in2it and in addition two venous samples were taken from 100 individuals. The results are checked to meet the assumption that there is no difference between the first and the second measurement. Table 12 shows that no systematic difference was pointed out between the paired measurements. A difference between the measurements would be unexpected. It was difficult for the primary care centres to persuade the patients to participate in the evaluation and have two capillary samples collected for the in2it instrument. Therefore it was demonstrated that the agreement between venous and capillary sample results in the hospital laboratory was good (table 12) despite the different matrix.

Table 12. Comparison of the 1st and 2nd measurements on in2it

HbA1c	n	Mean 1st measurement (HbA1c %, DCCT)	Mean 2nd measurement (HbA1c %, DCCT)	Mean difference 2nd – 1st measurement (HbA1c %, DCCT)	95% CI for the mean difference, (HbA1c %, DCCT)
capillary	40	6,34	6,31	0,03	-0,06 - +0,13
venous	100	6,99	6,99	0,00	-0,05- +0,06
capillary/venous	40	6,34	6,31	0,03	-0,00 - +0,06

The conclusion is, that there are no significant difference between the first and the second measurements (table 12), or between the capillary and venous results from the same patient in the primary care evaluation.

5.5.3. *The precision of in2it*

Repeatability under standardised and optimal measuring conditions in a hospital laboratory was obtained with capillary blood samples (table 14) venous blood samples (table 13) and the combination of capillary and venous samples (table 15).The raw data is not shown.
Repeatability was calculated for three subgroups: the highest HbA1c-values (n=33), the lowest (n=33) and the middle level of HbA1c (n=34). The three groups are chosen according to their concentration in the comparison method.

Table 13. Repeatability of in2it with venous patient samples in the hospital laboratory

Level	Comparison method interval (%, DCCT)	n	Excluded results	in2it HbA1c mean (%, DCCT)	CV% (95% CI)
Low	5,0 — 5,7	33	0	5,5	3,1 (2,5 — 4,1)
Medium	5,7 — 7,7	34	0	6,4	3,7 (3,0 — 4,9)
High	7,7 — 12,7	33	0	9,1	2,1 (1,7 — 2,8)
All	5,0 — 12,7	100	0	7,0	3,1 (2,7 — 3,6)

The calculated CV values are practical measures of repeatability, but they also include some additional variance components arising from changes in conditions during the collection of measurement data: Three instruments and four lots of cartridges were used.

Table 14. Repeatability of in2it with capillary patient samples in the hospital laboratory

Level	Comparison method interval (%, DCCT)	n	Excluded results	in2it HbA1c mean (%, DCCT)	CV% (95% CI)
Low	5,0 — 5,7	20	0	5,5	3,8 (3,0 — 5,6)
High	5,8 — 10,1	20	0	7,2	4,1 (3,2 — 6,0)
All	5,0 — 10,1	40	0	6,4	4,0 (3,3 — 5,1)

The calculated CV values are practical measures of repeatability, but they also include some additional variance components arising from changes in conditions during the collection of measurement data: Three instruments and four lots of cartridges were used. Despite this, the goal of CV% less than 4% was fulfilled for both capillary and venous samples.

Discussion

Bio-Rad wanted to demonstrate that the in2it can measure both venous and capillary samples with good analytical quality in a hospital laboratory as well as in primary care.

It was difficult for the primary care centres to persuade the patients to participate in the evaluation and have two capillary samples collected for the in2it instrument as the analytical time is 10 minutes. Therefore it was demonstrated that the agreement between venous and capillary sample results in the hospital laboratory was good (table 12) despite the different matrix. It was then decided to measure one capillary and one venous sample in the same patient at the primary care centres.

Table 15. Repeatability of in2it with venous/capillary duplicate results in the hospital laboratory

Level	Comparison method interval (%, DCCT)	n	Excluded results	in2it HbA1c mean (%, DCCT)	CV% (95% CI)
Low	5,0 — 5,7	20	0	5,5	3,4 (2,6 — 4,9)
High	5,8 — 10,1	20	0	7,2	3,2 (2,5 — 4,7)
All	5,0 — 10,1	40	0	6,4	3,3 (2,7 — 4,2)

The first sample in each duplicate was capillary and second sample was venous. The calculated CV values are practically measures of repeatability, but they also include some additional variance components arising from changes in conditions during the collection of measurement data: three instruments and four lots were used.

The quality goal for repeatability was a CV of less than 4%. Considering the background which is the first capillary and the first venous result, three instruments and four lot numbers used, a CV% of 3,3 is good.

5.5.4. *External quality control*

External control is possible in in2it. During the evaluation the controls in two levels that were used daily in Tosoh were also used in in2it. The controls were from Bio-Rad and they were manufactured to be used in all kinds of HbA1c instruments. The controls had a certificate for the target in the in2it instruments.
The reproducibility was assessed with the Bio-Rad control high and low in four lot numbers of test cartridges. Control material may have other matrix effects than whole blood, and may therefore give other results than results achieved with blood. The measurements were carried out in duplicates daily during the evaluation period. The reproducibility of in2it is shown in table 16. See raw data in attachment 2

Table 16. Reproducibility achieved with in2it and four lots in the hospital laboratory

Target	n	n	mean 5,5% (4,6—6,4)	mean 10,0% (8,7—11,3)	cv% 5,5 DCCT%	cv% 10,0 DCCT%
lot	low	high	low	high	low	high
29824	4	4	5,7	10,2	4,3	4,2
30176	16	10	5,8	10,4	5,2	3,9
30321	2	1	5,8	10,1	2,4	
30448	8	8	5,8	10,4	2,6	4,1
all	30	23	5,8	10,4	4,2	3,9

Discussion

The CV achieved with the control material was 4,2% and 3,9% for the low and the high control material, respectively. The CV% with the control material is higher than in the genuine patient material of 100 and 80 patients (3,1%, table 13 and table 20). However, this is often seen. The lower the CV% the better utility as a control material. The goal for imprecision with patient samples was a CV less than 4,0%.

5.5.5. *The trueness (bias) of in2it in the hospital laboratory*

The target value of the low control was 5,5 HbA1c% and the target value of the high control was 10,0 HbA1c%. The bias at the two concentrations (table 16) was 5,1% and 4,1% respectively.

Bias was also calculated for the 100 patients divided in three subgroups of HbA1c-values. The three groups were chosen according to their concentration in the comparison method.

Table 17. Bias of In2it HbA1c with venous and capillary patient samples in the hospital laboratory

Level group	Comparison method interval (%, DCCT)	n	Ex-cluded results	Comp. method mean (%, DCCT)	Bias (95% CI) units (%, DCCT)	Bias (95% CI) (%)
Venous samples						
Low	5,0 — 5,7	33	0	5,5	+0,1 (+0,0 — +0,2)	+2,0 (+0,8 — +3,4)
Medium	5,7 — 7,7	34	0	6,4	−0,1 (−0,2 — +0,0)	−1,2 (−2,6 — +0,2)
High	7,7 — 12,7	33	0	9,1	−0,0 (−0,1 — +0,1)	−0,3 (−1,7 — +1,0)
All	5,0 — 12,7	100	0	7,0	+0,0 (−0,1 — +0,1)	+0,2 (−0,6 — +1,0)
Capillary samples						
Low	5,0 — 5,7	20	0	5,4	+0,1 (+0,0 — +0,2)	+2,3 (+0,8 — +3,8)
High	5,8 — 10,1	20	0	7,2	+0,1 (−0,2 — +0,2)	+1,1 (−0,6 — +2,7)
All	5,0 — 10,1	40	0	6,3	+0,1 (−0,0 — +0,2)	+1,7 (+0,6 — +2,8)

The bias was between -1,2 % and +2,0%. Therefore both capillary and venous samples fulfil the goal for bias less than 4% in the hospital laboratory.

