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UNIVERSITÀ DEGLI STUDI DI MILANO

Centre for Metrological Traceability in Laboratory Medicine (CIRME)

site: <http://users.unimi.it/cirme>

CIRME
University of Milano

SYMPOSIUM

Traceability in laboratory medicine: A matter of patient safety

CHAIR: Mauro Panteghini (IT) CO-CHAIR: Christos Kroupis (GR)

10.30 - 12.30
ROOM: CONFERENCE ROOM 1

Traceability of HbA_{1c} measurements: weak and strong points

Andrea Mosca
CIRME, Dept. Physiopathology and transplantation
University of Milano, Milano (IT)

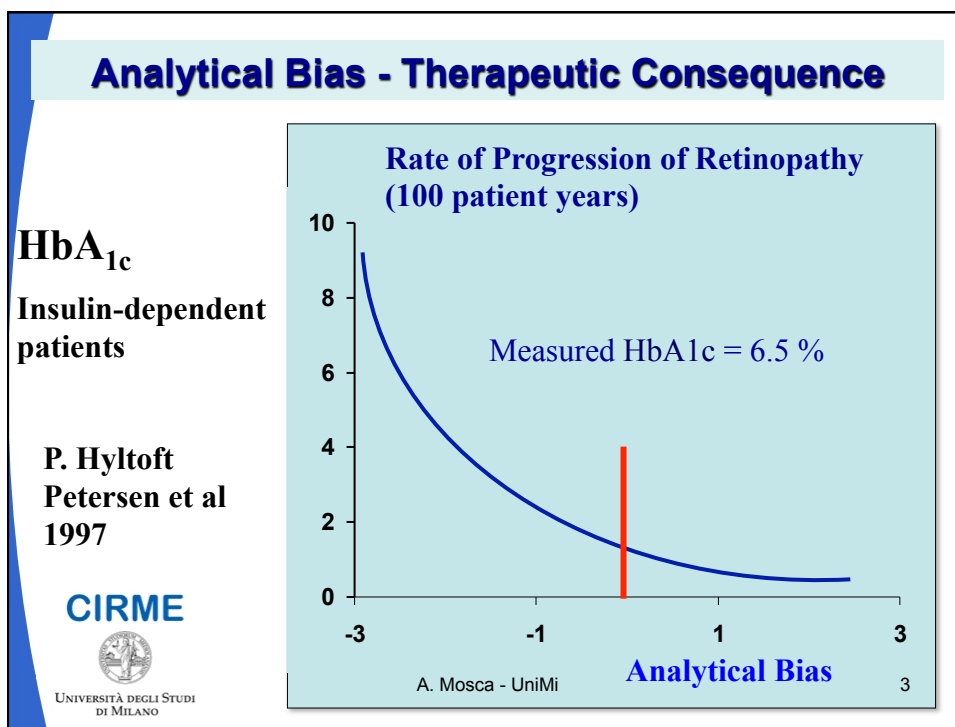
prologue

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Centro Interdipartimentale per la Riferibilità Metrologica in Medicina di Laboratorio (CIRME)

under the auspices of the



Scientific Meeting

STANDARDIZATION OF HETEROGENEOUS ANALYTE MEASUREMENTS: THE EXAMPLE OF HEMOGLOBIN A1c

6 November 2007

MILANO
Aula Magna - Università degli Studi di Milano
Via Festa del Perdono 7

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Programme

10.00 Meeting inauguration
Academic Authorities

MORNING SESSION
Chairpersons: M.M. Mueller, F. Ceriotti

10.30 The Centre for Metrological Traceability in Laboratory Medicine (CIRME): scope and activities
M. Panteghini (Milano, IT)

11.00 Defining HbA_{1c}: the indispensable decision to approach measurement standardization
J.O. Jeppsson (Malmö, SE)

11.30 The HbA_{1c} network: structure, performance and rules
C. Weykamp (Winteravijk, NL)

12.00 Implementation of the IFCC reference system for HbA_{1c} in clinical practice: how to educate clinicians
G. John (Norwich, UK)

12.30 Discussion

13.00 Break

AFTERNOON SESSION
Chairpersons: J. Hicks, A. Pontiroli

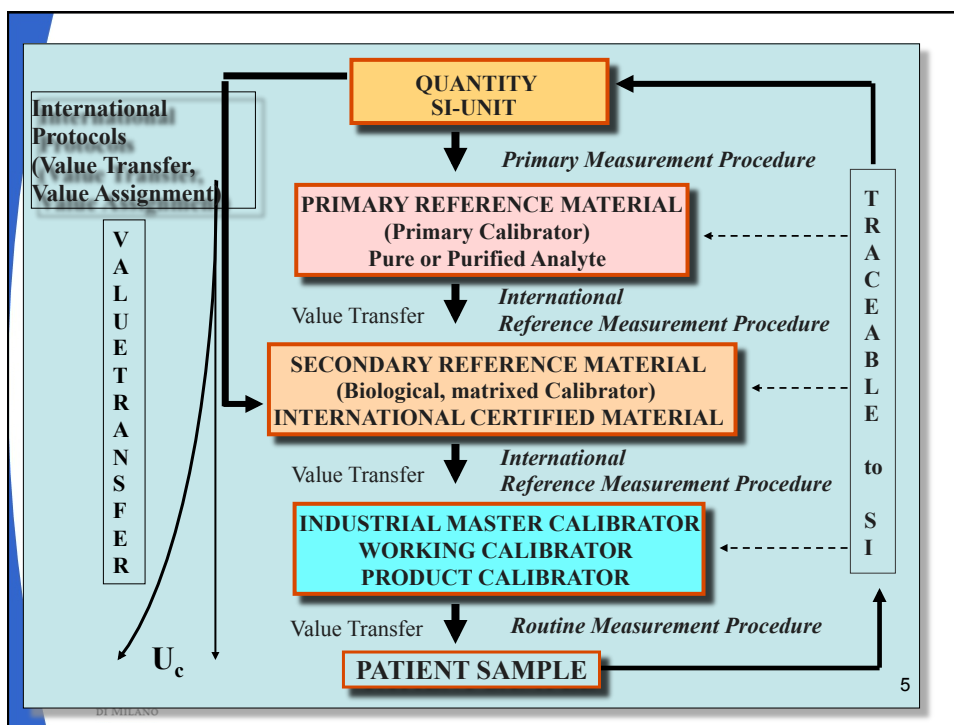
14.00 Appropriate ways of adopting the HbA_{1c} standardization in clinical practice: the diabetologist's view
E. Ferrannini (Pisa, IT)

