

Comparisons of Synthetic vs Real PT items

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Offering UK NEQAS EQA programmes in Clinical Biochemistry and beyond



Birmingham Quality



We are, and always have been, part of the NHS



EQA is more than a tick box exercise

UK NEQAS
International Quality Expertise

50 Years as World
Leaders in EQA
1969–2019



Birmingham Quality

NHS
University Hospitals Birmingham
NHS Foundation Trust

Comparisons of Synthetic vs Real PT items

The whole underlying underpinning article of faith is that your performance as described by the output of a Proficiency Testing [PT] Scheme/Programme truly reflects your performance in 'real life', both in terms of the results and interpretations, that you make day-in, day-out.

Most EQA is a compromise, but a successful EQA programme is one where the benefits of a particular approach outweigh any potential shortcomings.

In some physical PT/EQA you can actually send out real, genuine items. This is the ideal scenario. In my area of the biological/ health field where fresh, straight out of the arm, blood samples would be the natural EQA Material [EQAM], we do not have that luxury.

Comparisons of Synthetic vs Real PT items

Extreme example Point of Care Testing (POCT) ~ *finger prick blood*

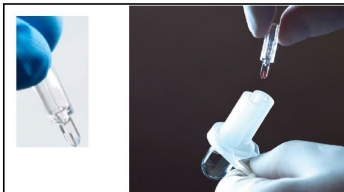
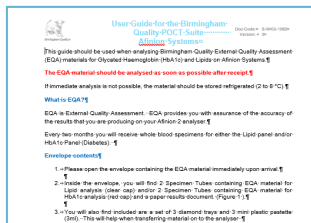
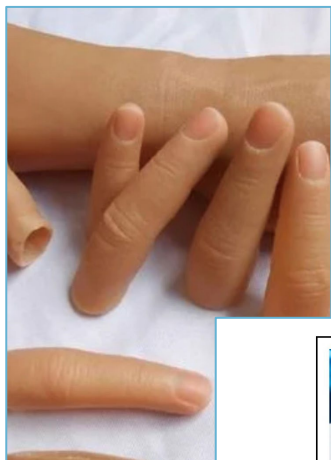


Figure 3 Steps showing application of EQA material to the Quo-Test

You can't send out severed fingers to mimic what the end user has as his regular sample presentation

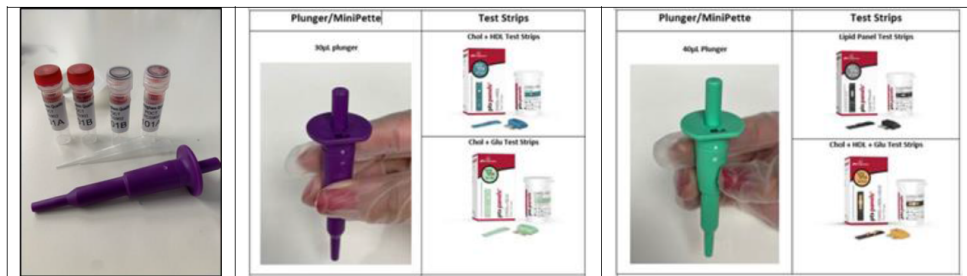


Figure 1. Specimen Tubes for the Lipid Panel (clear cap) and the Glycated Haemoglobin Panel (red cap) [You may not receive both sets of Specimen Tubes] and the 30 uL Purple and 40 uL Green Plunger/MiniPettes

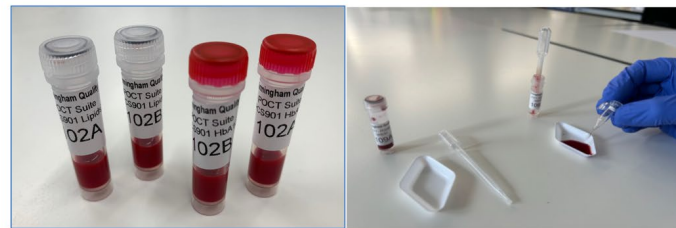


Figure 1. Specimens for HbA1c Panel (red cap) and Lipid Panel (clear cap) — Left and Specimen transferred into diamond tray and mini plastic pastette — Right



Comparisons of Real vs Synthetic EQA materials

Real	Synthetic
No worries about Commutability	Prove, not just assert, Commutability
Limited Concentration ranges	Wide and Challenging concentrations possible
Volume constraints	Can have enough volume to allow repeat distributions over many years
Limited sample types	Ability to challenge with different 'spikes' / isoforms and with inter-related concentrations and conduct Recoveries etc
Often restricted to a snapshot	Challenge at cut-offs and at different scenarios
Inability to source challenging Specimens	Construct, within reason, any Specimen you want

None of this affects choice of targets and use of Reference Method Values, which is a talk in itself

Homogeneity is always crucial, whether you are using Genuine or Synthetic EQA Specimens

EQA Providers are obliged to assess homogeneity as part of their ISO/IEC17043:2010 Accreditation requirements.

Most do this as a matter of course, but there are myths and legends as to how resources should be best targeted.

Well mixed, aqueous or serum-based samples are essentially simple to deal with.

Whole blood material requires extra care in mixing without causing damage to cells

Faecal material is difficult to deal with due its viscosity.

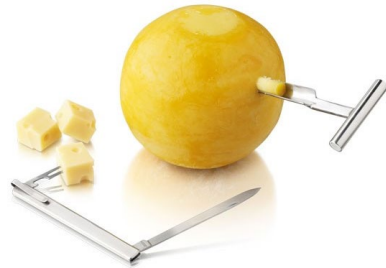
Lyophilised material needs assessing across the 'racks' with different positions / hotspots etc

You need to be checking what happens after your specimens have left the building as well as before.

It matters not a jot for the statistical handling of your results if they left your Laboratory in a perfect condition but were compromised to a varying degree after that. No Algorithm A, or even Algorithm Z, can fix this.

Homogeneity ~ MacKenzie's Hedgehog Jobby meets Countdown

a real life issue for the best way to measure FIT (Hb in Faecal Material)

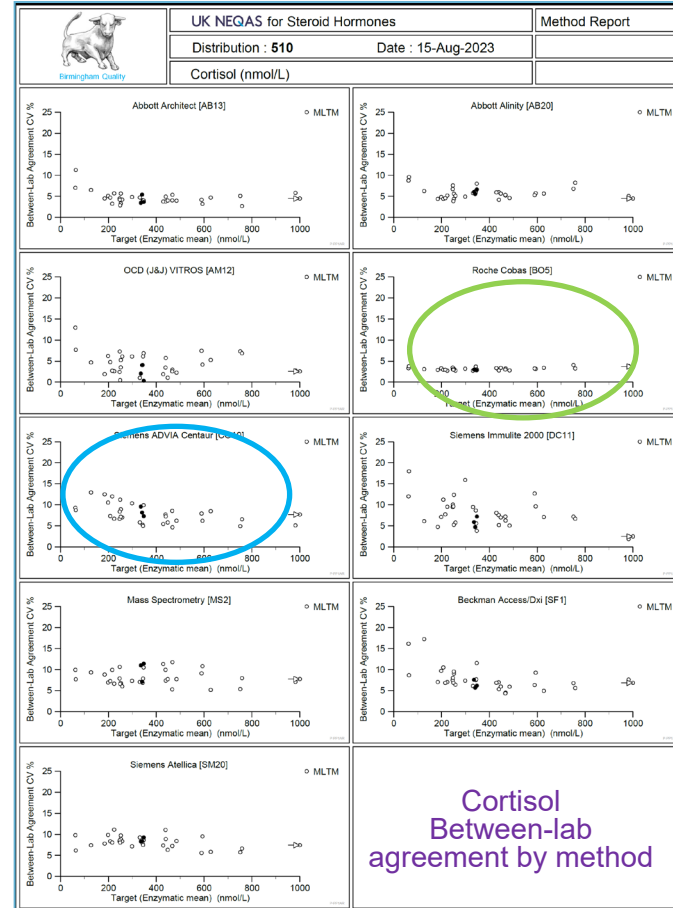
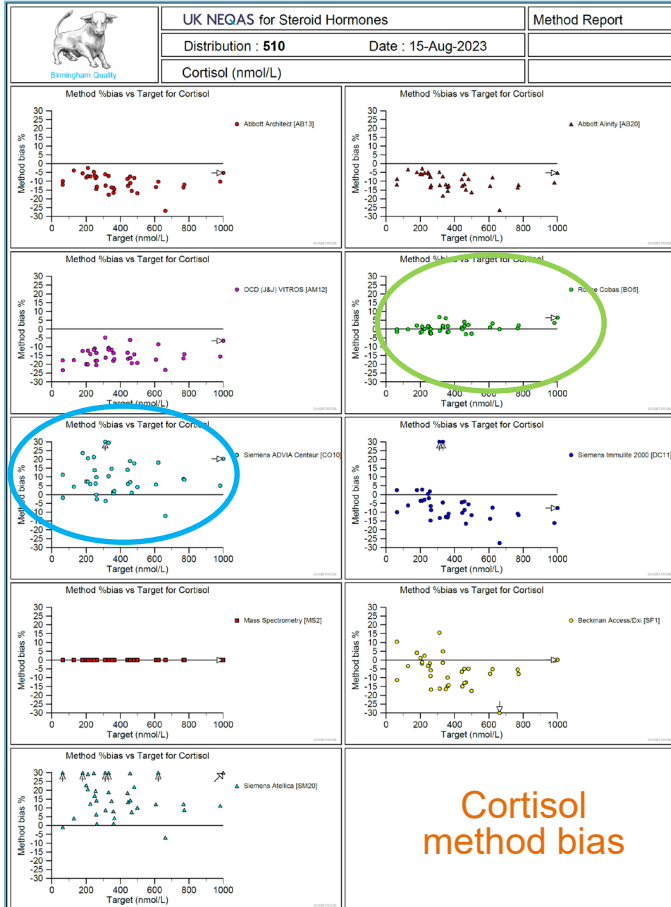