5.5.6. *The accuracy of in2it*

To evaluate the accuracy of the results on the in2it, the agreement between in2it and the comparison method is illustrated in three difference-plots. The plots show the deviations of single measurement results on in2it from the true value, and give a picture of both random and systematic deviation, reflecting the accuracy of in2it. The deviation is shown for the first measurements of the duplicate results only. Under standardised and optimal conditions four different lots of test cassettes were used. The allowed deviation in this evaluation was <±10%.

The accuracy of capillary samples on in2it, with four lots of test cassettes is shown in figure 5. The accuracy of venous samples on in2it is shown in figure 6, and the accuracy of capillary and venous samples together on in2it is shown in figure 7.

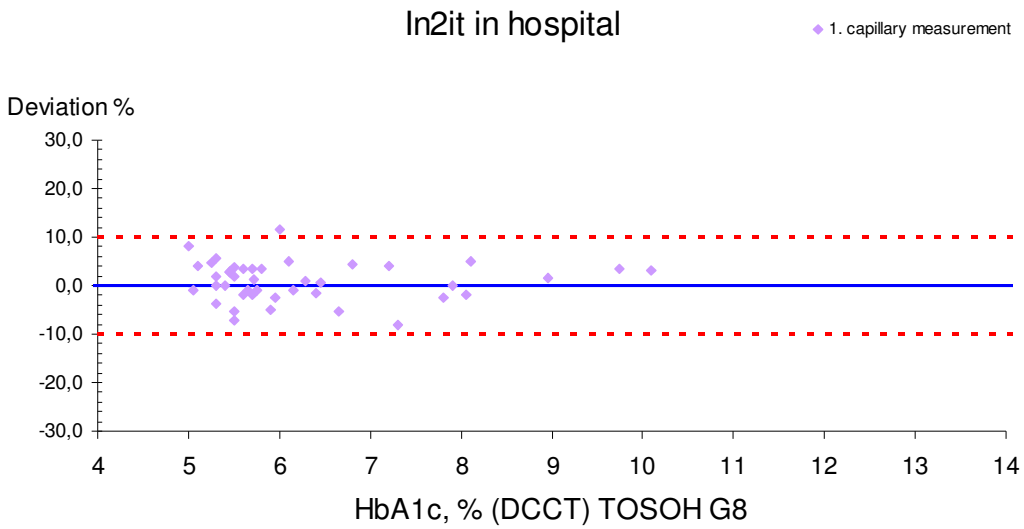

Figure 5. Difference plot. In2it results with capillary samples in the hospital laboratory.
The diagram shows the deviations of the capillary in2it HbA1c results from the venous comparison method results for 40 patient samples. X-axis = mean of comparison method duplicate results and Y-axis = ((the first in2it result– mean of the duplicate results with the comparison method)/ mean of the duplicate results with the comparison method) x 100. Stippled lines represent the tolerance limits ±10%. 95% of the results should be within the tolerance limits. There is one result outside the tolerance limits.

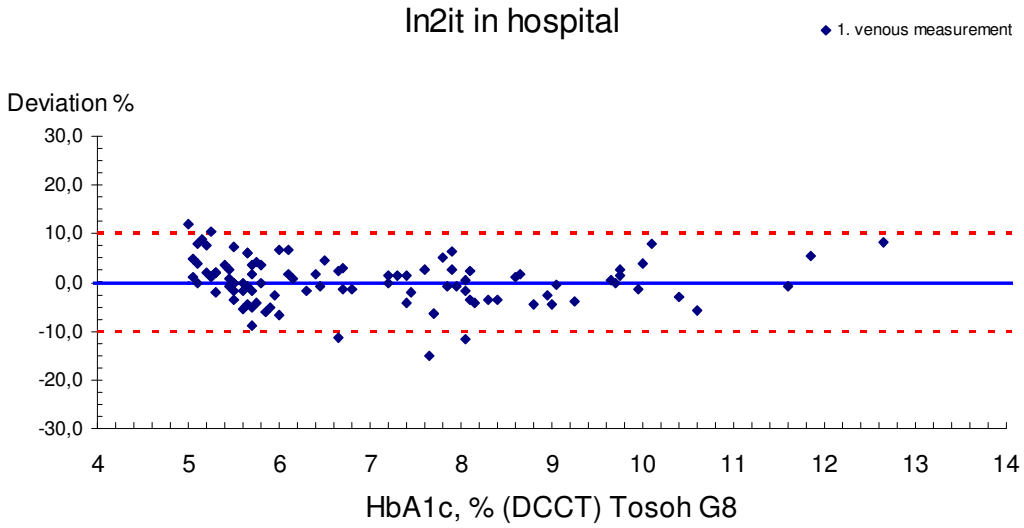

Figure 6. Difference plot, venous samples in the hospital laboratory.
The diagram shows the deviations of the venous in2it HbA1c results from the venous comparison method results for 100 patient samples. X-axis = mean of comparison method duplicate results and Y-axis = ((the first in2it result– mean of the duplicate results with the comparison method)/ mean of the duplicate results with the comparison method) x 100. Stippled lines represent the tolerance limits ±10%. 95% of the results should be within the tolerance limits. There are five results outside the tolerance limits.

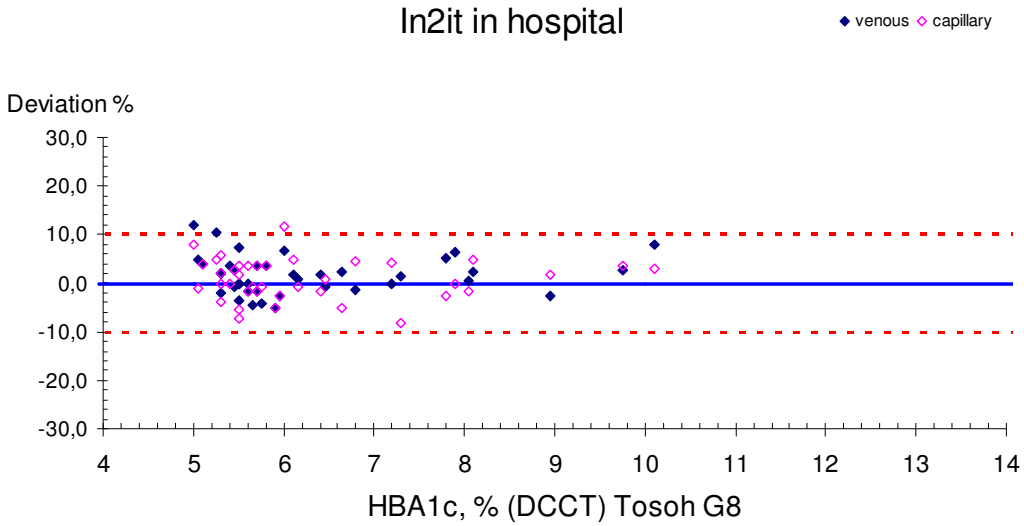

Figure 7. Difference plot, capillary and venous samples in the hospital laboratory.
The diagram shows the deviations of both the capillary as well as the corresponding venous in2it HbA1c results from the venous comparison method results for 40 patient samples. X-axis = mean of the comparison method duplicate results and Y-axis = ((the first in2it result– mean of comparison method, duplicate results)/mean of comparison method, duplicate results) x 100. Stippled lines represent the tolerance limits ±10%. 95% of the results should be within the tolerance limits. There are three of 80 results outside the tolerance limits.

