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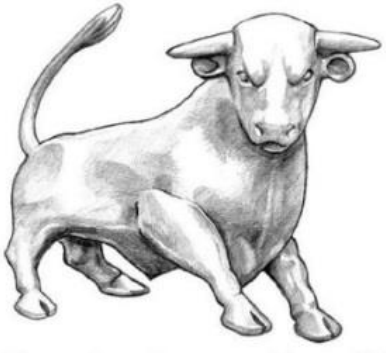
What is Commutability and how can it be examined?

Barcelona, EQALM October 2016

Finlay MacKenzie

Director, Birmingham Quality,
provider of UK NEQAS Services across Clinical Chemistry



Birmingham Quality

We have spoken about this before at EQALM Symposia

LUMC
LEIDEN UNIVERSITY MEDICAL CENTER

Commutability of control material: how should we examine it?

Christa Cobbaert, PhD, EurSpLM
on behalf of the SKML Chemistry Section
Chair Calibration 2.000
10 October 2013

skml

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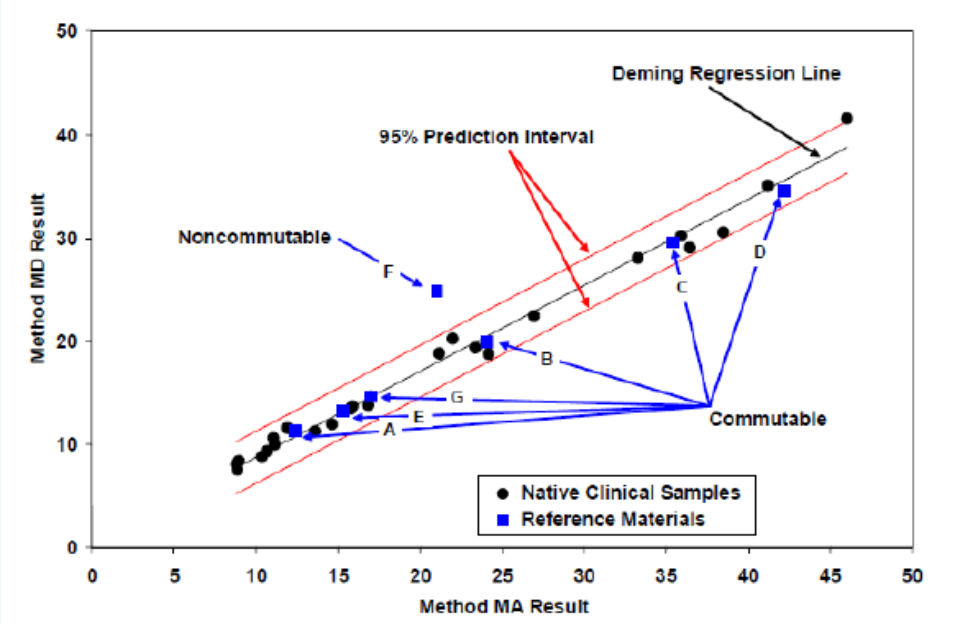
Christa Cobbaert showed this at the Bucharest EQALM Symposia in 2013

LUMC

CLSI EP30-A – assessment of commutability of RMs



Use of the Regression Protocol and 95% Prediction Interval to Evaluate Commutability of RMs between methods MA and MD.

EQALM, Bucharest, Romania 16 Sunday, 13 October 2013

Some definitions for ‘Commutability’

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‘Colloquial’ English:

Ability of a Standard/Calibrator/Control to show inter-assay properties similar to those of human samples.

CLSI EP30-A (formerly C53-A) definition:

The equivalence of the mathematical relationship among the results of different measurement procedures for a reference material and for representative samples of the type intended to be measured.