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Cortisol ~ Specimen Choice and Frequency might mask performance Characteristics of both Methods and of Laboratories



Siemens Centaur

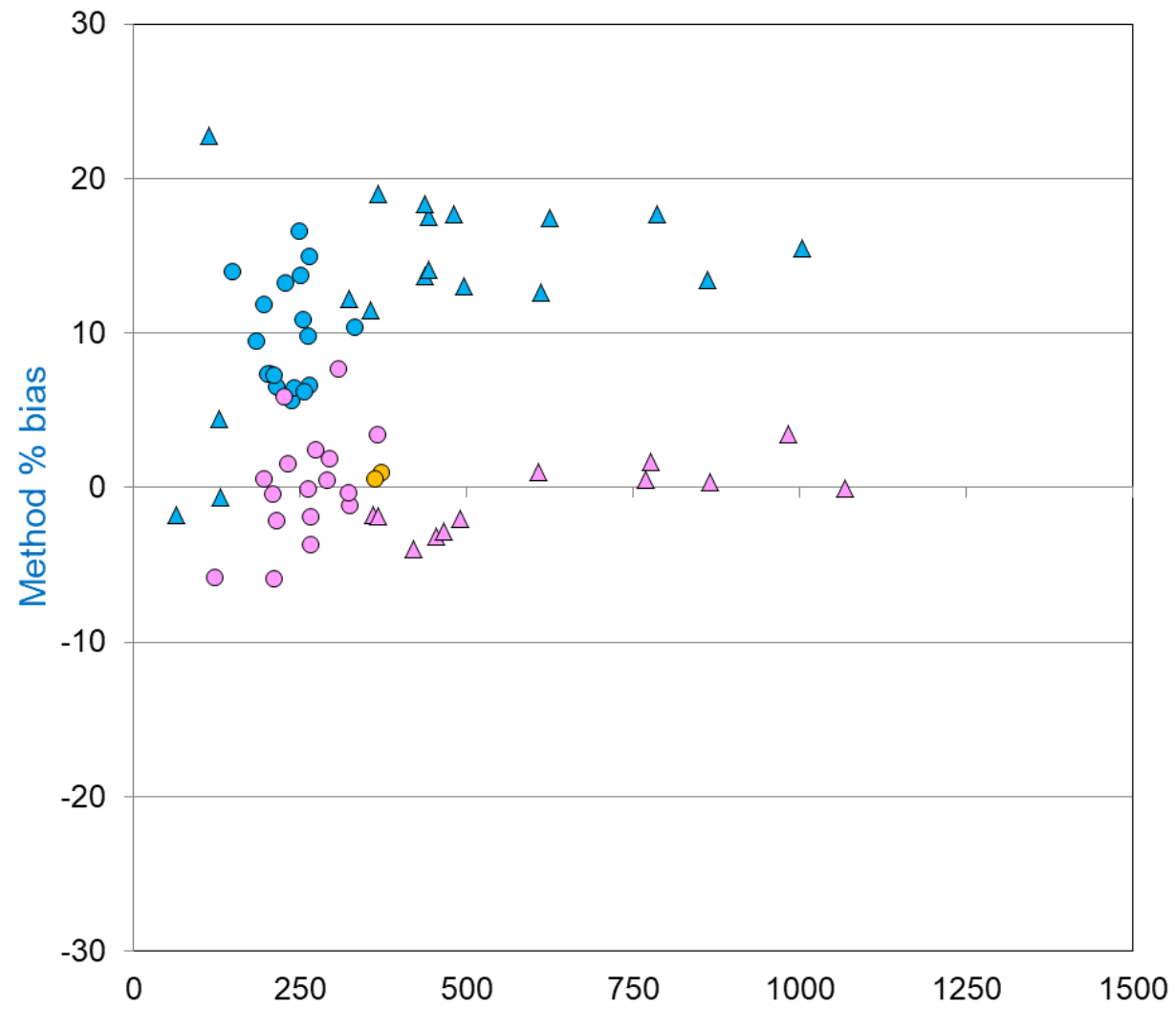
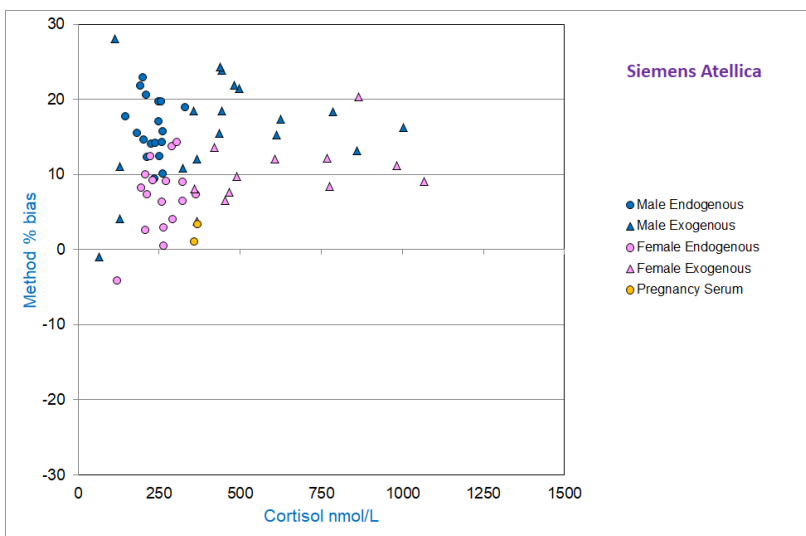
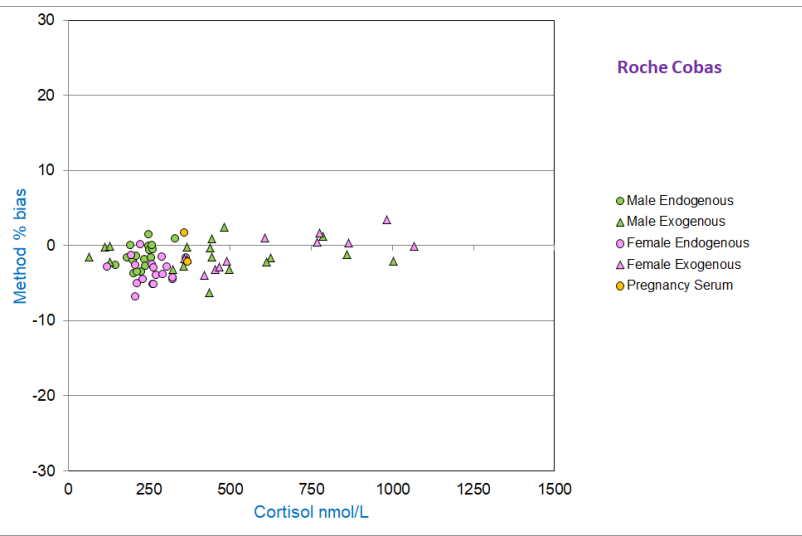
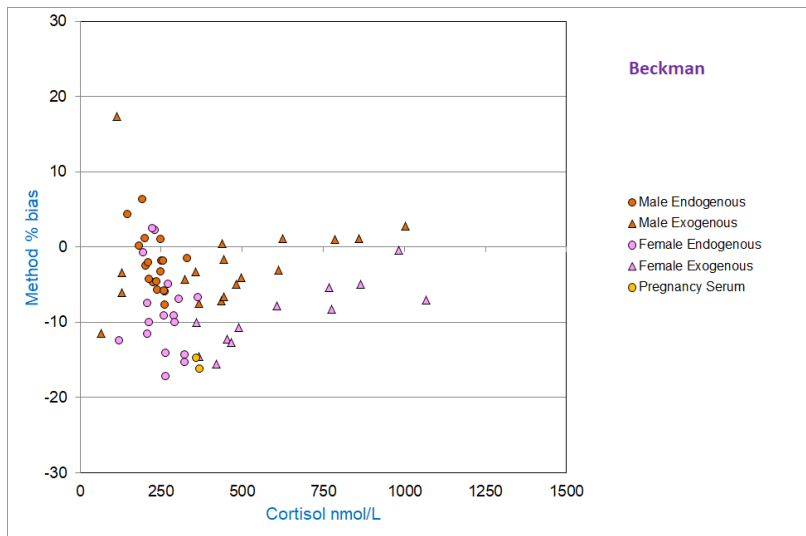
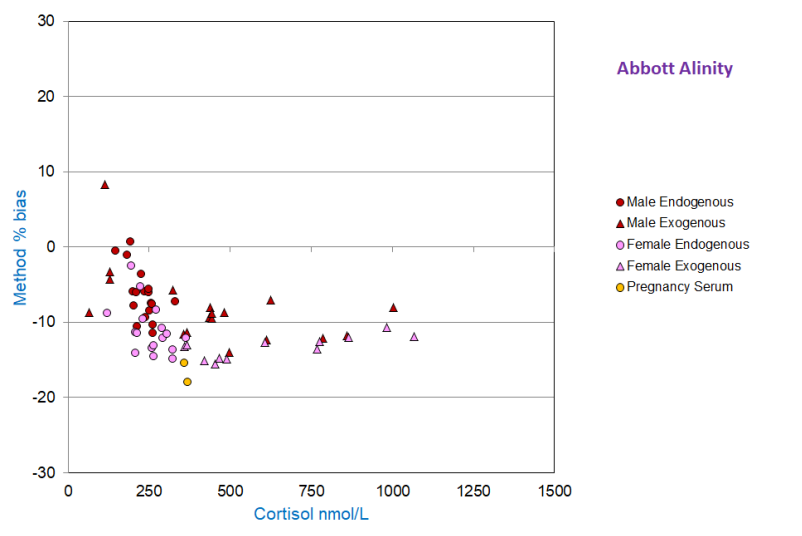