Comments
95% of the results should be within the tolerance limits to fulfil the quality goals for Total Error of <±10%.
Capillary samples: Only 1 of 40 results exceeds the maximal allowed deviation of ±10%. In the hospital laboratory the capillary sample results fulfil the quality goals for Total Error.
Venous samples: 5 of 100 results exceed the maximal allowed total error (±10%). Thus the venous sample results in hospital laboratory fulfil the quality goals for Total Error of less than ±10%.
Capillary and venous sample results together: The Total Error of the capillary and venous sample results together in the hospital laboratory evaluation fulfils the quality goals for Total Error.

5.5.7. *Interference of urea*
It was investigated in patients in haemodialysis if urea (carbamide) was interfering with the in2it HbA1c results. 11 of the 100 duplicates samples in table 18 were drawn before and after haemodialysis. These 11 duplicates did not differ from the 89 other duplicates.

Table 18. HbA1c in in2it and Tosoh before and after haemodialysis

	Before haemodialysis				After haemodialysis			
Patient	In2it HBA1c%	In2it HBA1c%	Tosoh HBA1c%	Urea mmol/L	In2it HBA1c%	In2it HBA1c%	Tosoh HBA1c%	Urea mmol/L
1	7,1	7,0	7,4	29,7	7,0	6,8	7,5	10,9
2	5,6	5,9	6,0	19,1	6,0	6,1	6,1	5,1
3	5,5	5,6	5,0	17,8	5,2	5,4	5,1	6,9
4	8,7	8,7	8,5	26,0	8,6	8,6	8,6	13,8
5	5,4	5,5	5,5	19,8	5,1	4,7	5,5	7,7
6	5,2	5,0	5,6	21,4	5,6	5,1	5,7	7,5
7	5,6	5,5	5,1	14,9	5,2	5,0	5,2	5,1
8	5,3	5,2	5,6	15,6	5,2	5,2	5,6	7,0
9	5,4	5,7	5,7	11,0	5,7	5,8	5,7	3,1
10	5,1	5,2	5,1	6,5	5,2	4,9	5,1	4,0
11	6,5	6,9	7,6	26,8	6,8	6,8	7,7	9,8

The mean urea concentration before haemodialysis was 19,0 mmol/L and the urea concentration after dialysis was 7,4 mmol/L. There was no haemolysis in any of the tubes.
The duplicates before dialysis do not differ from the duplicate results after dialysis – nor do the Tosoh results.

As the half-life of the carbamylated haemoglobin is months (22,23) and not minutes, no conclusion regarding interference with carbamylated haemoglobin can be made from this study.

5.5.8. *Interference of haemolysis*

It was investigated whether haemolysis in the EDTA tubes induced a higher deviation from the comparison method results. All tubes were centrifuged after measuring the Hba1c concentration in Tosoh. The degree of haemolysis was compared to figures used in the lab. The groups were:

Group I < 17 µmol/L Hb
Group II ~ 17 µmol/L Hb
Group III ~ 46 µmol/L Hb
Group IV ~140 µmol/L Hb

There was a slight degree of haemolysis ~ 17 µmol/L Hb in 5 tubes and moderate haemolysis in one tube ~ 46 µmol/L Hb after centrifugation (1885 g for 9 minutes).

Table 19. Haemolysis

in2it HbA1c (DCCT%)	Tosoh	deviation %	haemolysis group
10,3	10,0	3,0	II
8,2	8,4	-2,4	II
8,0	7,9	1,3	II
5,7	5,9	-3,4	II
8,2	7,9	3,8	II
7,4	8,1	-8,7	III

Haemolysis of about 17 µmol/L Hb seems to be of no importance for the deviation with the comparison method. The only samples with moderate haemolysis about 46 µmol/L Hb had a deviation of 8,7%. Further controlled investigations have to be performed for final conclusions on this subject.

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5.6. Analytical quality of in2it used in primary health care

5.6.1. *System Check*

The re-usable System Check Cartridge was run daily in one of the two primary care centres and irregularly in the other centre. The System Check Cartridge (SCC) was measured a total of 39 times. All results except one were 10,0 and one was 10,1 HbA1c%. Accept limits 9,0-11,0.

5.6.2. *The precision of in2it*

The duplicate measurements on the in2it in primary care were done on one capillary sample and one venous sample. The results are seen below for the two centres. The sampling was done in 49 days in primary care one and during 217 days in primary care two.

Table 20. Repeatability of Bio-Rad in2it HbA1c with 1st capillary and 2nd venous patient sample in the primary care centres

Level	Comparison method interval (%, DCCT)	n	Excluded results	Bio-Rad in2it HbA1c mean (%, DCCT)	CV% (95% CI)
Primary care centre 1					
Low	5,1 — 6,8	20	0	6,3	3,3 (2,6 — 4,8)
High	6,8 — 10,5	19	1	7,9	2,8 (2,2 — 4,2)
All	5,6 — 10,5	39	1	7,1	3,1 (2,5 — 4,0)
Primary care centre 2					
Low	5,3 — 6,4	20	0	6,0	5,7 (4,4 — 8,3)
High	6,4 — 11,1	20	0	7,5	4,7 (3,6 — 6,9)
All	5,3 — 11,2	40	0	6,7	5,2 (4,3 — 6,7)
Primary care centre 2					
First	5,5 — 11,1	20	0	6,8	4,5 (3,4 — 6,5)
Last	5,5 — 8,2	13	0	6,4	6,4 (4,7 — 10,4)

The calculated CV values are practically measures of repeatability, but they also include some additional variance components arising from changes in conditions during the collection of measurement data: in each duplicate one sample was a venous one and one sample was a capillary one. In total 4 lot numbers were used.

Comments

The imprecision in Primary care centre 1 was less than 4% for both high and low concentrations. The 40 measurements were performed within a short period of time.

The measurements in primary care centre 2 were carried out during 210 days. The CV% was higher than 4% and it was observed that the imprecision seemed to increase during the evaluation. This is usually not the case in evaluations. Therefore calculations were made for the

first and the last measurements and an additional evaluation was performed with the same two lots of test cartridges by SKUP personnel in the hospital laboratory, see later.

Table 21. Imprecision of in2it with control samples at the primary care centres

	GP1		GP2
	control	control	control
	HbA1c (DCCT%)		HbA1c (DCCT%)
Target	5,5	10,0	5,5
n	10	10	7
CV%	3,7	5,0	6,3

Comments
The CV in the control material was between 3,7 and 6,3% for the low control material and 5,0% for the control at the concentration level of 10,0% (DCCT), see also table 16. The CV% in the control material is also in primary care higher than in the genuine patient material of 40 patients.

5.6.3. *The quality control materials from Bio-Rad for in2it in primary care*

The target value of the low control was 5,5 HbA1c%, (range 4,6-6,4 DCCT%) for in2it and the target value of the high control as well as the System Check Cartridge was 10,0 HbA1c DCCT%. Accept range for the high control in in2it was 8,7-11,3 DCCT%.