VIM (JCGM 200: 2012, 3rd edition) definition:

Property of a reference material, demonstrated by the closeness of agreement between the relation among the measurement results for a stated quantity in this material, obtained according to two given measurement procedures, and the relation obtained among the measurement results for other specified materials.

after Cobbaert

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Most Laboratory people, *including me*, are intimidated by the statistics

3 Models, experimental designs and assumptions

In this guide it is assumed that the measured quantity is a concentration. In an article by Nilsson[2] the following general model for measurement results is suggested:

$$x_{ijk} = \mu_i + \beta(\mu_i) + b_j(\mu_i) + \delta_i + d_{ij} + e_{ijk} \quad (1)$$

where

x_{ijk}	obtained concentration in replicate k in run j of specimen i
μ_i	the true concentration of specimen i
$\beta(\mu_i)$	a common systematic error, which can be expressed by a continuous function of μ
$b_j(\mu_i)$	a random error component, which can be expressed by a continuous function of μ and is common to all measurements in run j

Göran Nilsson: Guide to assessment of commutability_8 1

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This is an oft quoted paper which led to an Editorial from Greg Miller and Gary Myers in Clin Chem 59:9 September 2013

"Commutability still matters"

Clinical Chemistry 59:9
1322–1329 (2013)

The Importance of Commutability of Reference Materials Used as Calibrators: The Example of Ceruloplasmin

Ingrid Zegers,[1*] Robert Beetham,[2] Thomas Keller,[3] Joanna Sheldon,[4] David Bullock,[5] Finlay MacKenzie,[5] Stefanie Trapmann,[1] Hendrik Emons,[1] and Heinz Schimmel[1]

It even had me as an author, so it must be good!

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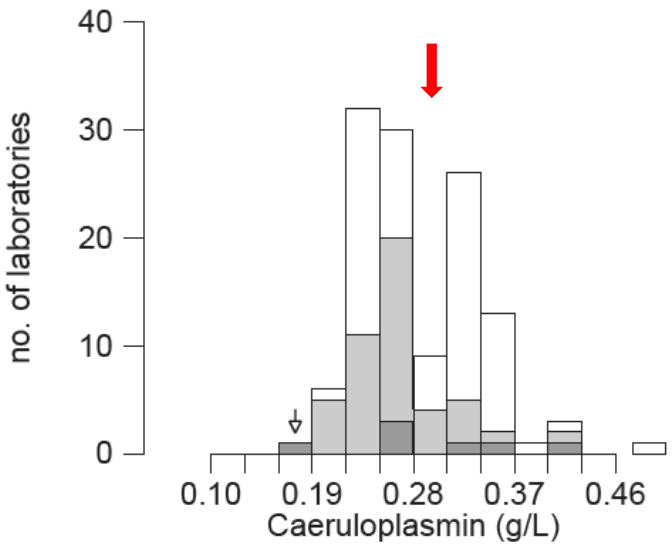
CAE – bimodal distribution of results

Specimen : 233A	n	Mean	SD	CV(%)
All methods [ALTM]	122	0.285	0.050	17.6
Nephelometry	66	0.294	0.053	18.1
Beckman Array reagents [1BK3]	10	0.346	0.018	5.2
Beckman Immage [1BK4]	24	0.329	0.019	5.9
Siemens (Dade Behring) [1BE8]	31	0.249	0.012	4.8
Turbidimetry	51	0.272	0.044	16.3
Dako reagents [2NV3]	6	0.230	0.038	16.4
Not stated, please specify [2UUU]	7	0.297	0.075	25.1
Roche Integra reagents [2RO2]	16	0.295	0.052	17.7
Roche Modular/Cobas [2BO11]	8	0.271	0.017	6.4
RID	5	0.309	0.022	7.1



The overall consensus mean, the ALTM, had no independent validity

We moved to having method principle means as targets, but essentially it was the specificity of the kit antibody rather than the method principle, per se, that was the issue.