Chart Area



Cortisol reminder

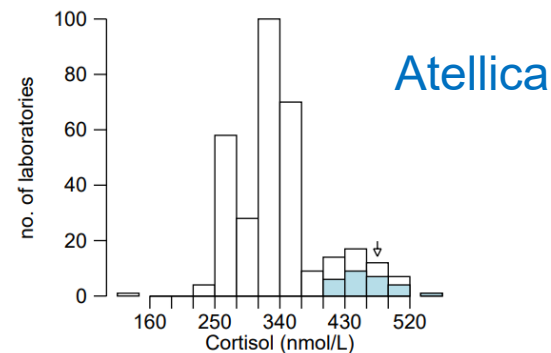
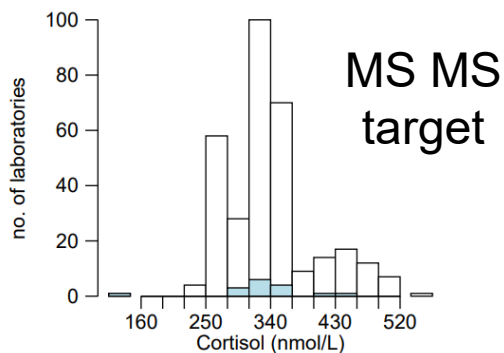
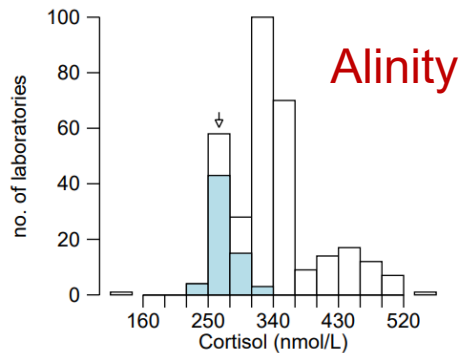
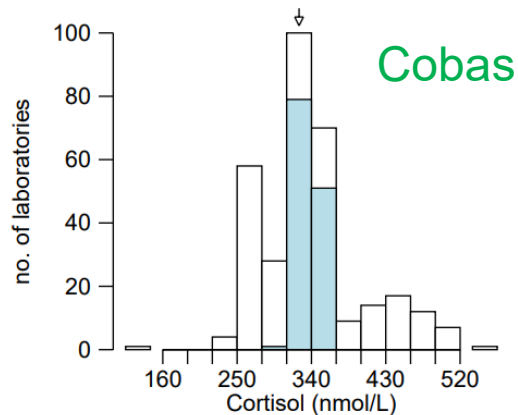
- Material - Endogenous Male, Endogenous Female and some with added Cortisol
- Field Method MS as target value; validated against Reference Method
- Sex differences in assays, which you can identify on the six month summary table

Pool (exclusion) [Type]	Distribution 499 16-Aug-2022			Distribution 500 20-Sep-2022			Distribution 501 18-Oct-2022			Distribution 502 22-Nov-2022			Distribution 503 10-Jan-2023			Distribution 504 07-Feb-2023		
	result	target	%bias	result	target	%bias	result	target	%bias	result	target	%bias	result	target	%bias	result	target	%bias
C630 [M,X,R]																64	64	-0.3
C629 [M,X,R]																143	128	+11.4
C558 [M,V]	257	201	+28.0															
C576 [M,V]	272	210	+29.7															
C599 [F,V]																		
C621 [M,N]																292	250	+16.9
C575 [M,V]	302	255	+18.3															
C651 [M,N]																		
C642 [F,N]				250	260	-3.7												
C606 [M,V]																		
C643 [F,X]				358	359	-0.3												
C604 [F,V]																		
C653 [M,X]																		
C645 [F,X]							456	466	-2.1									
C655 [M,X]																		
C647 [F,X]							644	607	+6.0									
C648 [F,X]				835	768	+8.7												
C649 [F,X]							1021	982	+3.9									
Method	CO10			CO10			CO10			CO10			CO10			CO10		