14.30 Why we need traceability in Laboratory Medicine
M.M. Mueller (Vienna, AT)

15.00 Standardization of hemoglobin A2: does HbA_{1c} history repeat itself?
A. Mosca (Milano, IT)

15.30 Discussion

16.00 Meeting conclusions
J. Hicks (Washington DC, US)



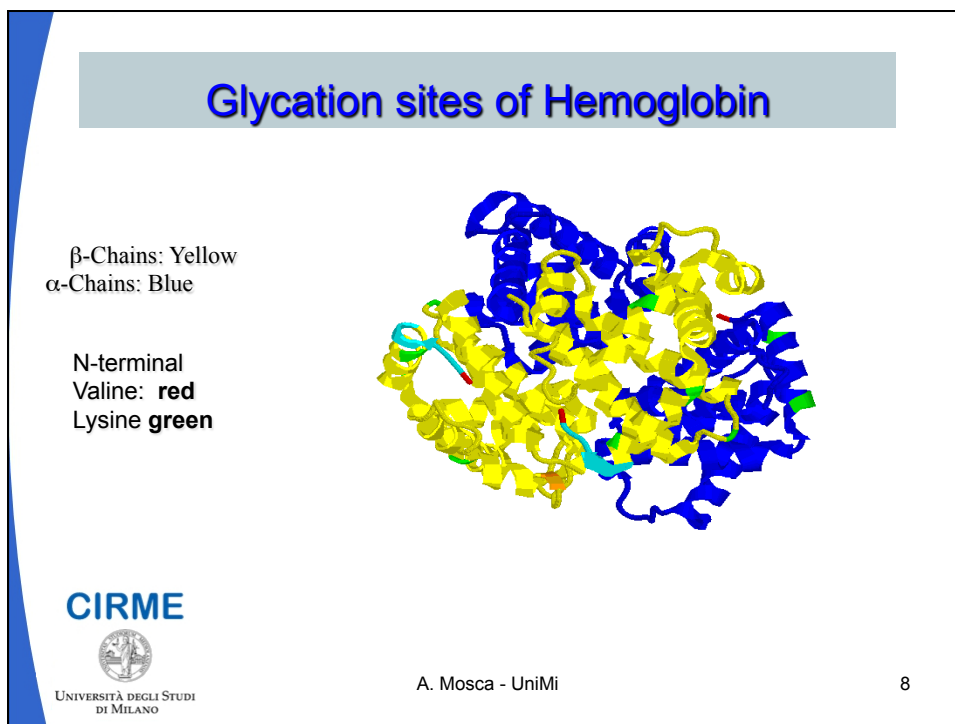
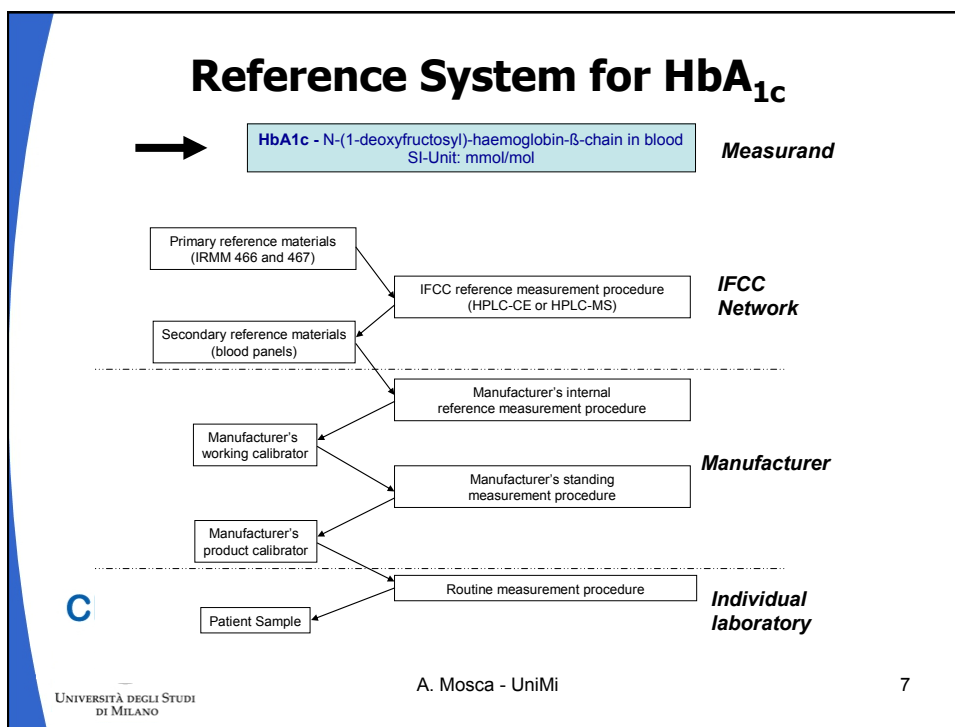
agenda

- IFCC reference system for HbA_{1c}
 - Top of the chain
 - Middle of the chain
 - Bottom of the chain
- Conclusions and future activities

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top of the chain

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The Analytical Challenge

Proteolytic cleavage of β -chain (146 amino acids)

HbA₀-peptide

Glu-C



HbA_{1c}-peptide

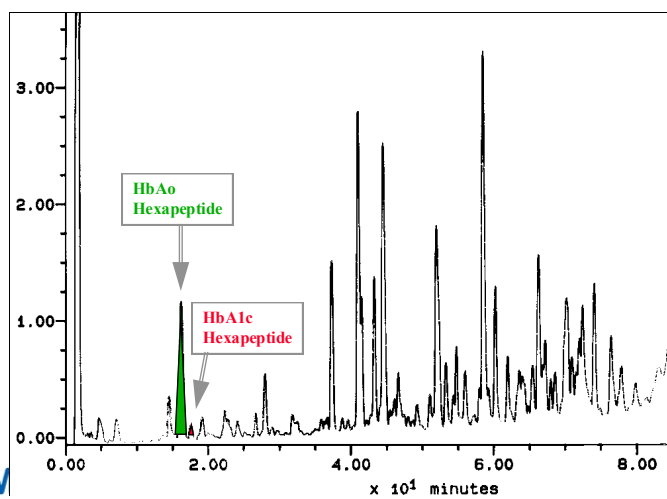


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Photometric detection of peptides



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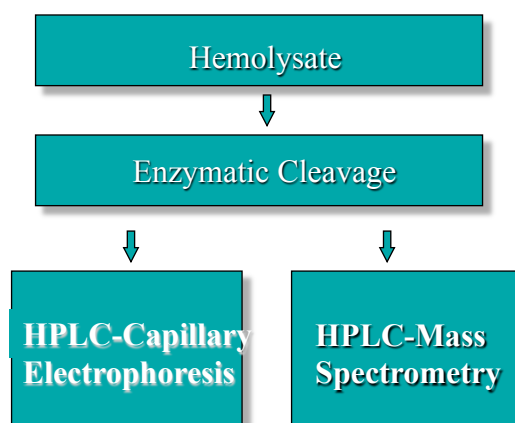
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C18 Chromatography

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Flow Chart for Reference Methods



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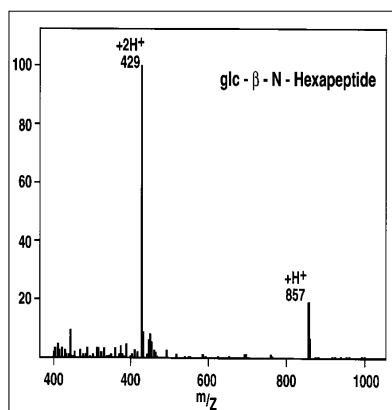
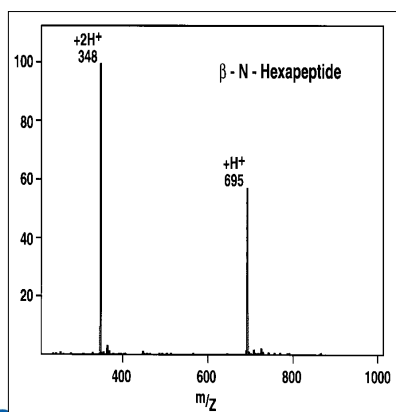
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Approved by IFCC 2001

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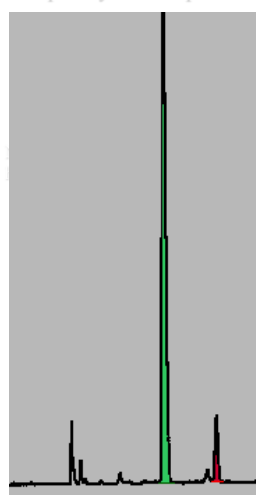
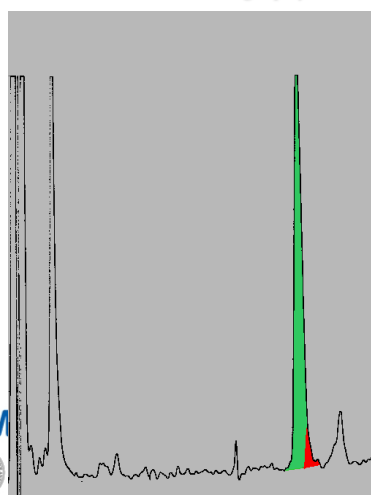
ESI mass spectra of nonglycated and glycated β N-terminal hexapeptides