IgG ~ All methods constant on storage

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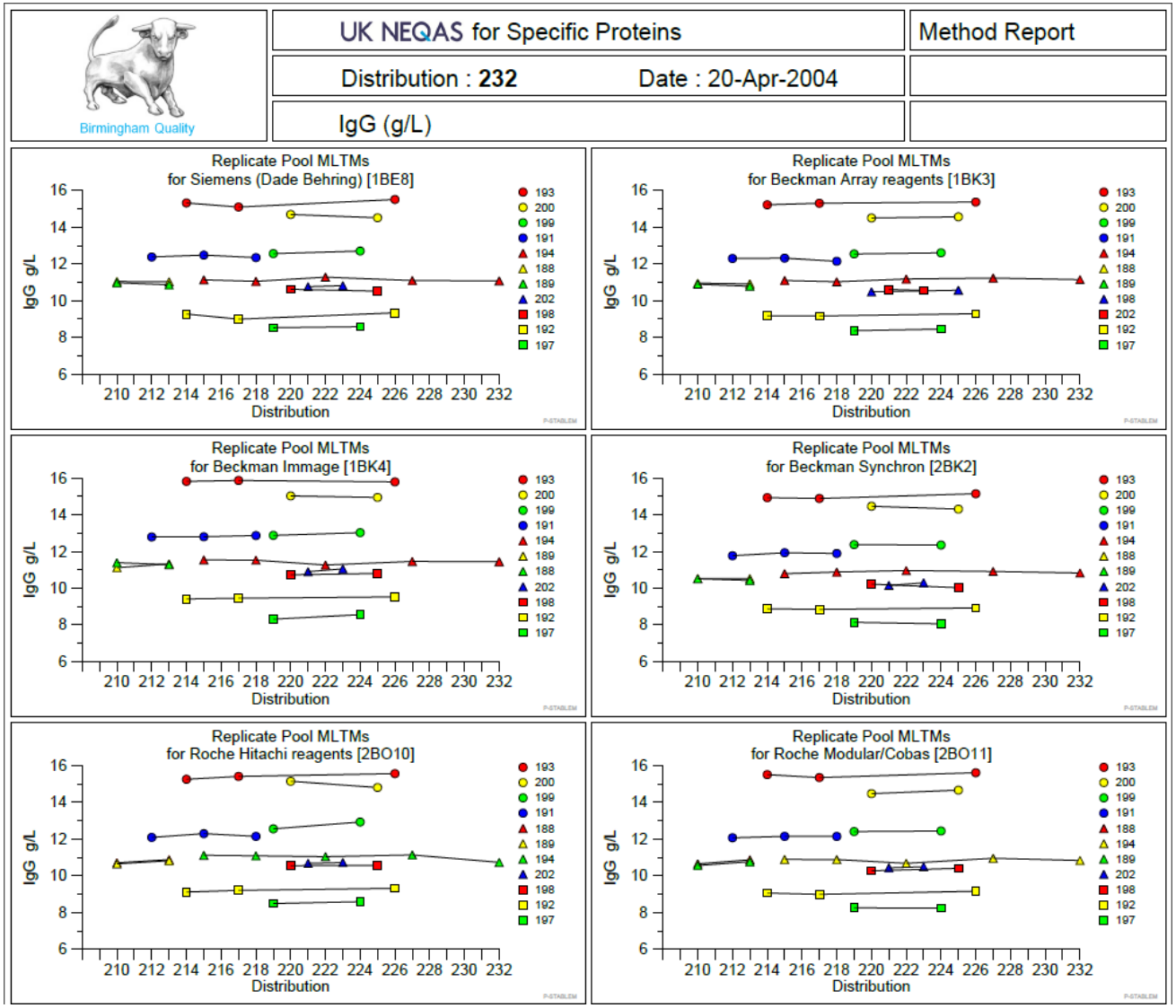