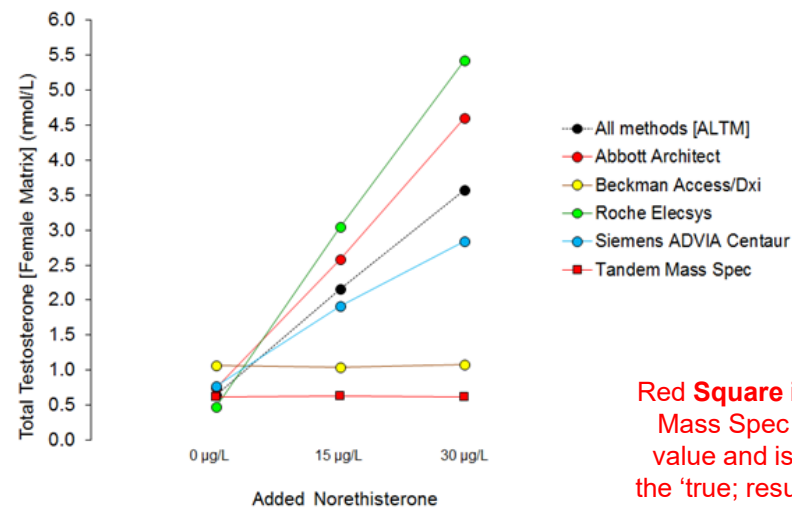
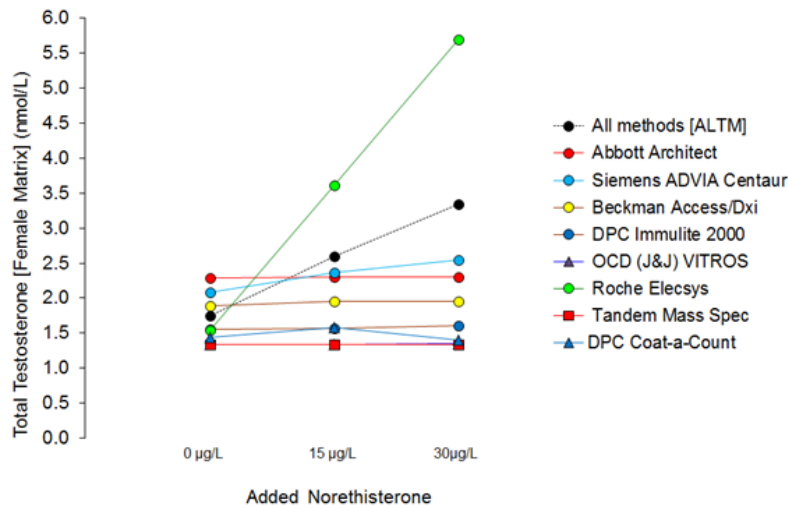
Tri-modal Distribution on Pregnancy serum ~ Cortisol 510A

Specimen : 510A	n	Mean	SD	CV(%)
All methods [ALTM]	318	335	57	17.0
Abbott Alinity [AB20]	65	271	16	6.0
Abbott Architect [AB13]	18	273	9	3.4
Beckman Access/Dxi [SF1]	27	348	26	7.6
Mass Spectrometry [MS2]	16	332	36	11.0
Not stated, please specify [UUU]	3	368		
OCD (J&J) VITROS [AM12]	5	293	6	2.0
Roche Cobas [BO5]	131	338	10	3.0
Siemens ADVIA Centaur [CO10]	18	429	41	9.6
Siemens Atellica [SM20]	27	459	38	8.3
Siemens Immulite 2000 [DC11]	6	458	27	5.9

Parameter	Value
Your result	338
Target (Mass Spectrometry [MS2])	332
Standard Uncertainty	12
Your specimen: %bias	+1.9 ◆
Accuracy Index	23
Your method mean Roche Cobas [BO5]	338



Norethisterone interference in Testosterone Assays



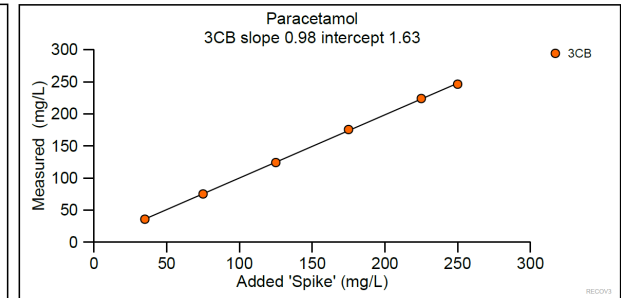
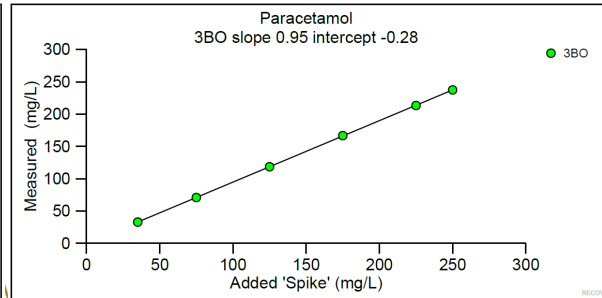
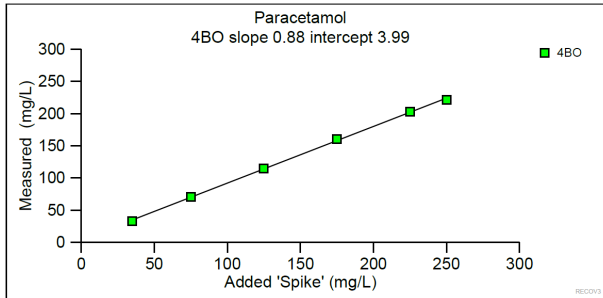
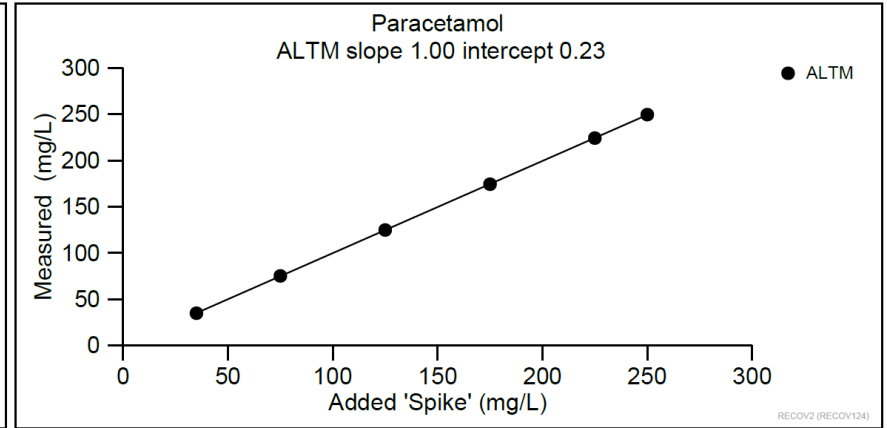
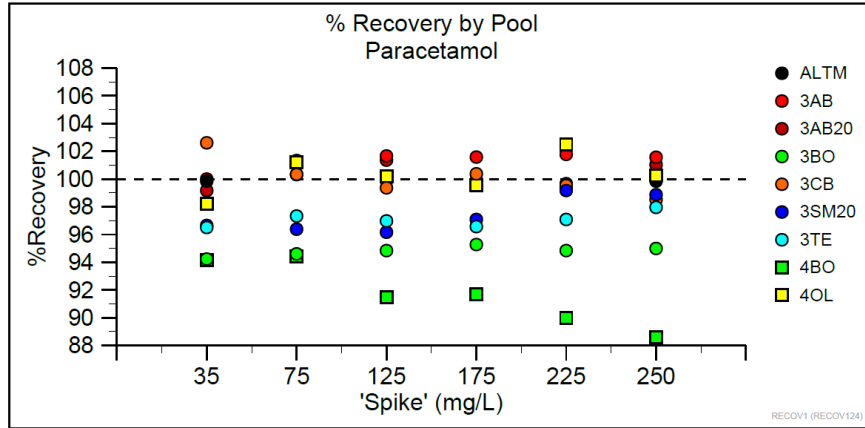
Red Square is Mass Spec value and is the 'true' result

Distribution of Serum Total Testosterone concentrations for pooled female serum samples containing 0, 15 and 30 µg/L added Norethisterone at Distribution 379 (left), November 2011 and Distribution 457 (right), October 2018.