Table 22. Deviation of in2it HbA1c with the control samples at the primary care centres

	GP1		GP2
	low control	high control	low control
	HbA1c (DCCT%)		HbA1c (DCCT%)
Target	5,5	10,0	5,5
n	10	10	7
mean	5,7	10,0	5,6
CV%	3,7	5,0	6,3
deviation %	+3,5	+0,3	+1,0

Comments:
The GP's were asked to run a duplicate control every day in2it was used. The GP's should take no action on the results. GP1 run the low or the high control every day while the GP2 run the low control or the System Check Cartridge, see 5.6.1. 27 results in the control material were reported. The deviations from the target of the control samples were in the two primary care centres between +0,3 to +3,5%. It therefore seems likely that the material could be useful as a control for in2it.

5.6.4. *The trueness (Bias) of in2it in primary care*

Bias was calculated for the 40 patients divided in two subgroups of HbA1c-values in each primary care centre. The subgroups were chosen according to their concentration in the comparison method

Table 23. Bias of in2it HbA1c with patient samples at the primary care centres

Level group	Comparison method interval (%, DCCT)	n	Ex-cluded results	Comp. method mean (%, DCCT)	Bias (95% CI) units (%, DCCT)	Bias (95% CI) (%)
GP1						
Low	5,0 — 6,8	20	0	6,2	+0,1 (+0,1 — +0,2)	+1,4 (−1,0 — +3,7)
High	6,8 — 10,5	20	1	8,0	−0,1 (−0,3 — +0,0)	−1,2 (−2,7 — +0,4)
All	5,0 — 10,5	40	1	7,1	+0,0 (−0,1 — +0,1)	+0,2 (−1,3 — +1,6)
GP2						
Low	5,3 — 6,4	18	0	5,8	+0,1 (+0,0 — +0,3)	+2,6 (−0,1 — +5,4)
High	6,4 — 11,1	19	0	7,4	+0,3 (+0,1 — +0,5)	+0,3 (−2,2 — +2,7)
All	5,3 — 11,2	37	0	6,6	+0,2 (+0,1 — +0,3)	+1,4 (−0,4 — +3,2)

The capillary and venous results in the primary care fulfil the quality goals for bias, less than ±4%.

The bias of genuine samples as well as control samples on the in2it instrument in both of the primary care centres is less than the allowed ±4% for all concentration intervals. Surprisingly the bias% is better in primary care than in the hospital laboratory where the bias % was 5,1 and 4,1 for the low and the high control, respectably.

5.6.5. *The accuracy of in2it*

The accuracy in the primary care centres of both capillary samples and venous samples on in2it, (four lots of test cassettes) is shown in figure 8 and 9.

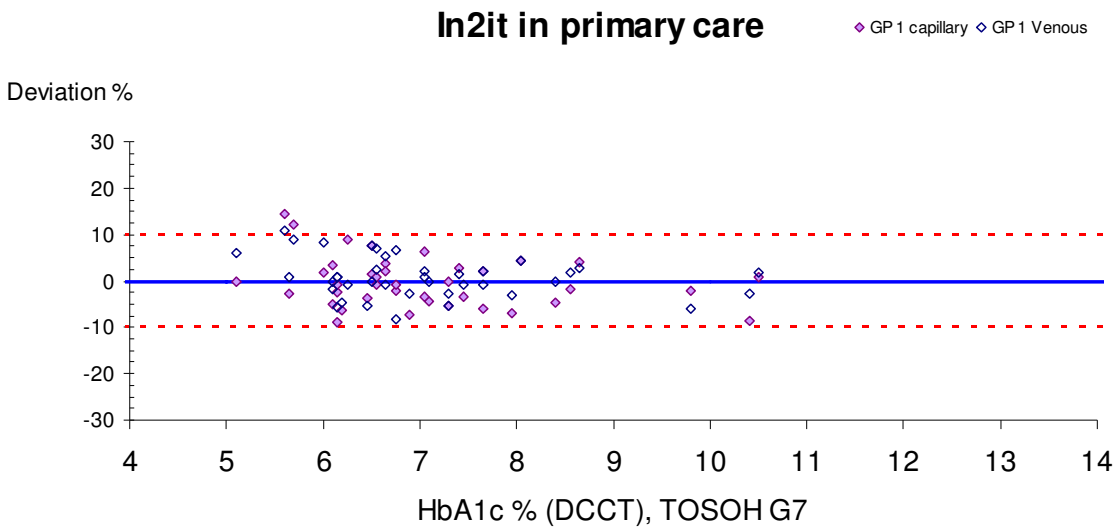

Figure 8. Difference plot, capillary and venous samples in the primary care centre 1.
The diagram shows the deviations of both the capillary samples as well as the corresponding venous in2it HbA1c results from the venous comparison method results for 40 patient samples. X-axis = mean of comparison method duplicate results and Y-axis = ((first in2it result– mean of comparison method, duplicate results)/mean of comparison method, duplicate results) x 100. Stippled lines represent the tolerance limits ±10%. 95% of the results should be within the tolerance limits. There are three of 80 results outside the tolerance limits.

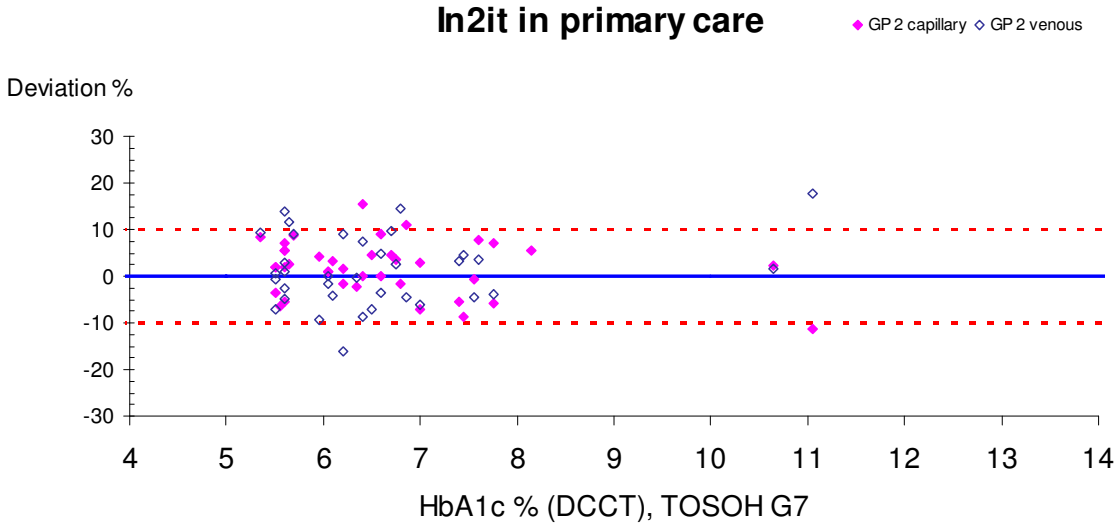

Figure 9. Difference plot, capillary and venous samples in the primary care centre 2.
The diagram shows the deviations of both the capillary samples as well as the corresponding venous in2it HbA1c results from the venous comparison method results for 40 patient samples. X-axis = mean of comparison method duplicate results and Y-axis = ((first in2it result– mean of comparison method, duplicate results)/mean of comparison method, duplicate results) x 100. Stippled lines represent the tolerance limits ±10%. 95% of the results should be within the tolerance limits. There are eight of 76 results outside the tolerance limits.