my control analyte

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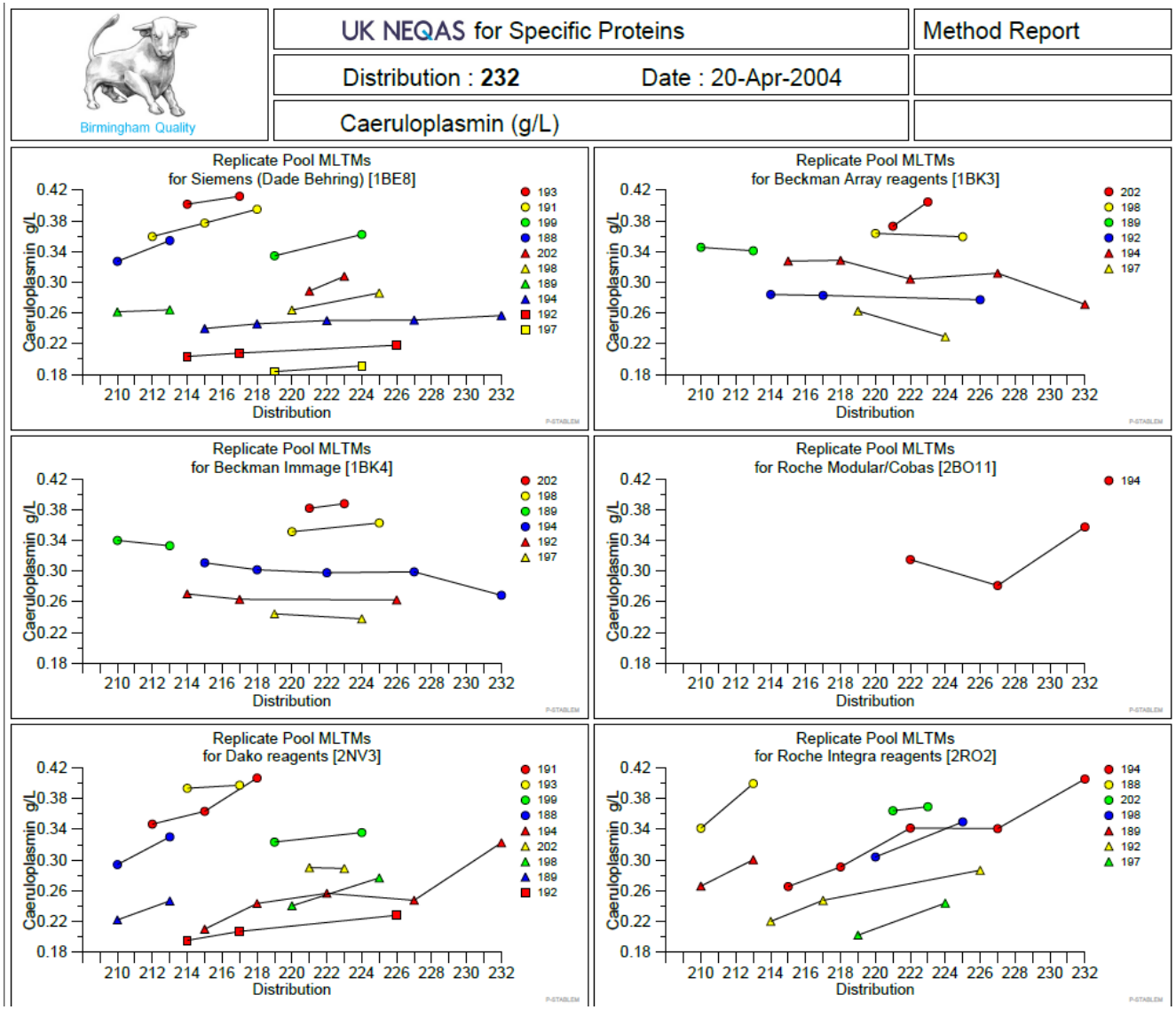
CAE ~ Some methods go up on storage; others go down