Serum concentrations of Norethisterone up to 15 µg/L (50 nmol/L) can typically occur after administration of 5 mg Norethisterone. When Norethisterone is prescribed for contraception, the administered dose is typically 350 µg daily, whereas Endometriosis or Menorrhagia can be up to 15 mg daily. Note Red Circle method's results changing from unaffected to affected, over time. You cannot assume that there will always be progress!

Paracetamol

Probing method bias by using Recovery experiments at a range of concentrations and also using different base materials to remove any matrix-related effects.



This type of experiment is possible only by using synthetic EQA; you could look at Reference Method Values in native specimens across a range of concentrations if it was possible to collect/bin and pool, but this doesn't really cut to the chase like this simple Recovery Experiment can.

Commutability

Commutability is a property of a reference material (RM) that relates to the closeness of agreement between results for a RM and results for clinical samples (CSs) when measured by 2 measurement procedures (MPs).

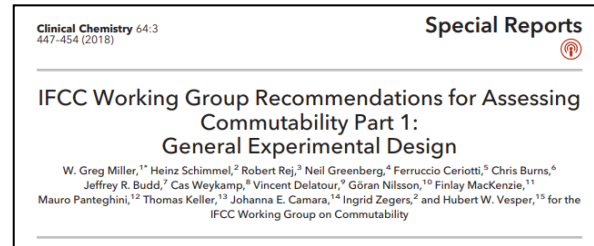
Commutability of RMs used in a calibration traceability scheme is an essential property for them to be fit for purpose. Similarly, commutability of trueness controls or external quality assessment samples is essential when those materials are used to assess trueness of results for CSs.

Part 1: General Experimental Design

Part 2: Using the Difference in Bias Between a Reference Material and Clinical Samples

Part 3: Using the Calibration Effectiveness of a Reference Material

+ other papers including EQA (*in press*)



Commutability

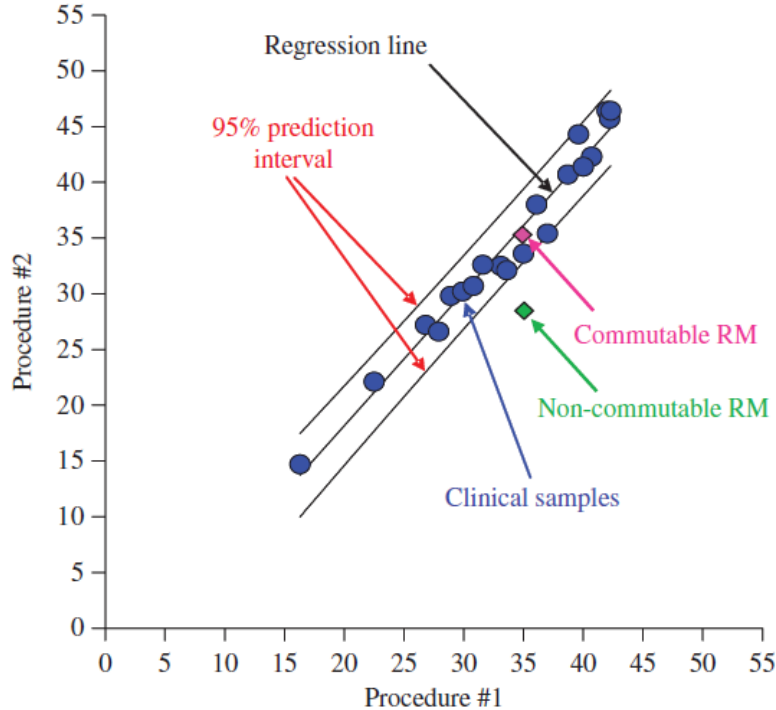


Figure 2: Schematic diagram showing the behaviour of a commutable (pink) and a non-commutable (green) reference material (RM) when assessed according to the Clinical and Laboratory Standards Institute guidelines [24, 25].
Note: Procedure #1 in x-axis should be reference measurement procedure when available.

DE GRUYTER

Clin Chem Lab Med 2019; 57(7): 967–973

Mini Review

Federica Braga* and Mauro Panteghini

Commutability of reference and control materials: an essential factor for assuring the quality of measurements in Laboratory Medicine

Rule 0 – you need specific assays!







IFCC Working Group on Commutability has been producing recommendations since 2018 ~ *this is from September 2023*

Clinical Chemistry 00:0
1–11 (2023)

Special Report

Recommendations for Setting a Criterion and Assessing Commutability of Sample Materials Used in External Quality Assessment/Proficiency Testing Schemes

Sverre Sandberg,^{a,b,c,*} Pernille Fauskanger,^a Jesper V. Johansen,^d Thomas Keller ^e Jeffrey Budd,^f Neil Greenberg,^g Robert Rej ^h Mauro Panteghini,ⁱ Vincent Delatour,^j Ferruccio Ceriotti ^k Liesbet Deprez,^l Johanna E. Camara,^m Finlay MacKenzie,ⁿ Alicia N. Lyle ^o Eline van der Hagen,^p Chris Burns,^q and W. Greg Miller;^r for the IFCC Working Group on Commutability in Metrological Traceability

Greg Miller leads a group of statisticians, EQA providers and Diagnostic Kit manufacturers bringing their expertise to the table. This is paper 5.

IFCC Working Group on Commutability has been producing recommendations since 2018 ~ *this is from September 2023*

Recommendations for setting a criterion and assessing commutability of sample materials used in external quality assessment/proficiency testing schemes

Supplemental files

Supplemental figure

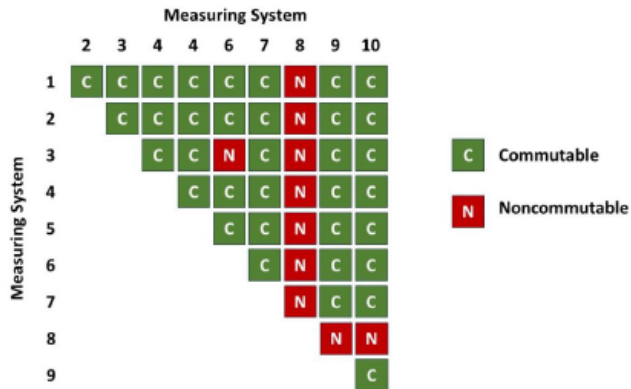


Figure S1. Example of commutability assessment conclusions for pairs of in vitro diagnostic medical devices (IVD-MDs). IVD-MD8 has a consistent pattern of non-commutability with clinical samples (CSs) for all other IVD-MDs and the external quality assessment material (EQAM) will need to have an IVD-MD8-specific target value. The EQAM is commutable with CSs for most of the other IVD-MDs and therefore EQAM results can be examined for equivalence among the IVD-MDs with one exception; IVD-MD6 cannot be compared with IVD-MD3.