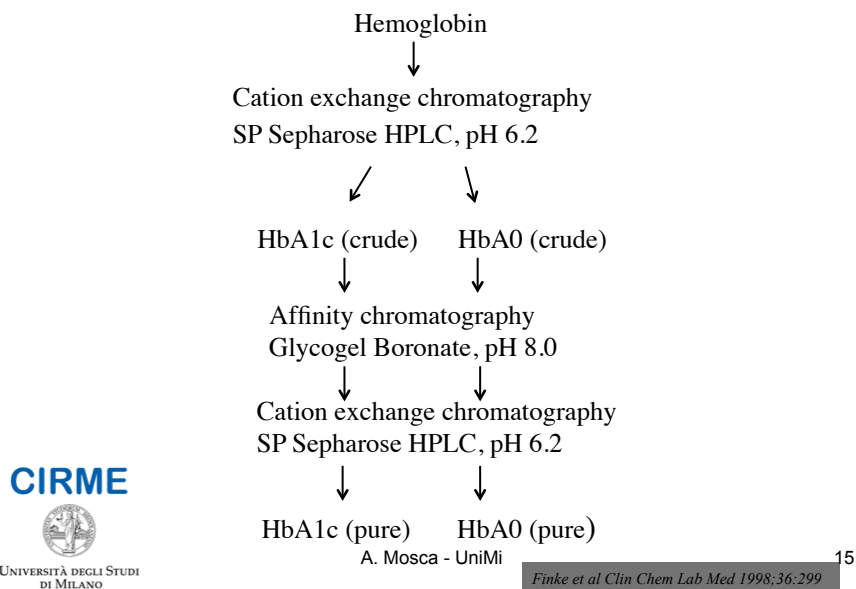
Two-dimensional separation of N-terminal hexapeptides of hemoglobin

C 18 Chromatography


Capillary Electrophoresis




Preparation of calibrators



HbA₀

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JOINT RESEARCH CENTRE
Institute for Reference Materials and Measurements

 **irm**
Institute for Reference Materials and Measurements

CERTIFIED REFERENCE MATERIAL
IRMM/IFCC- 467


CERTIFICATE OF ANALYSIS

HAEMOGLOBIN ISOLATED FROM WHOLE BLOOD	
Amount-of-substance fraction	
Certified value ¹⁾ [mmol/mol]	
HbA0/(HbA1c + HbA0) ²⁾	> 976

1) The certified value was calculated from the average of the results for the amount-of-substance fraction of HbA1c for two accepted datasets and converted into amount-of-substance fraction HbA0 (1000 - HbA1c mmol/mol). Measurements were carried out using the IFCC reference measurement procedure and were further confirmed by other methods. The certified value, expressed as mmol HbA0 per mol HbA1c plus HbA0, is traceable to the SI. With a 95 % probability, the true value of the material is above this level.
2) HbA1c is defined as the beta-N-(1-deoxyfructosyl-γ) haemoglobin. HbA0 is defined as the non-glycated haemoglobin.

This certificate is valid for one year after purchase.
Sales date:
The minimum amount of sample to be used is 20 µL.


Geel, March 2007


Signed: 
Prof. Dr. Hendrik Emons
Unit for Reference Materials
EC-IRMM
Rietlaanweg 111
2440 Geel, Belgium

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HbA_{1c}

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Institute for Reference Materials and Measurements

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Institute for Reference Materials and Measurements

CERTIFIED REFERENCE MATERIAL
IRMM/IFCC- 466

CERTIFICATE OF ANALYSIS


HAEMOGLOBIN ISOLATED FROM WHOLE BLOOD		
Amount-of-substance fraction		
Certified value ¹⁾ [mmol/mol]		
Uncertainty ²⁾ [mmol/mol]		
HbA1c/(HbA0 + HbA1c) ³⁾	934	22

1) The certified value was calculated from the average of the results for the amount-of-substance fraction of HbA0 versus HbA0 plus HbA1c for three accepted datasets and converted into amount-of-substance fraction HbA1c (1000 mmol/mol - HbA0 mmol/mol). Measurements were carried out using the IFCC reference measurement procedure and were further confirmed by other methods. The certified value, expressed as mmol HbA1c per mol HbA1c plus HbA0, is traceable to the SI.
2) The certified uncertainty is the expanded uncertainty estimated in accordance with the Guide to the Expression of Uncertainty in Measurement (GUM) with a coverage factor k = 2, corresponding to a level of confidence of about 95 %.
3) HbA1c is defined as the beta-N-(1-deoxyfructosyl-γ) haemoglobin. HbA0 is defined as the non-glycated haemoglobin.

This certificate is valid for one year after purchase.
Sales date:
The minimum amount of sample to be used is 20 µL.

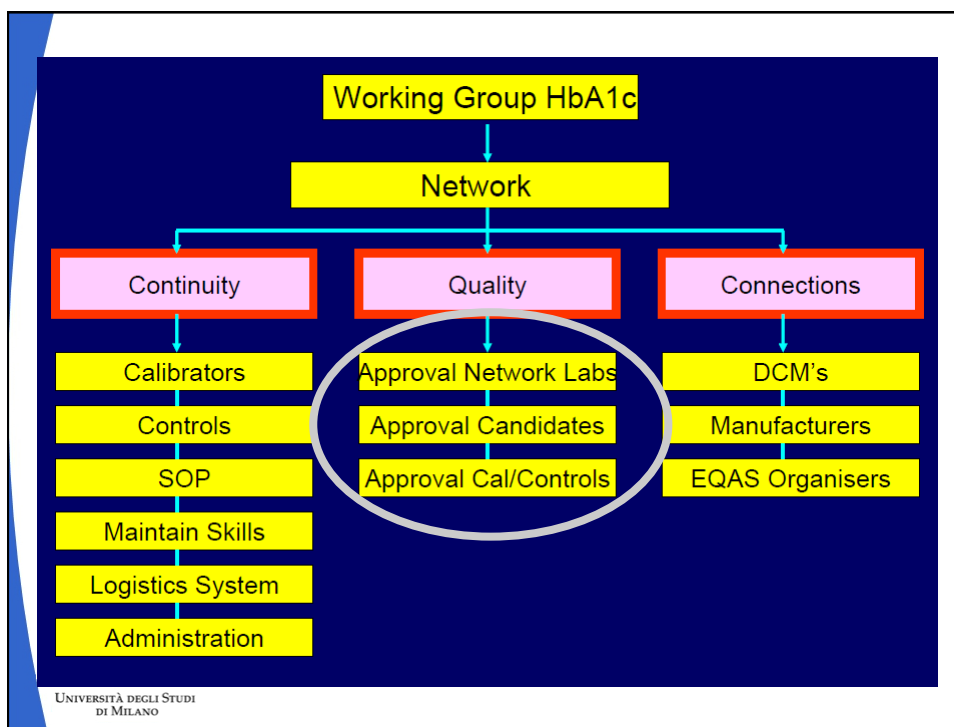
U_c = 1.18 %

Geel, March 2007

Signed: 
Prof. Dr. Hendrik Emons
Unit for Reference Materials
EC-IRMM
Rietlaanweg 111
2440 Geel, Belgium