Comments
95% of the results should be within the tolerance limits to fulfil the quality goals for Total Error of <±10%.
In primary care centre 1 there are three of 80 results outside the tolerance limits. Both capillary and venous samples had a deviation less than ±10% in primary care centre 1and fulfilled the quality goals for allowed deviation.
In primary care centre 2 there are eight of 76 results outside the tolerance limits. The venous samples had a deviation higher than ±10%, this probably originates from the not significantly higher imprecision in primary care centre 2.

5.7. Additional evaluation

The Total Error less than ±10% for the combination of capillary and venous samples was fulfilled in hospital and primary centre 1 but not in primary centre 2. The CV was higher but not significantly higher in primary centre 2.

In the hospital laboratory an additional evaluation (January 22nd to January 26th) was performed. In the additional evaluation the instrument and lot number used in the primary care centre 2 and the instrument and lot number used in the hospital laboratory were used. Both lot numbers were about to expire. The evaluation stopped when they expired.

Table 24. Additional evaluation in hospital laboratory

LOT	**30176**	**30176**	**30321**	**30321**	**30321**
Date	22-01-2010	22-01-2010	25-01-2010	26-01-2010	26-01-2010
Tosoh HbA1c	11,8	11,8	5,7	9,7	9,7
Instrument used at	GP2	Hospital	GP2	GP2	GP2
Sample	A	A	B	C	C
	12,2	12,0	5,4	9,7	7,8
	11,9	12,0	5,5	9,7	10,8
	12,2	12,4	5,9	9,9	9
	12,1	12,7	5,8	9,8	7,9
	12,7	12,6	6,0	9,8	
	12,4	12,5	6,1	9,7	
	12,3	12,6	5,7	9,6	
	12,2	12,5	5,6	9,7	
	12,4		6,1	9,9	
	12,7		5,8	9,8	
			5,9		
			5,5		
			6,0		
			5,3		
mean	12,3	12,4	5,8	9,8	8,9
CV%	**2,0**	**2,2**	**4,6**	**1,0**	**15,7**

First the instrument used in the hospital laboratory and the instrument used in the primary care were compared using sample A. The lot number 30176 had a good CV% in the testing in both hospital and primary care.

The next day (the 25th) the instrument used in GP2 was used with the lot number used in primary care in sample B (HbA1c 5,7%) The CV% was 4,6. It was noticed, that some of the foil packages that contained the test cartridges were wet on the inside, which indicates that the cartridges had leaked.

During the evaluation it was mentioned to the evaluators, that test cassettes leaking fluids should not be used. No such packages were seen during testing. However, in the additional evaluation in the hospital it was discovered that a cartridge could have low-level leakage which was not visible. It appeared as if the leakage could induce a higher CV% even if there was nothing to notice when inspecting the package visually.

The following day (the 26th) was the last day before the expiry date of the lot. Before the testing of sample C (HbA1c 9,8%) it was registered if the packages that contained the test cartridges were wet inside. Of the 14 packages, 10 were considered dry and four were wet.
If only dry test cartridges were chosen for measurements, the CV% for the results was 1,0% (n=10). The four, which had visible or perceptible moistness, produced an imprecision of 15,7%.

The leakage is likely to occur either randomly or by the aging of some lots – but not all. The testing performed earlier had a better CV% than the later one in Primary care centre 2; however, at least one lot had a low CV% at the expiry date.

The additional evaluation revealed that not all lots leaked by age. The solution to the problem might be a 'leakage detector' in the package.

5.8. Evaluation of user-friendliness

5.8.1. *Evaluation of user-friendliness*

Each evaluating person evaluated the user-friendliness and filled in the form. Indicating for 0 and 1 point they had to give the reason. Any free comments belonging to the four sub-areas were placed under the table concerning the area, or after all the tables if more suitable. The total rating of each row was not determined by the arithmetic mean of the individual ratings in the row. In the same way, the total rating of each table was not determined by the arithmetic mean of the individual ratings on the rows above. The total ratings were more an overall assessment of the property described on the row or in the headline of the table. Thus could a single bad rating justify an overall bad rating if that property seriously influences on the user-friendliness of the system. Below the filled in user-friendliness forms and comments from all the evaluators in hospital laboratory and primary care have been compiled into one form.

Table 25. Assessment of the information in the manual / insert

Information in manual / insert about:	**0 point**	**1 point**	**2 point**
General impression	Un-satisfactory	Less satisfactory	Satisfactory
Table of contents	Un-satisfactory	Less satisfactory	Satisfactory
Preparations / Pre-analytic procedures	Un-satisfactory	Less satisfactory	Satisfactory
Specimen collection	Un-satisfactory	Less satisfactory	Satisfactory
Measurement / Reading	Un-satisfactory	Less satisfactory	Satisfactory
Measurement principle	Un-satisfactory	Less satisfactory	Satisfactory
Sources of error	Un-satisfactory	Less satisfactory	Satisfactory
Fault-tracing / Troubleshooting	Un-satisfactory	Less satisfactory	Satisfactory
Index	Un-satisfactory	Less satisfactory	Satisfactory
Readability / Clarity of presentation	Un-satisfactory	Less satisfactory	Satisfactory
Available in Danish, Norwegian and Swedish	Un-satisfactory	Less satisfactory	Satisfactory
Rating for information in manual			Satisfactory

Comments: none

Table 26. Assessment of Time factors

Time factors	**0 point**	**1 point**	**2 point**
Duration of preparations / Pre-analytical time	>10 min.	6 to 10 min.	<6 min.
Duration of analysis	>20 min.	10 to 20 min.	<10 min.
Required training time	>8 hours	2 to 8 hours	<2 hours
Stability of test, unopened package	<3 months	3 to 5 months	>5 months
Stability of test, opened package	<14 days	14 to 30 days	>30 days
Rating of time factors			Satisfactory

Comments: none

Table 27. Assessment of Quality control possibilities

Quality Control	**0 point**	**1 point**	**2 point**
Internal quality control*	Un-satisfactory	Less satisfactory	Satisfactory
External quality control*	Un-satisfactory	Less satisfactory	Satisfactory
Stability of quality control material, unopened	<3 months	3 to 5 months	>5 months
Stability of quality control material, opened	≤1 days	2 to 6 days	>6 days or disposable
Storage conditions for control material, unopened	–20°C	+2 to +8°C	+15 to +30°C
Storage conditions for control material, opened	–20°C	+2 to +8°C	+15 to +30°C
Usefulness of the Quality Control *	Un-satisfactory	Less satisfactory	Satisfactory
Rating of quality control			Satisfactory

*In this report internal quality control is defined as the use of a control material with known target. External quality control is defined as control material with unknown target sent to a user who returns the result. It is the use of the material and not the material itself that defines the term. For in2it it is possible to use internal and external control material (fresh EDTA blood or lyophilised certificated material)

Comments from primary care centre: very unusual and time demanding to mix the controls every week. Storage only one week is too short