On the surface, simple to do, but there are multiple pair-wise comparisons to make ~ not practically easy to perform due to specimen volumes, logistics etc etc

Spec. Pool Description / Additions

195A	335	Single donation human serum
195B	336	Single donation human serum
195C	337	Single donation human serum

- All methods
- Compensated Kinetic Jaffe [10]
- Abbott Alinity [10AB20]

Your A score is 93
 Your B score is -3.3
 Your C score is 2.9

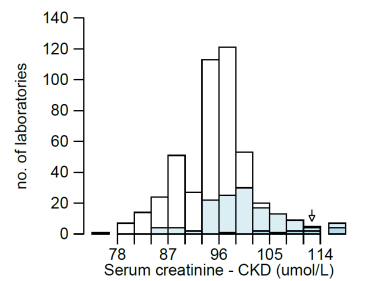
The A limit is 200
 The B limit is +/- 10.0
 The C limit is 10.0

Creatinine

this is just to set the scene for the type of results we get in the Scheme

Specimen : 195A

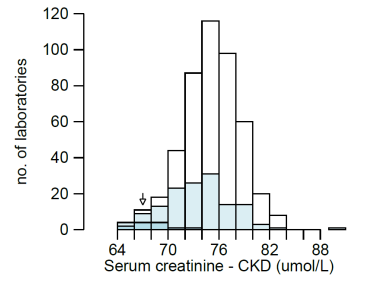
	n	Mean	SD	CV(%)
All methods [ALTM]	464	96.0	5.8	6.0
Compensated Kinetic Jaffe [10]	137	101.1	6.3	6.2
Abbott Alinity [10AB20]	12	111.7	9.2	8.2
Beckman AU [10OL]	11	92.0	4.7	5.1
Roche Cobas [10BO]	78	99.4	4.1	4.1
Enzymatic [9]	320	94.2	5.1	5.4
Abbott Alinity [9AB20]	57	88.3	2.5	2.8
Abbott Architect [9AB]	30	85.6	4.1	4.8
Beckman AU [9OL]	32	96.8	2.8	2.9
Roche Cobas [9BO]	167	97.0	2.1	2.2
Siemens ADVIA [9TE]	15	90.9	2.8	3.1
Siemens Atellica [9SM20]	15	94.5	2.4	2.5



Your result 114
 Target value (Enzymatic [9]) 94.2
 Standard Uncertainty 0.4
 Your specimen: %bias +21.1 ▲
 'Reference Method' 93.4
 Abbott Alinity [10AB20] 111.7

Specimen : 195B

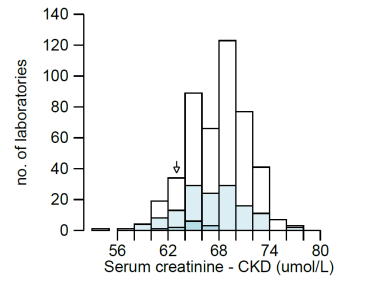
	n	Mean	SD	CV(%)
All methods [ALTM]	466	75.7	3.3	4.3
Compensated Kinetic Jaffe [10]	139	74.0	3.9	5.3
Abbott Alinity [10AB20]	12	68.6	2.1	3.1
Beckman AU [10OL]	13	73.7	4.1	5.5
Roche Cobas [10BO]	78	75.6	3.4	4.5
Enzymatic [9]	320	76.4	2.8	3.7
Abbott Alinity [9AB20]	57	73.6	1.5	2.0
Abbott Architect [9AB]	30	73.9	1.8	2.4
Beckman AU [9OL]	32	80.6	2.1	2.6
Roche Cobas [9BO]	167	77.3	1.8	2.3
Siemens ADVIA [9TE]	15	73.8	2.2	3.0
Siemens Atellica [9SM20]	15	75.0	1.1	1.5



Your result 68
 Target value (Enzymatic [9]) 76.4
 Standard Uncertainty 0.2
 Your specimen: %bias -10.9 ▼
 'Reference Method' 75.7
 Abbott Alinity [10AB20] 68.6

Specimen : 195C

	n	Mean	SD	CV(%)
All methods [ALTM]	464	68.4	3.5	5.1
Compensated Kinetic Jaffe [10]	137	67.5	3.7	5.5
Abbott Alinity [10AB20]	12	65.6	1.7	2.6
Beckman AU [10OL]	11	63.0	3.3	5.2
Roche Cobas [10BO]	78	68.6	3.6	5.3
Enzymatic [9]	320	68.8	3.4	4.9
Abbott Alinity [9AB20]	57	65.0	1.5	2.3
Abbott Architect [9AB]	30	64.3	1.9	2.9
Beckman AU [9OL]	32	72.8	1.7	2.3
Roche Cobas [9BO]	167	70.1	1.8	2.6
Siemens ADVIA [9TE]	15	67.4	1.6	2.3
Siemens Atellica [9SM20]	15	69.2	1.4	2.0



Your result 64
 Target value (Enzymatic [9]) 68.8
 Standard Uncertainty 0.2
 Your specimen: %bias -7.0 ▼
 'Reference Method' 66.9
 Abbott Alinity [10AB20] 65.6

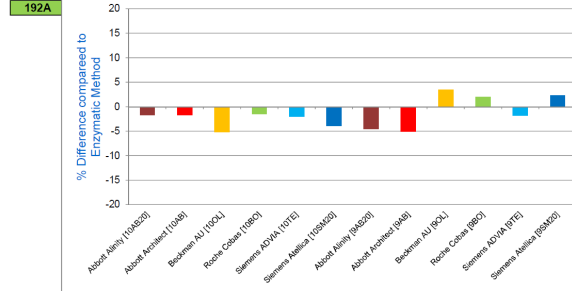
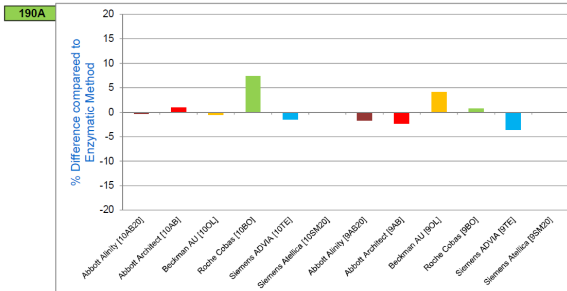
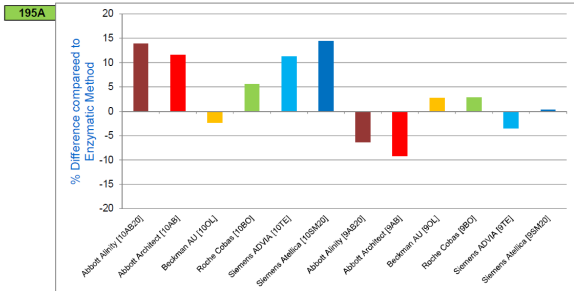


Creatinine Fingerprint bias plots, colour coded by method - 3 Distributions, 9 Specimens

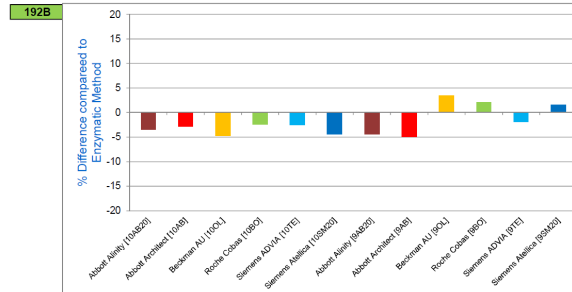
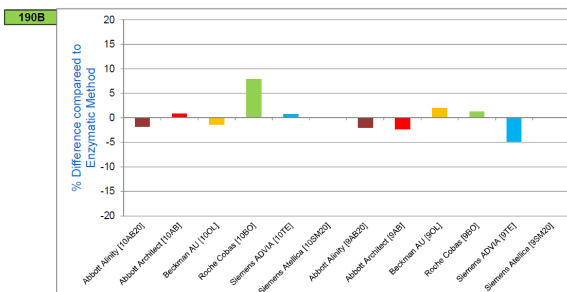
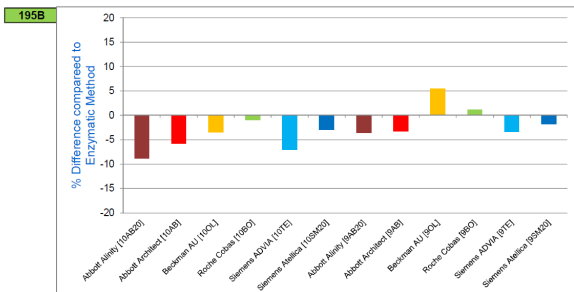
% Bias