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Clin Chem
2004; 50:
166-74


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

WIELAND HOELZEL,¹ CAS WEYKAMP,² JAN-OLOF JEPSSON,³ KOR MIEDEMA,^{4*} JOHN R. BARR,⁵ IAN GOODALL,⁶ TADAO HOSHINO,⁷ W. GARRY JOHN,⁸ UWE KOBOLD,⁹ RANDIE LITTLE,⁹ ANDREA MOSCA,¹⁰ PIERLUIGI MAURI,¹¹ RITA PARONI,¹² FRANSISCUS SUSANTO,¹³ IZUMU TAKEI,¹⁴ LINDA THIENPONT,¹⁵ MASAO UMEMOTO,¹⁶ and HSIAO-MEI WIEDMEYER,⁹ on behalf of the IFCC WORKING GROUP ON HbA_{1c} STANDARDIZATION

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IFCC HbA_{1c} Network
Reference Laboratories
operating the
IFCC HbA_{1c} Reference Measurement Procedure

CERTIFIED REFERENCE MATERIAL
IFCC HbA_{1c} NETWORK PURE HbA₀
CERTIFICATE OF ANALYSIS

HbA ₀ TM isolated from human whole blood		
Batch:	14224300	
Expiry Date:	February 2019	
Parameter	Certified Value	Uncertainty
HbA ₀	≥ 999.8 mmol/mol TM	
Total Hb	146.0 mg/gram TM	2.11 mg/gram TM

(1) HbA₀ is defined as the non-glycosylated hemoglobin.
(2) The certified value of HbA₀ is expressed as mmol HbA₀ per mol (HbA₀ + HbA_{1c}) and measured according to the SOP of the IFCC HbA_{1c} Reference Measurement Procedure (1, 2).
(3) Total Hb is expressed as mg/gram and measured according to the SOP of the IFCC HbA_{1c} Reference Measurement Procedure (1, 2).
(4) The uncertainty is the expanded uncertainty at the 95% level of confidence (k=2).

Winterswijk, 3 February 2012
Signed: 
Dr. C.W. Weykamp
IFCC HbA_{1c} Network Coordinator

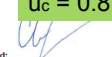


IFCC HbA_{1c} Network
Reference Laboratories
operating the
IFCC HbA_{1c} Reference Measurement Procedure


CERTIFIED REFERENCE MATERIAL
IFCC HbA_{1c} NETWORK PURE HbA_{1c}
CERTIFICATE OF ANALYSIS

HbA _{1c} TM isolated from human whole blood		
Batch:	30226400	
Expiry Date:	February 2019	
Parameter	Certified Value	Uncertainty
HbA _{1c}	889.5 mmol/mol TM	1.4 mmol/mol TM
Total Hb	38.52 mg/gram TM	0.12 mg/gram TM

(1) HbA_{1c} is defined as the beta-N-(1-deoxyfructosyl) hemoglobin. HbA_{1c} is defined as the non-glycosylated hemoglobin.
(2) The certified value of HbA_{1c} is expressed as mmol HbA_{1c} per mol (HbA₀ + HbA_{1c}) and measured according to the SOP of the IFCC HbA_{1c} Reference Measurement Procedure (1, 2).
(3) Total Hb is expressed as mg/gram and measured according to the SOP of the IFCC HbA_{1c} Reference Measurement Procedure (1, 2).
(4) The uncertainty is the expanded uncertainty at the 95% level of confidence (k=2).

Winterswijk, 3 February 2012
Signed: 
Dr. C.W. Weykamp
IFCC HbA_{1c} Network Coordinator


Uc = 0.8 %



Intended Purpose
The material has only one purpose: to be used together with IFCC HbA_{1c} Network pure HbA₀ to manufacture the primary calibrators (Pcal) for the IFCC HbA_{1c} Network of Reference Laboratories operating the IFCC HbA_{1c} Reference Measurement Procedure.

Product description
The material is prepared from human whole blood obtained from non-diabetic volunteers. The material is deep frozen (-70°C) and contains 50 mmol/L MES, 10 mmol/L KCN, 2 mmol/L EDTA and the pH is 6.2.

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IFCC HbA_{1c} Network
Reference Laboratories
operating the
IFCC HbA_{1c} Reference Measurement Procedure

IFCC HbA_{1c} NETWORK PRIMARY CALIBRATORS
PRODUCT CERTIFICATE

Calibrator set IFCC HbA _{1c} Reference Measurement Procedure					
Batch:	Pcal 2012				
Expiry Date:	February 2019				
Raw materials					
IFCC HbA _{1c} Network pure HbA _{1c}	Batch:	30226400			
IFCC HbA _{1c} Network pure HbA ₀	Batch:	14224300			
Assigned Values					
Vial #	HbA _{1c} TM mmol/mol Hb	Ratio TM [HbA _{1c}]/[HbA ₀]	U ⁽¹⁾	Total Hb TM (mg)	Volume TM (µL)
Pcal 2012 - A	0.0	0.00000	0.01	1	30.0
Pcal 2012 - B	29.3	0.03018	0.16	1	30.0
Pcal 2012 - C	58.7	0.06236	0.32	1	30.0
Pcal 2012 - D	87.5	0.09459	0.48	1	30.0
Pcal 2012 - E	117.4	0.13302	0.59	1	30.0
Pcal 2012 - F	146.9	0.17220	0.71	1	30.0

(1) HbA_{1c} is defined as the beta-N-(1-deoxyfructosyl) hemoglobin and expressed as mmol HbA_{1c} per mol (HbA₀ + HbA_{1c}). The concentration is calculated from the mixed amounts of pure HbA_{1c} (1) and pure HbA₀ (2) according to the SOP of the IFCC HbA_{1c} Reference Measurement Procedure (3, 4, 5).
(2) The Ratio [HbA_{1c}]/[HbA₀] is the ratio of the HbA_{1c} concentration in mmol/mol and the total hemoglobin concentration in mmol/mol (1000 × HbA₀ concentration in mmol/mol) according to the SOP of the IFCC HbA_{1c} Reference Measurement Procedure (3, 4, 5).
(3) The uncertainty (U) is the expanded uncertainty at the 95% level of confidence (k=2) and calculated according to ref. 6.
(4) Before dispensing the calibrator solutions in the vials, the total hemoglobin concentration is adjusted to 33.3 mg/mL. Then 30.0 µL is dispensed which results in 1 mg hemoglobin/vial. This concept facilitates convenient and precise handling of the calibrators: for the enzymatic digestion the content does not have to be removed from the vials as simply 50 µL of the enzyme solution can be added to the vial.


Approval Measurements
Prior to release the calibrator set has been evaluated and approved by the following network laboratories as part of the 2012 California IFCC HbA_{1c} intercomparison study (7).

CHU de Reims (HPLC-ESIMS)	Roche Diagnostics GmbH (HPLC-ESIMS)
INSTAND e.v. (HPLC-ESIMS and HPLC-CE)	School of Medicine Keio University (HPLC-ESIMS)
Isala (HPLC-CE)	Shanghai Center for Clinical Laboratory (HPLC-CE)
Korea Centers for Disease Control and Prevention (HPLC-ESIMS)	Siemens HealthCare Diagnostics (HPLC-ESIMS)
Queen Beatrix Hospital (HPLC-CE)	Suraksha Diagnostics Pvt. Ltd (HPLC-CE)
Institute of Biopathological medicine (HPLC-ESIMS and HPLC-CE)	Università degli Studi di Milano (HPLC-ESIMS and HPLC-CE)
ReCCs (HPLC-ESIMS)	University of Missouri School of Medicine (HPLC-CE)

Uc = 0.27 %

Uc = 0.26 %


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Intended Purpose
The material has only one purpose: to be used together with IFCC HbA_{1c} Network pure HbA₀ to manufacture the primary calibrators (Pcal) for the IFCC HbA_{1c} Network of Reference Laboratories operating the IFCC HbA_{1c} Reference Measurement Procedure.

Product description
The material is prepared from human whole blood obtained from non-diabetic volunteers. The material is deep frozen (-70°C) and contains 50 mmol/L MES, 10 mmol/L KCN, 2 mmol/L EDTA and the pH is 6.2.