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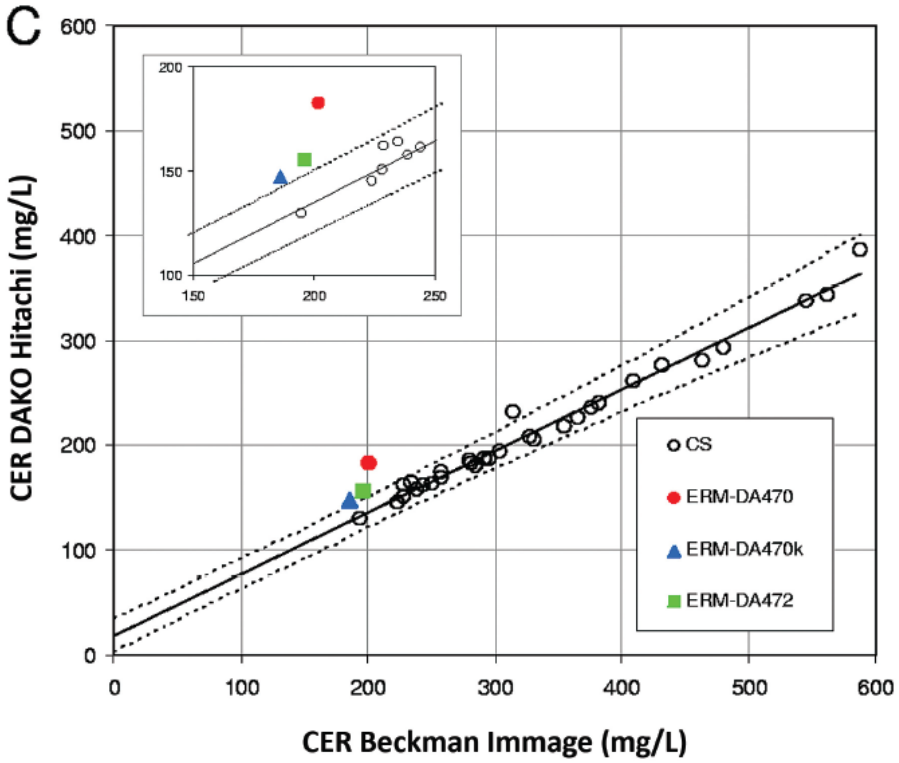
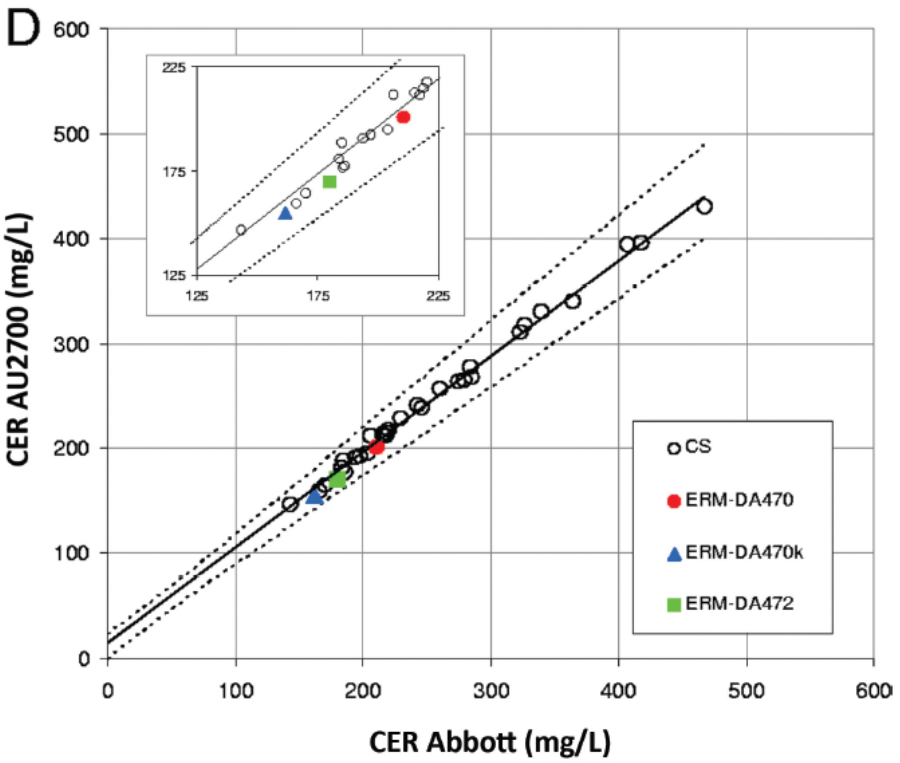
Reference Materials do not behave the same way in all methods ~ consequently the ERM-DA470k/IFCC could not have a value assigned for Caeruloplasmin