Table 28. Assessment of Operation facilities

Operation facilities	**0 point**	**1 point**	**2 point**
To prepare the test / instrument	Un-satisfactory	Less satisfactory	Satisfactory
To prepare the sample	Un-satisfactory	Less satisfactory	Satisfactory
Application of specimen	Un-satisfactory	Less satisfactory	Satisfactory
Specimen volume	Un-satisfactory	Less satisfactory	Satisfactory
Number of procedure step	Un-satisfactory	Less satisfactory	Satisfactory
Instrument / test design	Un-satisfactory	Less satisfactory	Satisfactory
Reading / Interpretation of the test result	Un-satisfactory	Less satisfactory	Satisfactory
Sources of errors	Un-satisfactory	Less satisfactory	Satisfactory
Cleaning / Maintenance	Un-satisfactory	Less satisfactory	Satisfactory
Hygiene, when using the test	Un-satisfactory	Less satisfactory	Satisfactory
Storage conditions for tests, unopened package	–20°C	+2 to +8°C	+15 to +30°C
Storage conditions for tests, opened package	–20°C	+2 to +8°C	+15 to +30°C
Environmental aspects: waste handling	Special precautions	Sorted waste	No precautions
Intended users	Biomedical scientists	Laboratory experienced	GP personnel or patients
Size and weight of package	Un-satisfactory	Less satisfactory	Satisfactory
Rating of operation facilities			Satisfactory

Comments:

- Easy way to achieve an HbA1c result, however
- GP2 did not think the instrument would become part of the instruments in the centre – the patients also had lipids controlled, and it was a wish to have these results as well during patient consultation.
- The test cartridges have to be stored in a refrigerator
- A box of ten tests cartridges does occupy a lot of space
- The instrument makes annoying noise when running

6. References

1. C.G. Fraser & P. Hyltoft Petersen, Quality goals in external quality assessment are best based on biology, Scand J Clin Lab Invest 1993; 53 suppl 212. Chapter I. Quality planning.

2. Ricos R, Alvarez V, Cava F, Garcia-Lario JV, Hernandez A, Jimenez CV, Minchinela J, Perich C, Simon M. Biological Variation Database & Desirable Quality Specifications http://www.westgard.com/guest21.htm

3. Rohlfing C, Wiedmeyer HM, Little R, Grota L, Tennill A, England J, Madsen R, Goldstein D. Biological variation of glycohemoglobin. Clin Chem 2002; 48:1116-1118

4. Sacks DB. Bruns DE et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem. 2002 Mar;48(3):436-72.

5. American Diabetes Association. Test of glycemia in diabetes. Diabetes Care. 2002; 25:S97-9DA

6. Kvalitetskrav og kvalitetsvurdering for hyppigt udførte klinisk biokemiske og klinisk mikrobiologiske analyser i almen praksis. Konsensus dokument udarbejdet af Laboratorieudvalget under Sygesikringens og PLO´s Faglige Udvalg vedr. Almen Praksis i samarbejde med DEKS og Dansk Selskab for Klinisk Biokemi's Videnskabelige udvalg. Nov 2003. www.skup.dk

7. Gilbert RE, Goodall I, Young V, Jerums G. Interlaboratory variation of GHb assays in Victoria, Australia. Diabetes Care 1996;19(7):730-734.

8. Guthrie R, Hellman R, Kilo C, et al. A multisite physician's office laboratory evaluation of an immunological method for the measurement of HbA_{1c}. Diabetes Care 1992;15(11):1494-1498.

9. Halwachs-Baumann G, Katzensteiner S, Schnedl W, Pürstner P, Pieber T, Wilders-Truschnig M. Comparative evaluation of three assay systems for automated determination of hemoglobin A_{1c}. Clin Chem 1997;43(3):511-517.

10. Skeie S, Thue G, Sandberg S. Use and interpretation of HbA1ctesting in general practice. Implications for quality of care. Scand J Clin Lab Invest 2000;60:349-56.

11. Hoelzel W, Weykamp C et al. IFCC Reference System for Measurement of Hemoglobin A_{1c} in Human Blood and the National Standardization Schemes in the United States, Japan, and Sweden: A Method-Comparison Study, Clin Chem 2004;50:1, 166-174

12. DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus N Engl J Med 1993; 329: 977-86

13. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphnylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) Lancet 1998;352:837-53

14. Jeppsson JO, Kobold U, Barr J, Finke A, Hoelzel W, Hoshino T, Miedema K, Mosca A, Mauri P, Paroni R, Thienpont L, Umemoto M, Weykamp C; International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Approved IFCC reference method for the measurement of HbA1c in human blood. Clin Chem Lab Med. 2002 Jan;40(1):78-89.

15. Nordin G, Dybkaer R Recommendation for term and measurement unit for HbA1c. Clin Chem Lab Med 2007: 45: 1081-2

16. Felding P et al. Hæmoglobin A1c i Danmark. DSKB-nyt. 2009;2:24-26 www.dskb.dk

17. http://www.skup.nu/ SKUP/2008/65 Afinion HbA1c
Attachment 1, "Standardisation of HbA1c" and "Attachment 2, "The Comparison Method." and www.skup.dk HbA1c, SKUP/2008/65. visited 19th September 2010

18 Produktcertifikat HbA1c-kalibratorer. DEKS

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

20. Burnett RW, "Accurate Estimation of Standard Deviations for Quantitative Methods Used in Clinical Chemistry". Clinical Chemistry 1975; 21 (13): 1935 – 1938.

21. Diem K and Seldrup J. Geigy Scientific Tables Vol 2. Introduction to statistics, Statistical tables, Mathematical Formulae. Edited by Lentner C CIBA-GEIGY 1982 pp239

22. Cynthia M Balion, Thomas F Draisey and Roger J Thibert Carbamylated hemoglobin and carbamylated plasma protein in hemodialyzed patients. Kidney International (1998) 53, 488–495; doi:10.1046/j.1523-1755.1998.00777.x

23. Wynckel A, Randoux C et al. Kinetics of carbamylated haemoglobin in acute renal failure. Nephrol Dial Transplant. 2000 Aug;15(8):1183-8.

Attachments

List of attachments

Attachments with raw data are included only in the report to Bio-Rad and SKUP

Attachment 1 Facts about the system

a) Name of the analyser	***in2it™ (I) System Analyzer***

Physical dimensions	*140mm (W) x 100mm(H) x 145mm (D)*
Manufacturer (with address)	*Bio–Rad Laboratories Deeside,* *CH5 2NU,* *UK* *Phone +44 1244 288888* *Fax +44 1244 833401*
Distributor (with address)	*Denmark:* Orion Diagnostica A / S Postadresse: Moellevej 9A, 2990 Nivå, Danmark Telefon: +45 49 755050 Fax: +45 49 755055 E-mail: orion@oriondiagnostica
	Norway: Orion Diagnostica A / S, Norge Postadresse: PO Box 321,1372 Asker, Norge Gade: Solbråveien 43,1383 Asker, Norge Telefon: +47 66 78 56 30 Fax: +47 66 78 56 59 E-mail: firmapost@oriondiagnostica
	Sweden: Orion Diagnostica AB Postadresse: POBox 520, SE-192 05 Sollentuna, Sverige Besøgsadresse: Djupdalsvägen 7, SE-192 51 Sollentuna, Sverige Telefon: +46 8 623 64 40 Fax: +46 8 623 64 80 E-mail: info@oriondiagnostica.com Website: www.oriondiagnostica.se

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

Component	Sample materials	Volume of the analysis
HbA1c test	*Venous blood/ capillary blood/ control*	*10µl*

c) Analysis principles (reference to the instruction manual)

Parameter	Principle
HbA1c	*Boronate affinity chromatography*

d) Area of analysis

Component	Area of analysis	Designation
HbA1c test	*Diabetes mellitus*	*Point-of-care, in-vitro diagnostic for treatment monitoring*

e) Time for analysis per component (precisely stated)