% Bias

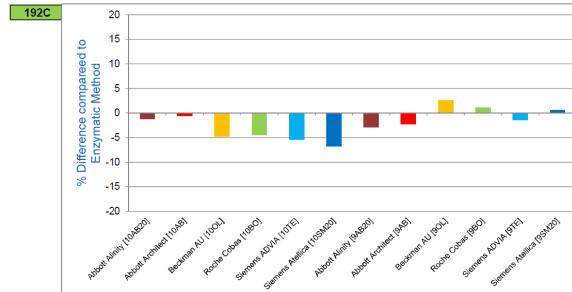
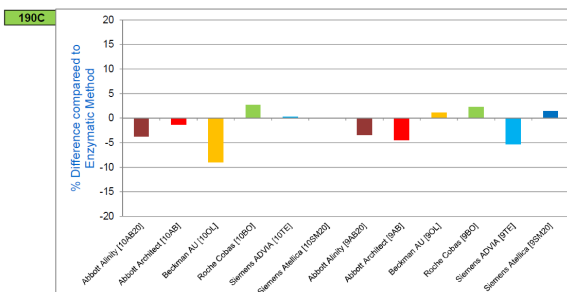
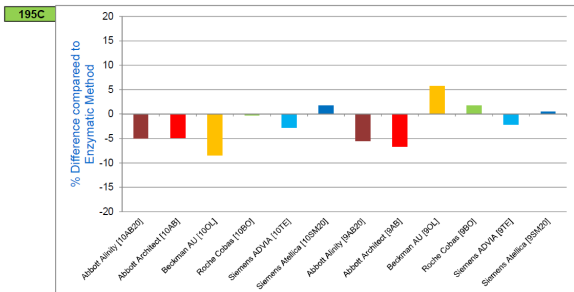
% Bias



124.052 u



134.367 u



289.576 u

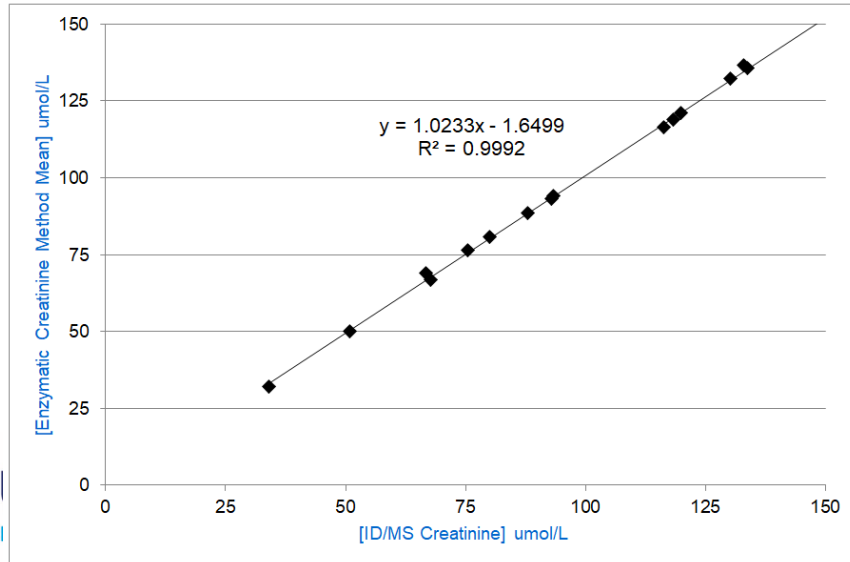
Creatinine *(and most measurands)*

Interfering substances are 'diluted out' when multiple donations are 'pooled' together:

- IQC, by its very nature has to use pooled material
- Some EQA providers only use pooled material
- Pooled material is very useful in EQA for:
 - Schemes with large numbers of participants
 - Multiple distributions of the same pool to assess assay stability

If we know different assays give different results, then why not use an MLTM target value?

- Our Target Values are what we consider the 'best estimate' of the truth to be.
- Creatinine – enzymatic method mean, which is periodically validated by analyses of **many** of the pools by a reference method



At a reference method creatinine of 100 umol/L the enzymatic mean is 100.7 umol/L



Birmingham Quality

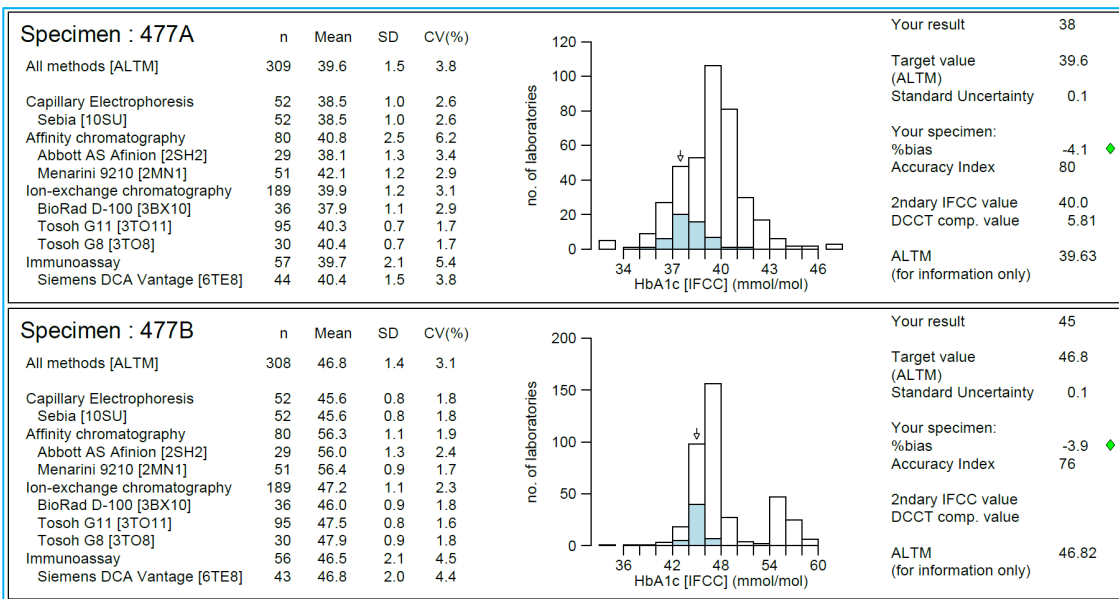


University Hospitals Birmingham
NHS Foundation Trust

Glycated Haemoglobins Scheme

- Accredited **ISO/IEC 17043:2010**
- Three Whole blood specimens
- ~ 500 Participants
- 2 Analytes in the Scheme
 - HbA1c [IFCC] and [DCCT]
- Samples are from Diabetic and Non Diabetic donors, and Manipulated Whole Blood


Spec.	Pool	Pool description / Treatments / Additions
477A	844	Non-diabetic volunteer donor
477B	845	Manipulated human whole blood
477C	846	Non-diabetic volunteer donor

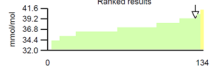




PCS901 has 150 Participants measuring HbA1c and a further 150 measuring Lipids.
 PCS902 has almost 1000 Lipid and HbA1c users in total, using a different HbA1c device.
We do go down to as few as 20 Participants for unique combinations/frequencies!



Participant SP123456

Both samples OK this time, but one out back at
 Distribution 106. so overall performance yellow

	Birmingham Quality POCT Suite [PCS901]	Identity :
	Distribution : 108 Date : 27-Mar-2023	Page 2 of 2
	Diabetes/Lipids B2	

Device details (1) Device number (2) User Initials	Comments Your branch number : The specimens in this Distribution were Human Blood. 108A and 108B (HbA1c) were Pools 230 and 231 108A and 108B (Others) were Pools 316 and 317
Specimen : 108A HbA1c POCT ✓ Result 39 mmol/mol 🎯 Target 36.8 mmol/mol 	Specimen : 108B HbA1c POCT ✓ Result 50 mmol/mol 🎯 Target 48.5 mmol/mol 
History HbA1c POCT 101 24 Jan 2022 A B ✓ ✓ 102 28 Mar 2022 A B ✓ ✓ 103 06 Jun 2022 A B ✓ ✓ 104 08 Aug 2022 A B ✓ ✓ 105 03 Oct 2022 A B ✓ ✓ 106 19 Dec 2022 A B ✓ ✗ 107 23 Jan 2023 A B ✓ ✓ 108 27 Mar 2023 A B ✓ ✓	
Recent Performance 🟡 HbA1c POCT 🟢 Participation (8 out of 8) Key: Good (Green), Acceptable (Yellow), Poor (Red)	