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Greg Miller et al

In draft; not for wider circulation prior to publication

Some approaches to assessing commutability: IFCC WG-C *(Miller et al 2015-2017)*

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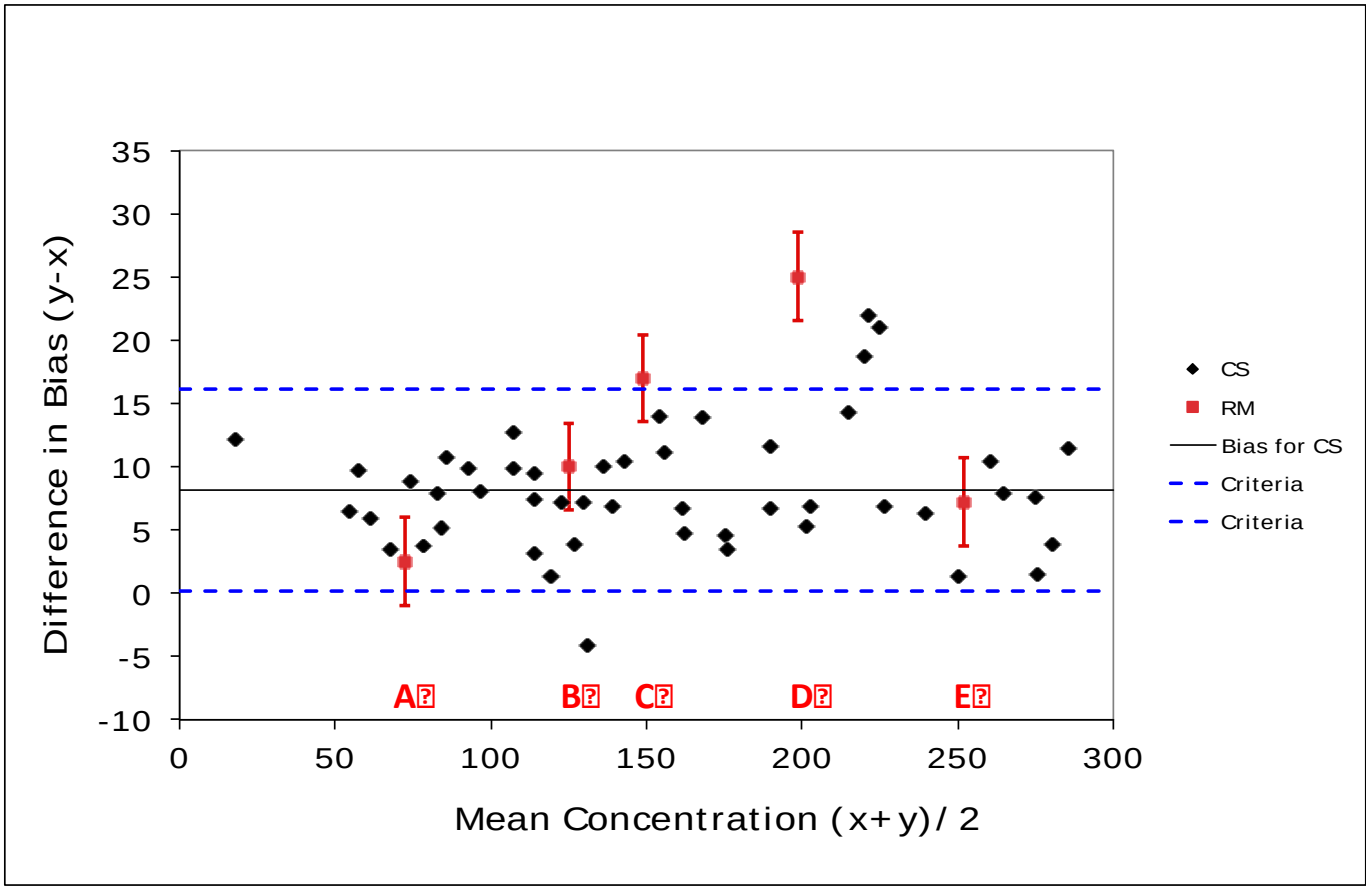
Figure 1.

The difference in bias between two measurement procedures (x and y) is shown for a panel of clinical samples (CS) and for five candidate reference materials (RM) labelled

A, B, C, D and E.

The error bars indicate the uncertainty in the estimate of the difference in bias. The black line is the mean bias for the CS.



The dashed blue lines are the criteria established for a decision regarding the commutability of the RMs. RMs "B" and "E" are commutable with the CS because the difference in bias and its uncertainty are within the criteria. RMs "A" and "C" are indeterminate because the uncertainty is not completely within the criteria. RM "D" is not commutable with the CS because the difference in bias and its uncertainty are outside the criteria.