Component	Pre-analysis time (with an explanation)	Analysis time
HbA1c	*< 1 minute (pick up sample in Blood Key, insert key into cartridge, insert cartridge into Analyzer)*	*10 minutes*

f) Calibration

Is calibration possible?	*No*

g) Recommended maintenance

Maintenance	How often?
None	

h) Control materials

Is control material available (from the producer or other companies)?	*Yes*

i) Marketing

In which country is the analyser marketed?	*Australia, Austria, Belgium, Canada, China, Czech, Denmark, Finland, France, Germany, Hong Kong, India, Israel, Italy, Korea, Latin America, Netherlands, New Zealand, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, UK, US*
When did the analyser first appear on the Scandinavian market?	*2010*
When did the analyser receive CE approval?	*before 2007*

j) Language

In which Scandinavian language is the manual?	*Danish*

k) Memory

What is the storage capacity of the analyser and what is stored?	*200 records. Each record is Patient ID, Operator ID, Instrument ID, Test number, Test type, Cartridge Lot, HbA1c value, Calibration, Date, Time, Firmware version.*
Is it possible to identify patients?	*Yes*
If yes, describe this:	*The Patient ID can accept up to 15 alphanumeric characters. If the operator uses patients' names in the Patient ID field then the patient could be identified. The in2it does not require any particular format for the Patient ID, and it can be left blank.*

l) Power supply

Electric network connection	*100–240V, 50–60Hz, 0.8A (mains supply)*
Battery	*Yes*
If yes, which type and how many batteries	*4 x AA cells*

m) Electronic communication

Can a printer be connected to the analyser?	*Yes (dedicated in2it printer, available separately)*
Can a barcode reader be connected to the analyser?	*Yes (dedicated in2it barcode reader, available separately)*
Interface	*Yes*
If yes, which port is required?	*RS-232 9 pin D via dedicated cable (available separately)* *USB connection to PC running in2it System Software (available separately)*
Communication method	
Transfer mode	*Data export only*
Transfer protocol	*Text format*

n) Standards and controls

	Standard	Control
Name		*Level 1, Level 2*
Volume		*500µl*
Shelf life unopened		*12 months at 2–8°c*
Shelf life opened		*7 days after reconstitution*
Any comments:		*After reconstitution, may be frozen for up to 3 months at -20°c*

o) Reagents

Component	Time and temperature, unopened	Time and temperature, opened
in2it A1C cartridge	*Up to 12 months at 2–8°c* *Or* *Up to 11 months at 2–8°c plus up to 30 days at 15–25°c*	*N/A*

p) Additional information

Attachment 3 Raw data, Control, Hospital
Raw data of Bio-Rad in2it HbA1c control in the hospital laboratory

date	low	low	high	high	lot	instrument
23-03-2009	5,8	5,7			29824	IB-008527
27-03-2009	5,4	6			29824	IB-008527
23-03-2009			10,4	9,7	29824	IB-008527
27-03-2009			10,7	10,1	29824	IB-008527
27-04-2009	5,5	5,9			30176	IB-008076
27-04-2009	5,4	5,8			30176	IB-008444
24-04-2009			10	9,9	30176	IB-008444
22-04-2009	5,9	5,6			30176	IB-008527
01-04-2009	5,6	6			30176	IB-008527
30-03-2009	5,9	5,6			30176	IB-008527
31-03-2009	6,1	6,3			30176	IB-008527
24-04-2009	5,9	6,1			30176	IB-008527
27-04-2009	5,2	5,4			30176	IB-008527
22-04-2009			10,2	10,7	30176	IB-008527
01-04-2009			9,9	10,8	30176	IB-008527
30-03-2009			10,7	10,7	30176	IB-008527
31-03-2009			10,9	10,8	30176	IB-008527
28-04-2009	5,7	5,9			30321	IB-008527
28-04-2009				10,1	30321	IB-008527
29-04-2009			10,4	9,7	30448	IB-008076
05-05-2009	6	5,8			30448	IB-008076
06-05-2009			10,4	10,3	30448	IB-008076
05-05-2009			11,2	10,8	30448	IB-008444
29-04-2009	5,6	6,1			30448	IB-008527
06-05-2009	5,8	5,8			30448	IB-008527
12-05-2009	5,8	5,8			30448	IB-008527
12-05-2009			10,7	10,4	30448	IB-008527

Attachment 6 Comments from BioRad

Bio-Rad Laboratories

Diagnostics Group
4000 Alfred Nobel Drive
Hercules, CA 94547
Telephone: 510 724-7000
Fax: 510 741-5823

November 8, 2010

SKUP
Esther Jensen
Hillerod Hospital
Klinisk Biokemisk Afdeling
Dyrehavevej 29, indgang 16A
DK-3400 Hillerod

Re: Comments on the SKUP evaluation of Bio-Rad in2it™ A1C Analyzer

Dear Esther,

In 2009, Bio-Rad requested an evaluation from SKUP of the in2it™ Analyzer for hemoglobin A_{1c} testing. The testing was performed in the Department of Clinical Biochemistry, Odense University Hospital and HIllerod Hospital and the final report # SKUP/2010/78 was sent to Bio-Rad for final comments.

Please see our comments below with regard to the evaluation performed on the Bio-Rad in2it™ Analyzer and the final SKUP report:

- The in2it Analyzer instrument gearbox has been redesigned to improve the performance and reduce the sound while running tests.
- New packaging has been introduced to reduce the volume size of the in2it A_{1c} Test Cartridge Kit box (10 tests), resulting in a 45% reduction in box size (2028cm^3 versus 3731cm^3).
- Improvements have been made since the original study done in 2009 to the in2it A_{1c} Test Cartridges and blood key design, improving the usability of how the blood sample is added to the cartridge.
- The in2it A_{1c} Test Cartridges are stable for 30 days when stored at room temperature (15 - 25 degrees Celsius). If used past the 30 days recommended in the IFU, leakage of the test cartridges could occur.

Thank you for the time taken to evaluate the in2it™ Analyzer. If I can be of any assistance in the future, please feel free to contact me directly.

Best regards,

Corinna Nunn
Product Manager
Bio-Rad Laboratories
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corinna_nunn@bio-rad.com

Attachment 7 Reply to comments from BioRad from SKUP

Scandinavian evaluation of laboratory equipment for primary health care

Corinna Nunn
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SKUP in Denmark

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Biochemistry
Hillerød Hospital
Dyrehavevej 29
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Phone +45 48 29 48 29
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13th November 2010

Dear Corinna

Thank you for your comments to the SKUP/2010/78 report performed in the Department of Clinical Biochemistry, Odense University Hospital and Hillerod Hospital.

It is pleasant that Bio-Rad has made improvements in the user friendliness of in2it™ Analyzer after our evaluation and comments.
SKUP has not tested the in2it Analyzer after the improvements.

I have to mention the fact, that all in2it A_{1c} Test Cartridges during the evaluation were kept in a walk-in refrigerator when stored in hospital. No Test Cartridges used in the evaluation had been kept at room temperature (15 - 25 degrees Celsius) for more than a couple of days.
Still some lot had a leakage not visible of the test cartridges.