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REPORT

Intercomparison Studies Shanghai-1 and Shanghai-2

of the

IFCC Network on Standardisation of HbA_{1c}

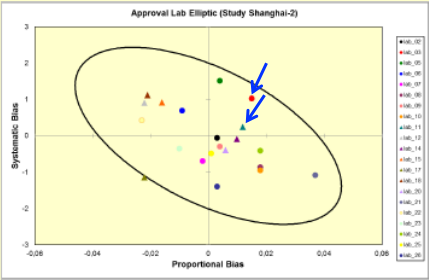



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Dr. Cas Weykamp, IFCC Network Coordinator
Carla Siebelder, BSc, Associate IFCC Network Coordinator
1 November 2016

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Lab	Systematic Bias (absocs)	Proportional Bias (slope)	Combined Statistical Test Critical Value 10.6
lab_02	-0.06	0.003	0,1
lab_03	1.03	0.015	6,9
lab_05	1.52	0.004	7,1
lab_06	0.70	-0.009	0,9
lab_07	-0.69	-0.002	1,5
lab_08	-0.87	0.018	1,9
lab_09	-0.30	0.004	0,2
lab_10	-0.95	0.018	2,1
lab_11	0.24	0.012	1,7
lab_12	0.91	-0.022	2,5
lab_14	-0.09	0.010	0,7
lab_15	0.92	-0.016	1,8
lab_17	-1.15	-0.022	14,3
lab_18	1.12	-0.021	2,9
lab_20	-0.40	0.006	0,3
lab_21	-1.08	0.037	6,7
lab_22	0.43	-0.023	2,8
lab_23	-0.35	-0.010	1,5
lab_24	-0.41	0.018	1,7
lab_25	-0.48	0.001	0,5
lab_26	-1.39	0.003	4,4





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IFCC
International Federation
of Clinical Chemistry
and Laboratory Medicine
Network on Standardization of HbA_{1c}

Certificate

Approval of Network Laboratories operating the IFCC Reference Measurement Procedure for HbA_{1c}

This certifies that Centro per la Riferibilità metrologica in Medicina di Laboratorio (CIRME), Università degli Studi di Milano, Milano, Italy participated in and passed the criteria* of the intercomparison studies of the Network of Reference Laboratories operating the IFCC Reference Measurement Procedure for HbA_{1c} and has the status of approved Network Laboratory in 2017.

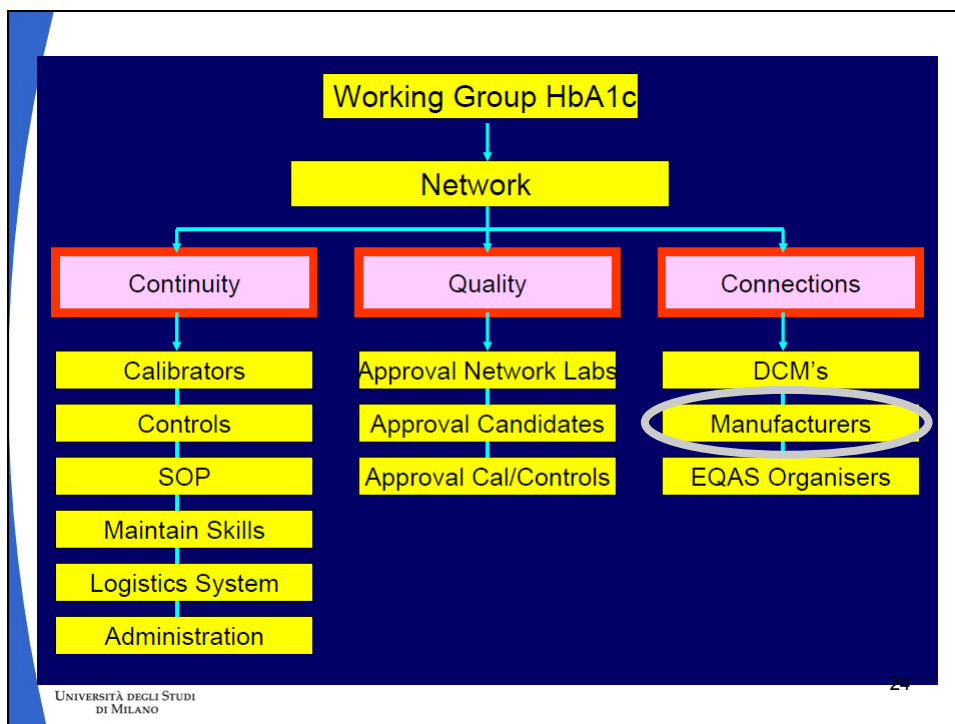
Date of issue: 1 November 2016 Certification expires: 31 December 2017

[Signature]
IFCC Network Coordinator

* According to Konnerk et al. in "Statistical Rules for Laboratory Networks, Journal of Testing and Evaluation, March 2006, vol 34, Paper ID/ITE 14982"

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4.2.1.4 Monitoring Programme

To prove traceability (especially in respect to the IVD directive), manufacturers appreciate the availability of an independent monitoring programme. This programme is available from the IFCC network. In summary, participating manufacturers receive 24 frozen whole blood samples once a year. Following the list with deadlines, every two weeks a specimen is assayed. Results are submitted via the interactive website of the IFCC HbA_{1c} Network; immediately after the deadline for submission is passed the report can be requested from the website. The report shows the submitted result in comparison to the target value. Additionally trend reports (either related to time or to HbA_{1c} content) can be requested and once the annual cycle is completed the annual report deals with precision and linearity. Results are strictly confidential: only the manufacturer has access to his results but he is free to use the results. Manufacturers get a certificate of traceability on which their performance in terms of deviation from the IFCC target, precision and linearity are specified. Details and certificate/ instructions can be downloaded from the website.