In draft; not for wider circulation prior to publication

Some approaches to assessing commutability: IFCC WG-C *(Miller et al 2015-2017)*

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- Definition of commutability
- Selecting clinical samples for inclusion in a commutability assessment
- Reference material(s) to be included in a commutability assessment
- Qualification of measurement procedures for inclusion in a commutability assessment
- Statistical designs to assess commutability
- Criteria to make a determination that a RM is commutable
- Replacement of a RM with a new preparation
- Correction to the assigned value of a non-commutable RM
- Modifications to the commutability assessment experimental design
- Information on commutability to be provided in the certificate for a RM.

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Why might a control not be 'Commutable?'

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Mixture:

Are the proportions of the measurand in question similar to those of human samples?

Do you have to compromise? e.g. PSA Bound/Free; ALP bone/liver isoforms etc.

In some peptide hormone IRP preparations a single, and perhaps not representative, pH was used in the purification process which gave an imbalance of isoforms present.

Stability:

Is the material stable or does it denature in an unpredictable way? Do the fixatives cross react? Are the excipients benign?

Homogeneity and Volume constraints:

If you have to pool serum to get sufficient volume this can give different results to single donation material. In Lipid Schemes the Freeze/Thaw Cycles can increase the differences seen between methods as more FFA released and interfere with methods to a different extent.

Lyophilisation

The act of lyophilisation is not a benign process and reconstitution doesn't return the serum to its original state.

Haematology Whole Blood Preparations

Not my area of expertise, but I believe that it is almost impossible to produce a single EQA material which is stable and will behave in an identical fashion across all manufacturers' platforms.

Some problems for 'checking for Commutability'

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All Field methods 'wrong':

The problem here was seen for Creatinine measurement in the1980s where all the methods agreed with each other; the problem was that they were all wrong

Some Field methods 'wrong':

The problem here was seen for Testosterone in a female matrix measurement in the early 2000s where most immunoassay methods agreed with each other; the problem was that they were non-specific and though the MSMS methods agreed with each other they were different to the immunoassay methods because they , the MSMS methods, were correct!

All Field methods equally 'correct':

The problem here was seen for Thyroglobulin and TgAb measurement in the 2000s where all the methods disagreed with each other; the problem was that there was no independent way of saying who was 'correct', whether or not an IS existed.

Note: MacKenzie, F in ~2001. *Just because the experts can't agree on what the correct answer is, it doesn't mean that all field methods are equally correct!*

Some answers may be much more wrong than others.

Practical Approaches

Testosterone in a female matrix; 2 targets in use

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Spec.	Pool	Pool description / Treatments / Additions
429A	FT402	Normal serum [F]
429B	FT403	Normal serum [F]
429C	FT404	Normal serum [F]

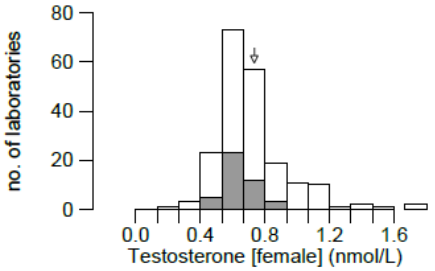
All methods
Tandem Mass Spec *

Your A score is 44
Your B score is -2.8
Your C score is 8.4

The A limit is 200
The B limit is +/- 20.0
The C limit is 20.0

Specimen : 429A

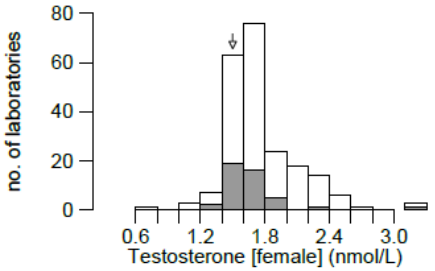
	n	Mean	SD	CV(%)
'Restricted' ALTM *	160	0.72	0.20	27.8
Abbott Architect	28	0.73	0.10	13.5
Beckman Access/Dxi	18	1.05	0.13	12.0
Roche Cobas/Modular	80	0.61	0.09	14.3
Siemens ADVIA Centaur	24	0.80	0.26	32.4
Siemens Immulite 2000/2500	3	0.84		
Tandem Mass Spec *	43	0.64	0.09	13.5
Tosoh AIA	3	0.96		



Your result 0.8
Target (Tandem Mass Spec *) 0.64
Standard Uncertainty 0.02
Your specimen: %bias +24.4
Accuracy Index 91
Your method mean Tandem Mass Spec * 0.64