On behalf of SKUP

Esther Jensen

Attachment 8 List of previous SKUP evaluations

Evaluation no.	**Component**	**Instrument/testkit**	**Producer**
SKUP/2010/82*	Glucose, protein, blood, leukocytes, nitrite	Medi-Test URYXXON Stick 10 urine test strip and URYXXON Relax urine analyser	Macherey-Nagel GmBH & Co. KG
SKUP/2010/81*	Glucose	mylife PURA	Bionime Corporation
SKUP/2010/79*	Glucose, protein, blood, leukocytes, nitrite	CombiScreen 5SYS Plus urine test strip and CombiScan 100 urine analyser	Analyticon Biotechnologies AG
SKUP/2009/75	Glucose	Contour	Bayer HealthCare
SKUP/2009/74	Glucose[1]	Accu-Chec Mobile	Roche Diagnostics
SKUP/2010/73	Leukocytes	HemoCue WBC	HemoCue AB
SKUP/2008/72	Glucose[1]	*Confidential*	
SKUP/2009/71	Glucose[1]	GlucoMen LX	A. Menarini Diagnostics
SKUP/2008/69*	Strep A	Diaquick Strep A test	Dialab GmbH
SKUP/2008/66	Glucose[1]	DANA DiabeCare IISG	SOOIL Developement co. Ltd
SKUP/2008/65	HbA1c	Afinion HbA1c	Axis-Shield PoC AS
SKUP/2007/64	Glucose[1]	FreeStyle Lite	Abbott Laboratories
SKUP/2007/63	Glucose[1]	*Confidential*	
SKUP/2007/62*	Strep A	QuikRead	Orion Diagnostica Oy
SKUP/2008/61	CRP	i-CHROMA	BodiTech Med. Inc.
SKUP/2007/60	Glucose[1]	*Confidential*	
SKUP/2007/59	Glucose[1]	Ascensia BREEZE2	Bayer HealthCare
SKUP/2006/58	HbA1c	*Confidential*	
SKUP/2007/57*	PT (INR)	Simple Simon PT	Zafena AB
SKUP/2007/56*	PT (INR)	*Confidential*	
SKUP/2007/55	PT (INR)	CoaguChek XS	Roche Diagnostics
SKUP/2007/54*	Mononucleosis	*Confidential*	
SKUP/2006/53*	Strep A	*Confidential*	
SKUP/2005/52*	Strep A	Clearview Exact Strep A Dipstick	Applied Biotech, Inc.
SKUP/2005/51*	Glucose[1]	FreeStyle	Abbott Laboratories
SKUP/2006/50	Glucose[1]	Glucocard X-Meter	Arkray, Inc.
SKUP/2006/49	Glucose[1]	Precision Xtra Plus	Abbott Laboratories
SKUP/2006/48	Glucose[1]	Accu-Chek Sensor	Roche Diagnostic
SKUP/2006/47	Haematology	Chempaq XBC	Chempaq
SKUP/2005/46*	PT (INR)	*Confidential*	
SKUP/2006/45	Glucose[1]	HemoCue Monitor	HemoCue AB
SKUP/2005/44	Glucose[1]	Accu-Chek Aviva	Roche Diagnostics
SKUP/2005/43	Glucose[1]	Accu-Chek Compact Plus	Roche Diagnostics

Evaluation no.	Component	Instrument/testkit	Producer
SKUP/2005/42*	Strep A	Twister Quick-Check Strep A	ACON laboratories, Inc.
SKUP/2006/41*	HbA1c	*Confidential*	
SKUP/2005/40	Glucose[1]	OneTouch GlucoTouch	LifeScan, Johnson & Johnson
SKUP/2005/39	Glucose[1]	OneTouch Ultra	LifeScan, Johnson & Johnson
SKUP/2004/38*	Glucose	GlucoSure Plus	Apex Biotechnology Corp.
SKUP/2004/37*	u-hCG	Quick response u-hCG	Wondsfo Biotech
SKUP/2004/36*	Strep A	Dtec Strep A testcard	UltiMed
SKUP/2004/35*	u-hCG	RapidVue u-hCG	Quidel Corporation
SKUP/2004/34*	u-hCG	QuickVue u-hCG	Quidel Corporation
SKUP/2004/33	PT (INR)	Hemochron Jr. Signature	ITC International Technidyne
SKUP/2004/32*	Strep A	QuickVue In-Line Strep A test	Quidel Corporation
SKUP/2004/31*	PT (INR)	*Confidential*	
SKUP/2004/30	Glucose[1]	Ascensia Contour	Bayer Healthcare
SKUP/2004/29	Haemoglobin	Hemo_Control	EKF-diagnostic
SKUP/2003/28*	Strep A	QuickVue In-Line Strep A test	Quidel Corporation
SKUP/2003/27*	Strep A	QuickVue Dipstick Strep A test	Quidel Corporation
SKUP/2003/26*	HbA1c	*Confidential*	
SKUP/2003/25*	HbA1c	*Confidential*	
SKUP/2003/24*	Strep A	OSOM Strep A test	GenZyme, General Diag.
SKUP/2002/23*	Haematology with CRP	ABX Micros CRP	ABX Diagnostics
SKUP/2002/22	Glucose[1]	GlucoMen Glycó	Menarini Diagnostics
SKUP/2002/21	Glucose[1]	FreeStyle	TheraSense Inc.
SKUP/2002/20	Glucose	HemoCue 201	HemoCue AB
SKUP/2002/19*	PT(INR)	Reagents and calibrators	
SKUP/2002/18	Urine–Albumin	HemoCue	HemoCue AB
SKUP/2001/17	Haemoglobin	Biotest Hb	Biotest Medizin-technik GmbH
SKUP/2001/16*	Urine test strip	Aution Sticks and PocketChem UA	Arkray Factory Inc.
SKUP/2001/15*	Glucose	GlucoSure	Apex Biotechnology Corp.
SKUP/2001/14	Glucose	Precision Xtra	Medisense
SKUP/2001/13	SR	Microsed SR-system	ELECTA-LAB
SKUP/2001/12	CRP	QuikRead CRP	Orion
SKUP/2000/11	PT(INR)	ProTime	ITC International Technidyne Corp
SKUP/2000/10	PT(INR)	AvoSure PT	Avocet Medical Inc.
SKUP/2000/9	PT(INR)	Rapidpoint Coag	
SKUP/2000/8*	PT(INR)	Thrombotest/Thrombotrack	Axis-Shield
SKUP/2000/7	PT(INR)	CoaguChek S	Roche Diagnostics
SKUP/2000/6	Haematology	Sysmex KX-21	Sysmex Medical Electronics Co
SKUP/2000/5	Glucose	Accu-Chek Plus	Roche Diagnostics
SKUP/1999/4	HbA1c	DCA 2000	Bayer
SKUP/1999/3	HbA1c	NycoCard HbA1c	Axis-Shield PoC AS
SKUP/1999/2*	Glucose	Precision QID/Precision Plus Electrode, whole blood calibration	Medisense
SKUP/1999/1	Glucose	Precision G/Precision Plus Electrode, plasma calibration	Medisense

*A report code followed by an asterisk, indicates that the evaluation for instance is a pre-marketing evaluation, and thereby confidential. A pre-marketing evaluation can result in a decision by the supplier not to launch the instrument onto the Scandinavian marked. If so, the evaluation remains confidential. The asterisk can also mark evaluations at special request from the supplier or evaluations that are not complete according to SKUP guidelines, e.g. the part performed by the intended users was not included in the protocol.

[1] Including a user-evaluation among diabetes patientsGrey area – The instrument is not in the Scandinavian market any more