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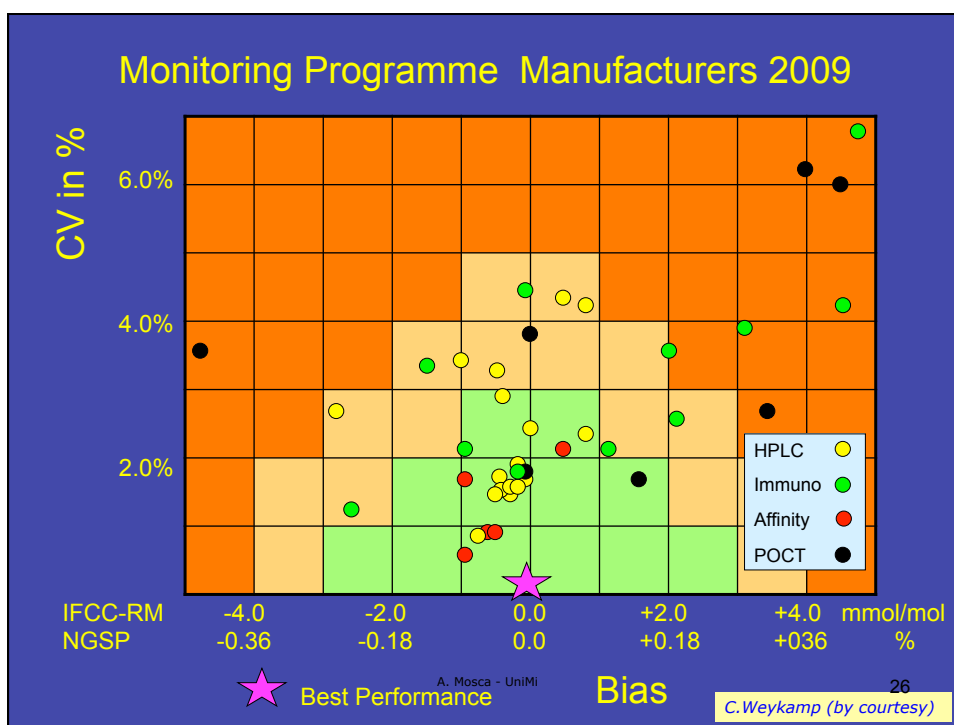
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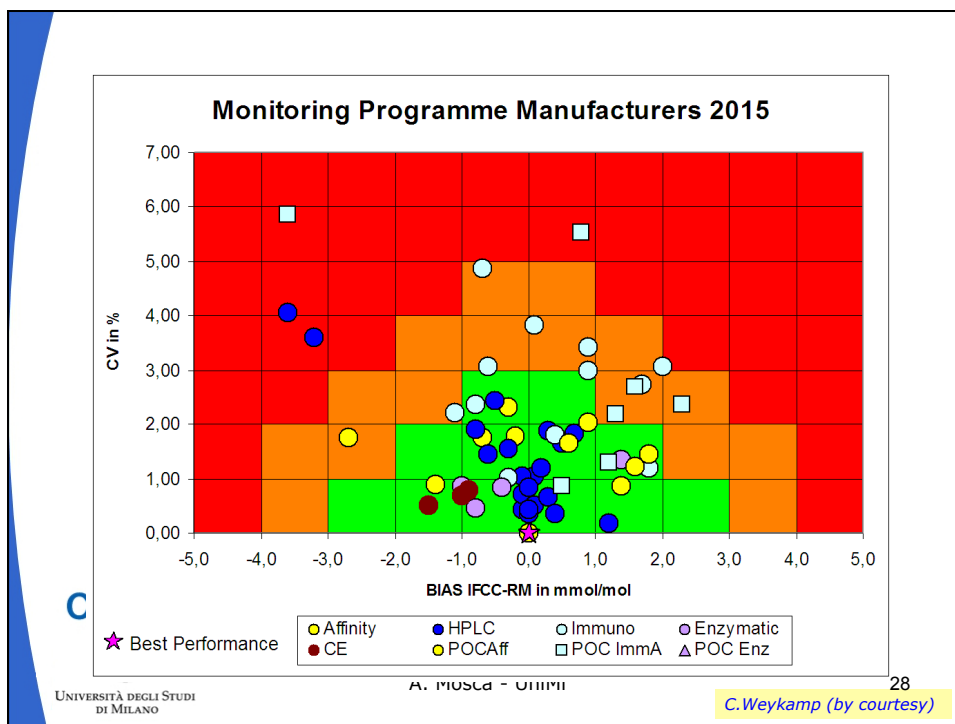
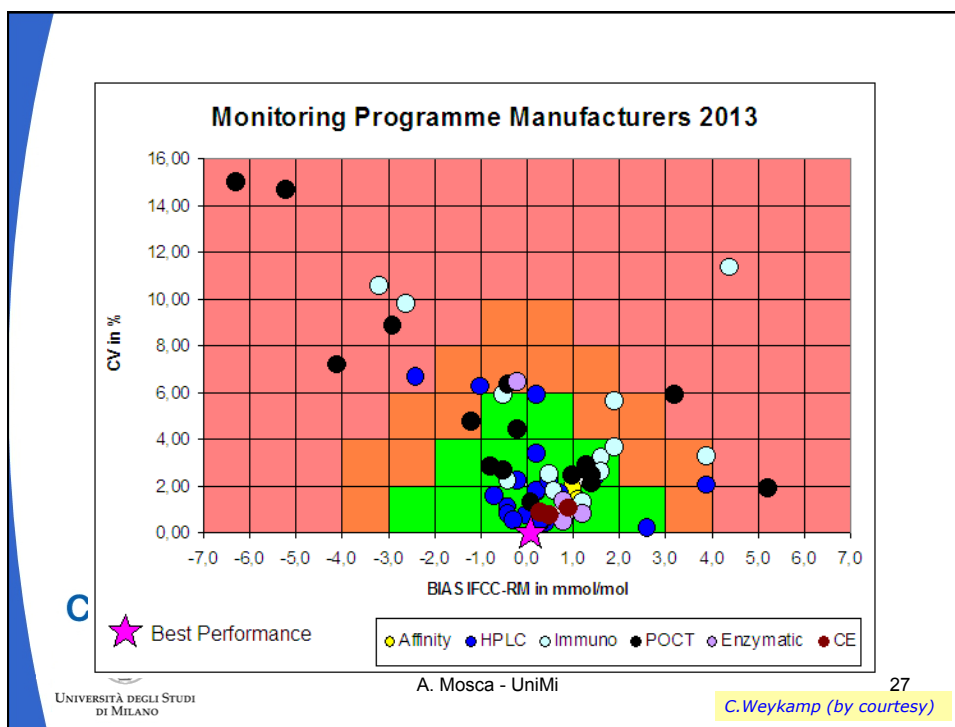
Procedure Manual - IFCC Network of Reference Laboratories for HbA_{1c}

Version 10-02-2011

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middle of the chain

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What information should be provided

- which kind of higher-order materials and methods to assign traceable values to the calibrators
- which kind of internal calibration hierarchy
- u_c of commercial calibrators

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Table 1
Metrological traceability and uncertainty information derived from calibrator package inserts of commercial systems measuring blood glucose marketed by four IVD companies.

Company	Platform	Principle of commercial method	Calibrator	Declared standard uncertainty ^a	Higher-order reference employed		Type of traceability chain used ^b	Combined standard uncertainty associated with the used chain ^c
					Method	Material		
Abbott	Architect	ND	Multiconstituent calibrator	2.70%	IDMS	NIST SRM 965	A	1.22–1.45% ^d
Beckman	AU	Hexokinase	System calibrator	ND	ND	NIST SRM 965	A	1.22–1.45% ^d
Roche	Synchron	Hexokinase	Synchron multicalibrator	ND	ND	NIST SRM 917a	D	1.60–3.00% ^e
	Cobas c	Hexokinase	C.f.a.s.	0.84%	IDMS	ND	B	1.70%
	Integra	Hexokinase	C.f.a.s.	0.62%	IDMS	ND	B	1.70%
	Modular	Hexokinase	C.f.a.s.	0.84%	IDMS	ND	B	1.70%
Siemens	Advia	Hexokinase	Chemistry calibrator	1.30%	Hexokinase	NIST SRM 917a	C	1.88–3.26% ^f
		GOD	Chemistry calibrator	0.80%	Hexokinase	NIST SRM 917a	C	1.88–3.26% ^f



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Verification of in vitro medical diagnostics (IVD) metrological traceability: Responsibilities and strategies

Federica Braga ^{*}, Mauro Panteghini

A. Mosca - UniMi

Clin Chim Acta 2014;432:55-61

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International Federation
of Clinical Chemistry
and Laboratory Medicine
Network on Standardization of HbA1c

Certificate

Traceability of Manufacturers to the IFCC Reference Measurement Procedure for HbA1c


This certifies that [redacted] using [redacted] participates in the Monitoring Programme to demonstrate traceability. In the Monitoring Programme of 2015 the following performance was seen:

Deviation from IFCC-target	at 30 mmol HbA1c/mol Hb :	0.1
	at 60 mmol HbA1c/mol Hb :	0.0
	at 90 mmol HbA1c/mol Hb :	-0.1
Reproducibility, coefficient of variation		0.42%
Linearity, correlation coefficient		0.9995


Date of issue: 4 December 2015

Certification expires: 31 December 2016

C



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Dr. C.W. Weykamp
IFCC HbA1cNetwork Coordinator

A. Mosca - UniMi

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Product certificate HbA1c





Product name XXXXXXXXXX

Product number 4755

Product code

Level	Product code	Colour cap
Low	Level 1	Green
High	Level 2	Red

Batch number and Expiry date

Level	Batch number	Exp. Date stored at 30°C / -16°C
Low	 05046/01	 2021/03
High	 06046/01	 2021/03