Specimen : 429B

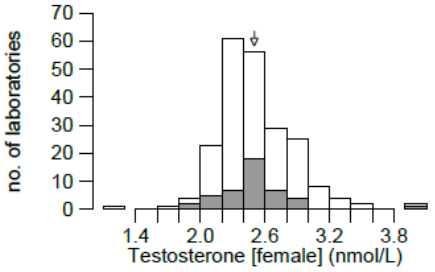
	n	Mean	SD	CV(%)
'Restricted' ALTM *	172	1.79	0.31	17.3
Abbott Architect	28	1.61	0.11	7.0
Beckman Access/Dxi	18	2.27	0.13	5.9
Roche Cobas/Modular	82	1.68	0.14	8.2
Siemens ADVIA Centaur	26	2.04	0.44	21.5
Siemens Immulite 2000/2500	11	1.76	0.35	20.1
Tandem Mass Spec *	44	1.66	0.16	9.9
Tosoh AIA	3	2.30		



Your result 1.6
Target (Tandem Mass Spec *) 1.66
Standard Uncertainty 0.03
Your specimen: %bias -3.3
Accuracy Index 18
Your method mean Tandem Mass Spec * 1.66

Specimen : 429C

	n	Mean	SD	CV(%)
'Restricted' ALTM *	172	2.53	0.32	12.5
Abbott Architect	28	2.35	0.15	6.4
Beckman Access/Dxi	18	2.95	0.16	5.3
Roche Cobas/Modular	82	2.41	0.15	6.4
Siemens ADVIA Centaur	26	2.82	0.29	10.1
Siemens Immulite 2000/2500	11	2.50	0.57	22.7
Tandem Mass Spec *	44	2.51	0.24	9.7
Tosoh AIA	3	3.02		



Your result 2.5
Target (Tandem Mass Spec *) 2.51
Standard Uncertainty 0.05
Your specimen: %bias -0.3
Accuracy Index 2
Your method mean Tandem Mass Spec * 2.51

What is commutability and how can it be examined? Finlay MacKenzie

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The issue of commutability is an ongoing problem not only for EQA Organisers, but for the manufacturers of diagnostic kits and for any producers of calibrators and controls.

Put simply, the in terms of a biological assay, commutability is the property whereby the assay behaves in an identical fashion when reacting with the compound/measurand of interest, whether that compound/measurand is in a kit calibrator, a clinical patient material, an IQC material, an EQA material or a Reference Standard.

Why might a material behave differently? If an assay is precisely, uniquely and exquisitely specific for its target compound then the matrix in which the compound resides, whether in terms of pH, protein or structurally similar compounds will not cause any problems. In the real world where biological systems are being used to measure other biological compounds, the scope for problems is high. There are cross reactivities, there are incomplete characterisation of what the target measurand actually is. The measurand may be a heterogeneous mixture that is always different between any two individuals. The measurand could be unstable in vitro, or even in vivo!

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In striving for a representative calibrator or International Standard, there may be isoforms that are not represented (or are over- or under- represented) in the material.

An assay may be able to measure, say, Analyte X perfectly and with a high level of precision across a wide concentration range from just above zero to higher than one might find in the most extreme clinical scenario. But if there is cross reactivity in this assay from a stabilizer which is only found in the IS or in controls, but which is never present in clinical specimens, then the assay may be considered unusable. This is not because of its own shortcomings, but merely by the necessity to have long shelf life standards.

There are groups, most notably an IFCC Working Group Chaired by Greg Miller, trying to quantify the degrees of commutability and perhaps more importantly trying to offer practical approaches that laboratory workers can utilise themselves in their own situations. These should be available later in 2016.

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The practical considerations are unashamedly pragmatic in their outlook. A material may never be suitable for every occasion or for every method — either for a method/procedure in current use or, hypothetically, one that has not yet been developed — but may enter routine use at some point in the future

This topic has come up before at previous EQALM meetings and all I want to do is to raise the profile of this issue. In particular where there always have been well known issues with non-commutability, I want to encourage the quantifying and reasons for non-commutability and to seek solutions to minimize their impact, rather than just accepting the status quo.

EQALM Abstract 2016