	Birmingham Quality POCT Suite [PCS901]	Identity :
	Distribution : 108 Date : 27-Mar-2023	Page 2 of 2
	Diabetes/Lipids B2	

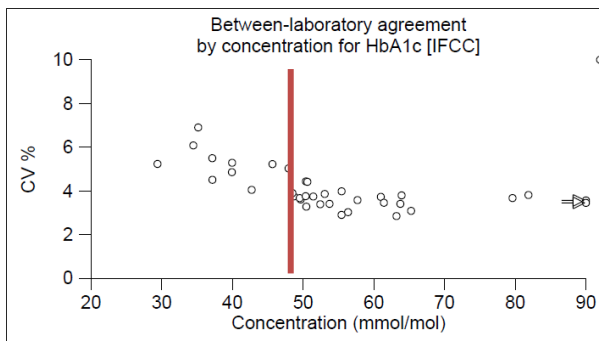
Device details (1) Device number (2) User Initials	Comments Your branch number : The specimens in this Distribution were Human Blood. 108A and 108B (HbA1c) were Pools 230 and 231 108A and 108B (Others) were Pools 316 and 317
Specimen : 108A HbA1c POCT ✓ Result 35 mmol/mol 🎯 Target 36.8 mmol/mol 	Specimen : 108B HbA1c POCT ✓ Result 48 mmol/mol 🎯 Target 48.6 mmol/mol 
History HbA1c POCT 101 24 Jan 2022 A B ✓ ✓ 102 28 Mar 2022 A B ✓ ✓ 103 06 Jun 2022 A B ✓ ✓ 104 08 Aug 2022 A B ✓ ✓ 105 03 Oct 2022 A B ✓ ✓ 106 19 Dec 2022 A B ✓ ✓ 107 23 Jan 2023 A B ✓ ✓ 108 27 Mar 2023 A B ✓ ✓	
Recent Performance 🟢 HbA1c POCT 🟢 Participation (8 out of 8) Key: Good (Green), Acceptable (Yellow), Poor (Red)	

Participant SP234567

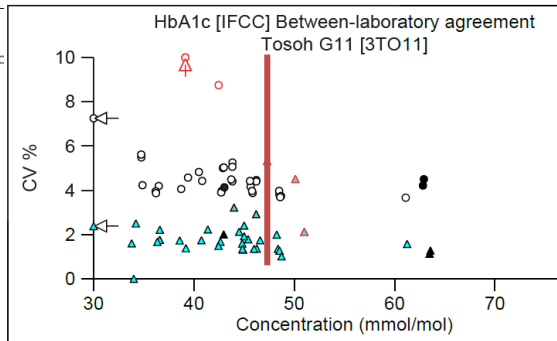
Both samples OK this time and all of the recent samples
 green, so overall performance green "Good".

The preferred material for our specimens is diabetic donor blood

The range of HbA1c concentrations available had changed over the years:

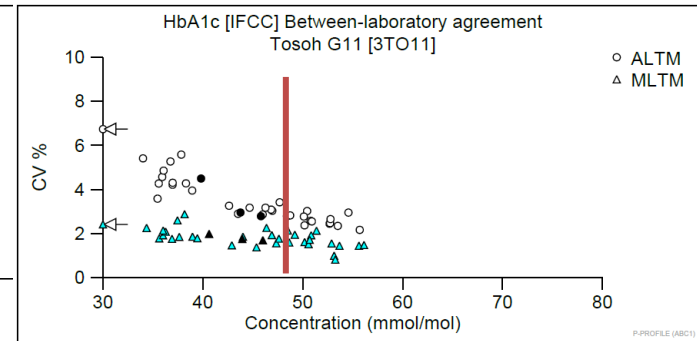


2010



2019

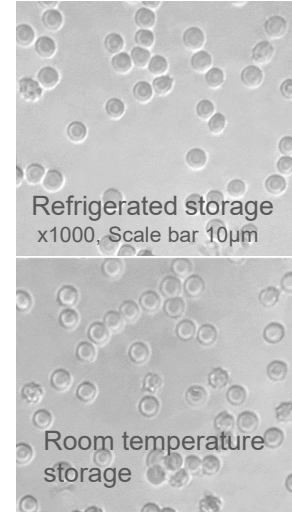
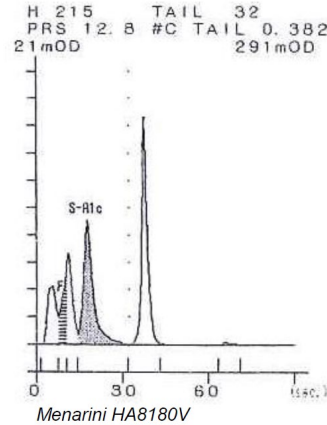
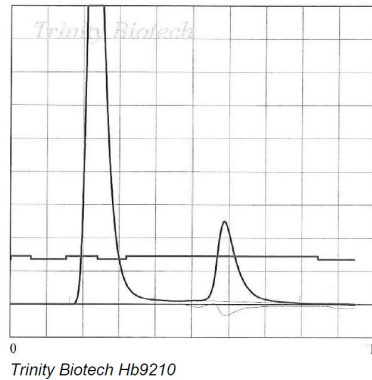
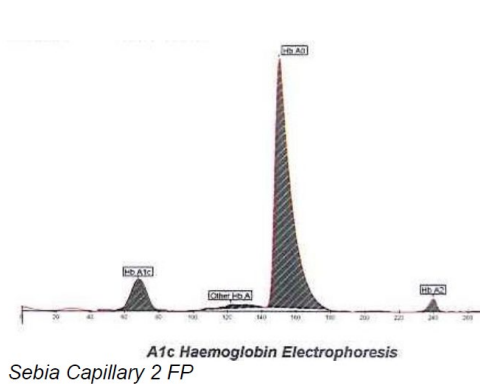
Majority of volunteer donors undergoing successful diabetes treatment



2023

use of in-house material helped to increase concentrations covered

Suitability for all methods



Curves for the in-house glycated specimen 437A provided by the European Reference Laboratory for Glycohemoglobin: capillary electrophoresis (Sebia), affinity chromatography (Trinity Biotech) and ion-exchange chromatography (Menarini).

In-house POCT testing performed on a range of devices including Afinion (Abbott) and DCA Vantage (Siemens).

Microscopic examination of intact cells of our synthetic material to prove integrity

Use Synthetic material to your Advantage

Check, check and check again its suitability, homogeneity and commutability but then use it to probe assays at a more frequent and more challenging areas than you might get with run-of-the-mill native specimens.

The future is in Value Added EQA, not Railway Timetables of PT means, SDs and CVs.

Every cloud has a silver lining. Synthetic EQA material is often a non-negotiable for some Schemes/Programmes because of volumes required, but don't let that fool you into thinking its second best.

It is different, yes, but you can use it to your advantage and raise the bar of Quality in your are of interest.

Probe with extended concentration ranges, interferences, cross reactivity, baseline security, parallelism, repeat distribution over years, clinical scenarios

Acknowledgements

All the Birmingham Quality Team are worthy of thanks but, in particular, Rachel Marrington for the Science and Andy Robins for the Computing and Yevheniia Mikheenko for the validation of the synthetic Glycated Haemoglobin material deserve a special mention for this talk.

Many thanks for listening, Finlay MacKenzie

Contact me at birminghamquality@uhb.nhs.uk

Comparisons of Synthetic vs Real PT items

Eurachem, Windsor 2023



Birmingham Quality



We are, and always have been, part of the NHS

Finlay MacKenzie

Director of Birmingham Quality, UHB NHS FT

Offering UK NEQAS EQA programmes in Clinical Biochemistry and beyond



EQA is more than a tick box exercise

UK NEQAS
International Quality Expertise

50 Years as World
Leaders in EQA
1969–2019



Birmingham Quality

NHS
University Hospitals Birmingham
NHS Foundation Trust