Reconstitution volume 0.6 mL with a precision of $\pm 1.0\%$

Haemoglobin

Level	Hb (mmol/L)
Low	7.1
High	7.0

Assigned Values*

Level	Certified Value (Expanded Uncertainty, k=2)	
	IFCC mmol/mol	DCCT %
Low	36.8 (0.7)	5.52 (0.06)
High	86.8 (1.5)	10.09 (0.14)

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bottom of the chain

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What should be done to prove the metrological traceability - uncertainties -

- The use of a traceable method
- The uncertainty of the commercial calibrators
- The long-term imprecision of the routine method

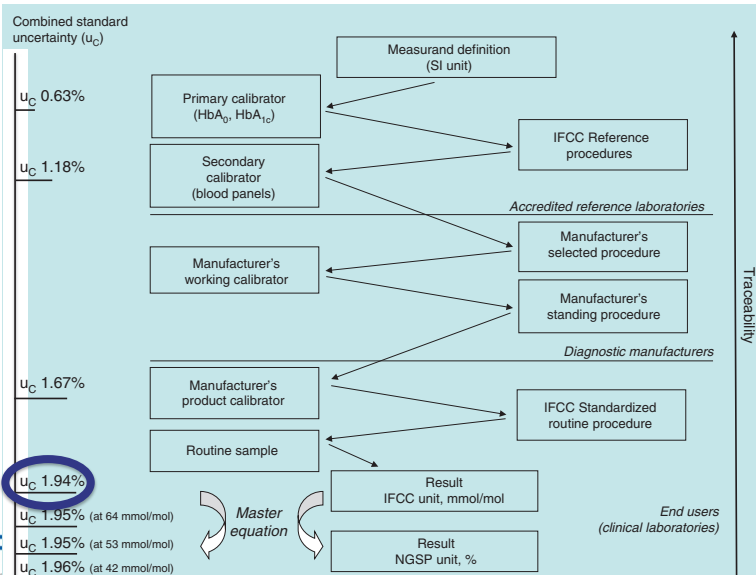
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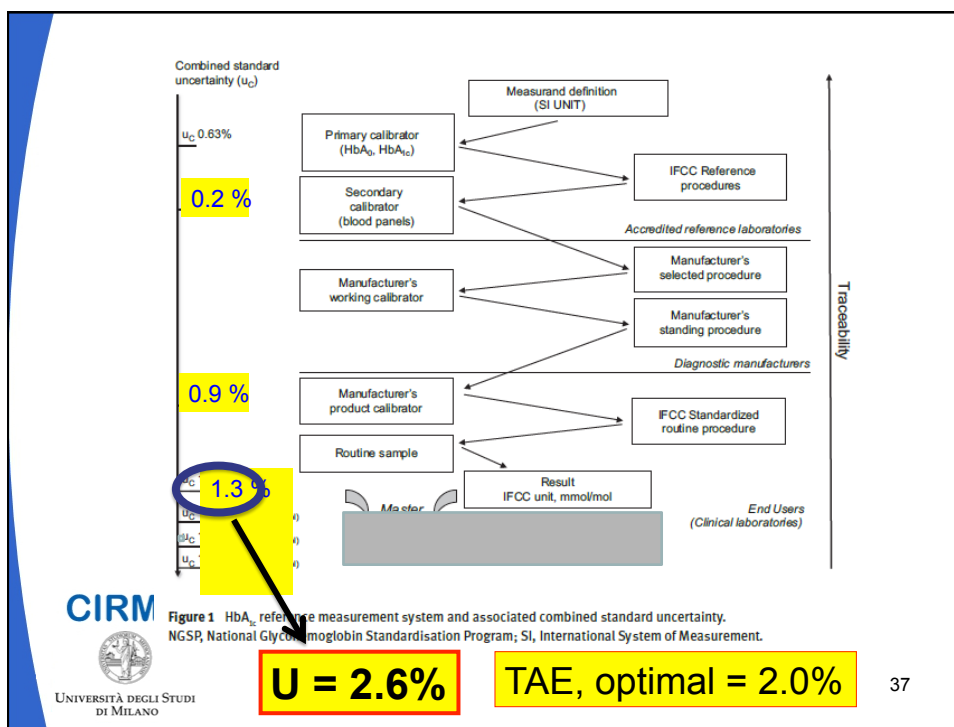
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Braga and Panteghini, Clin Chem Lab Med 2013;51:1719

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Other factors contributing to the uncertainty

- Bias
- Biological variation

$$u \text{ (composite)} = (u^2 \text{IQC} + u^2 \text{EQC} + u^2 \text{intra-individual})^{1/2}$$

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EDMA position paper – Estimation of uncertainty of measurement in medical laboratories. www.edma-ivd.be; 2006/09

What should be done to guarantee the long-term performance

- analytical goals
- EQAS

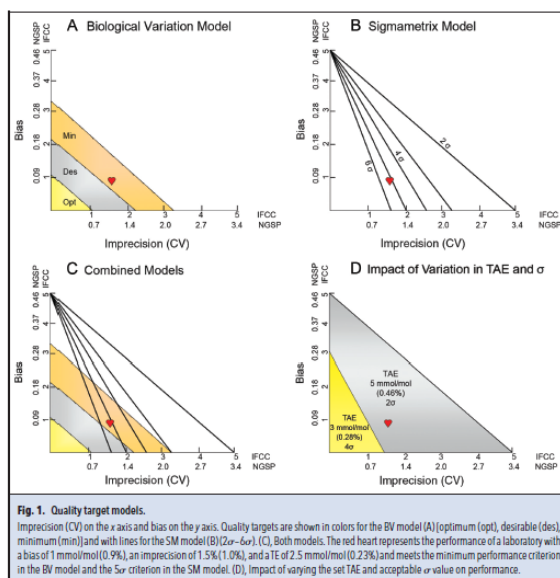
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Weykamp et al, Clin Chem 2015;61:752

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Revaluation of biological variation of glycated hemoglobin (HbA_{1c}) using an accurately designed protocol and an assay traceable to the IFCC reference system

Federica Braga ^{a,b,*}, Alberto Dolci ^b, Martina Montagnana ^c, Franca Pagani ^d, Renata Paleari ^a, Gian Cesare Guidi ^c, Andrea Mosca ^a, Mauro Panteghini ^{a,b}

Table 3
Analytical goals for HbA_{1c} measurement derived from data on biological variation.

Quality level	Imprecision, %	Bias, %	Total error, %
Optimal	≤0.6	≤±0.9	≤±2.0
Desirable	≤1.3	≤±1.9	≤±3.9
Minimal	≤1.9	≤±2.8	≤±5.9

Clin Chim Acta 2011;412:1412

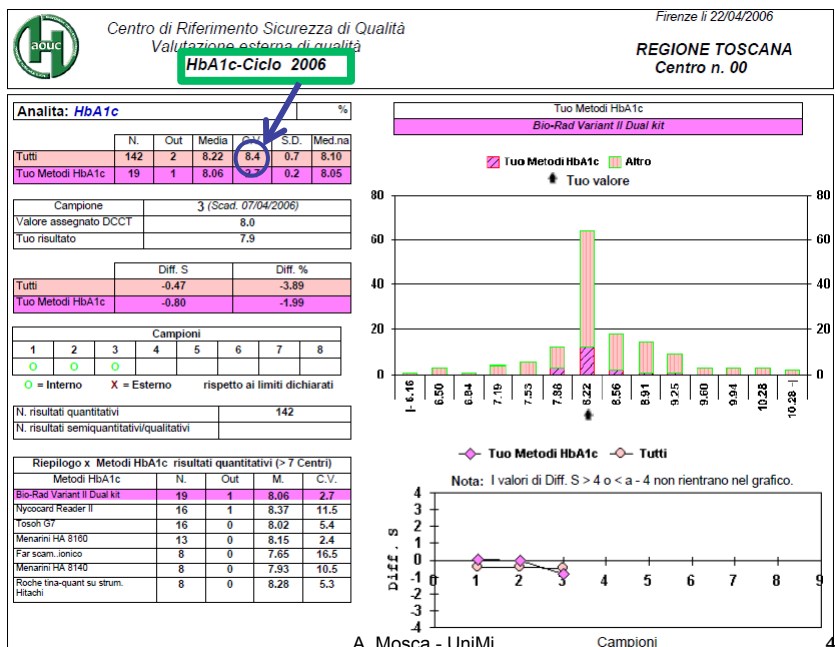
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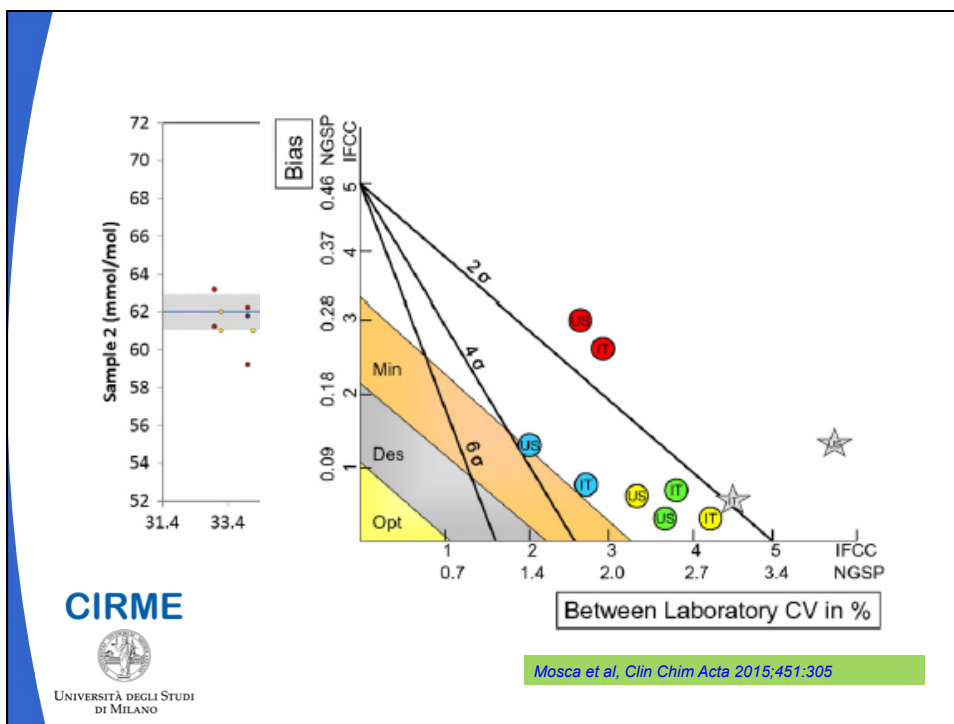
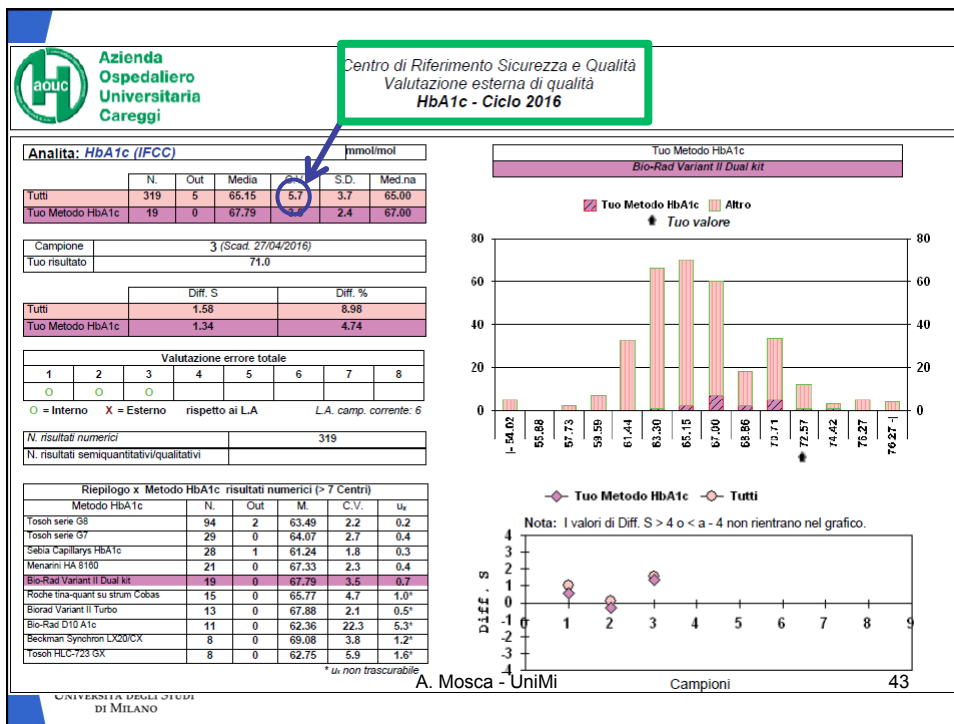


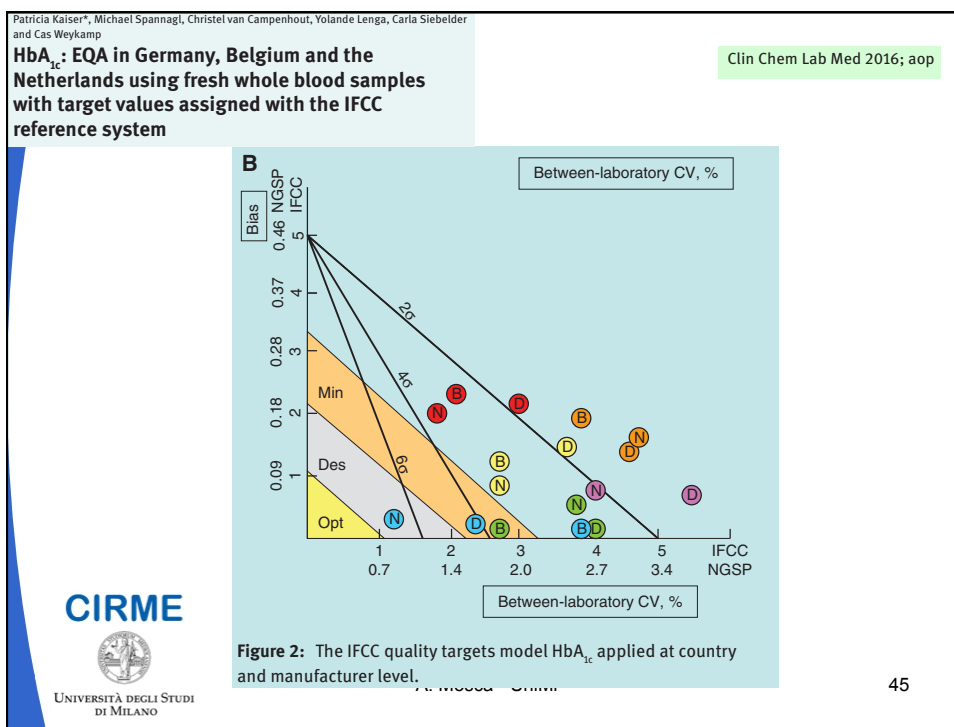
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Standardization of HbA_{1c}: are all the pieces in place?

- Top of the chain: YES (IFCC Network)
- Middle: probably YES (information not uniform and difficult to be released)
- Bottom: difficult to draw objective evidences (depending on country and rules); more efforts needed to achieve standardization overall

WHAT NEXT?

- Consensus on uncertainty
- Improving EQAS (EurA1c)
- Education and communication

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- The IFCC Network laboratories
- Manufacturers
- Mauro Panteghini and CIRME staff

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