Assessing the Commutability of WHO International Standards: Issues and Challenges

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Medicines and Healthcare Products Regulatory Agency

WHO International Standards

- WHO Collaborating Centres produce WHO International Standards (IS) for **Biologicals**

Broad spectrum of materials including sera, recombinant (glyco)proteins, viral lysates, whole cells, purified nucleic acids, carbohydrate antigens.

assurance ($130 million in the last 10 years)

- Approximately 50% of NIBSC's WHO standards have a diagnostic application

Commutability – What is it?

- The WHO guidelines for preparation of International Standards state -

- *"The behaviour of the reference standard should resemble as closely as possible the behaviour of test samples in the assay systems used to test them"*
  - General Considerations

- *"The concept of commutability seeks to establish the extent to which the reference standard is suitable to serve as a standard for the variety of samples being assayed."*
  - Glossary

What causes non-commutability?

Noncommutability of a reference material can be caused by

- Matrix effects
  - The influence of a property of the sample (interference), independent of the presence of the measurand, on the measured value of the measurand, often caused by processing in the preparation of a reference material:
    - e.g. pooling serum or plasma samples, purification, freezing, lyophilisation, adding preservatives etc.

- Target-specific effects
  - Presence of surrogate target e.g animal derived substitute, different viral strain.
  - Denaturation or degradation products of the target measurand.

A comprehensive commutability study

- General
  - Commutability should be validated among all combinations of methods for which the reference material will be used.
- Samples

  "The equivalence of the mathematical relationships among the results of different measurement procedures for a reference material and for **representative** samples of the type being measured".
  - Native clinical samples from both normal and diseased individuals (n=20)
    - Should have values that span the nominal values of the reference material.
    - Should exclude any samples that include substances that are stated to interfere with specific methods.
  - Pooled samples may be necessary where it is not practical to collect adequate quantities of individual samples
    - Non-specific interactions between donor samples, interference from a single donor sample, dilution of important sample-specific influences.

A comprehensive commutability study

- Samples cont.
  - Adding exogenous spike to native samples
    - Not recommended but may be the only way to create a “pseudo” clinical sample
  - Reference materials that require dilution should be tested for commutability at each dilution
- Sample stability
  - Clinical samples are non-lyophilised, so stability on shipping and the effects of freezing need to be determined prior to the study.
- Prequalification of participating laboratories
  - Determine those with unusually high imprecision and exclude.

How can we assess Commutability?

- Within a WHO collaborative study
- In a separate commutability study
- Through an External Quality Assurance scheme

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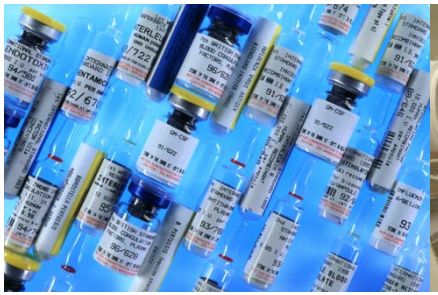
WHO International Standards

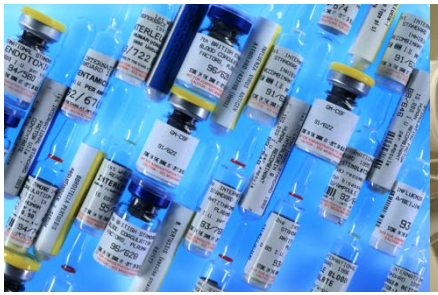
- What are the requirements for the production of a WHO International Standard?



  - Project Initiation
  - Sourcing materials
  - Process Development and Batch production
  - Collaborative Study
  - Stability testing
  - Establishment and Implementation

Implications for the assessment of commutability

- What are the requirements for the production of a WHO International Standard?



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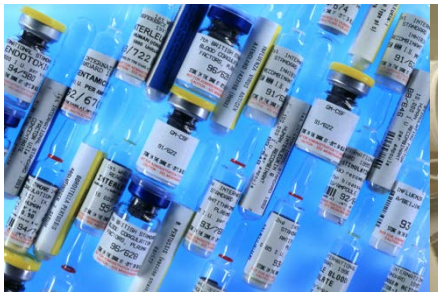

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Sourcing candidate materials

- Choice of materials - “like vs like” is not always possible.
  - Safety and ethical considerations with human-derived materials
  - Biological measurands are highly complex
    - Often a heterogeneous mixture of different variants or subtypes
  - Batch size is required to last for many years
    - Large volumes required-frequent necessity to pool source materials
    - Replacement strategy
  - Use of non-native materials (e.g. a plasmid or recombinant protein)
  - If purified materials are used – how will they be diluted (matrix)?

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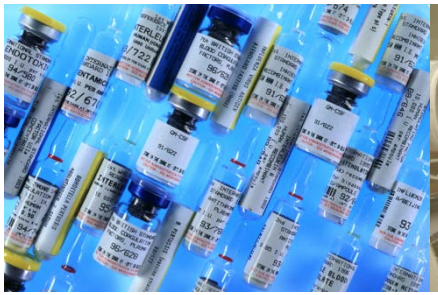

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Process development

- International Standards must maintain stability over their lifetime (often >15 years).
- They are shipped around the world and need to be stable at relatively high ambient temps for long periods.

- Most WHO ISs are freeze dried (possibly also concentrated or heat inactivated)
  - Optimal for stability, homogeneity, ease ofstorage/handling and transportation.

Implications for the assessment of commutability

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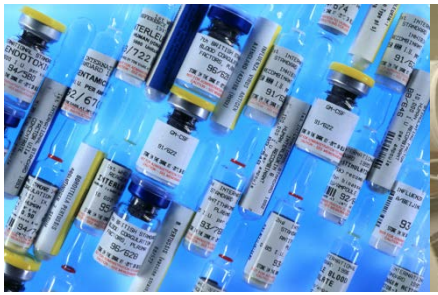

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Collaborative study

- Specific study design for the calibration of WHO International Standards
  - Wide range of participating laboratories giving good representation geographically (approx 10-30 labs)

Collaborative study: Participants

PWS &AS (09/140) Collaborative Study; 38 participants in 28 countries

Collaborative study

- Specific study design for the calibration of WHO International Standards
  - Wide range of participating laboratories giving good representation geographically (approx 10-30 labs)
  - Representative of all types of methods.
  - Representative of all types of end-users
    - Manufacturers, regulators, control laboratories, routine clinical labs etc
    - Importantly laboratories are not usually pre-qualified
      - Intention is to assess the performance of the candidate standards in less experienced laboratories

Collaborative study

- Participants provide time and resource freely and contribute a large number of assays and often >1 method.
    - Study samples usually include one or more candidate reference materials (including duplicates), previous standards, regional or manufacturers standards, degradation samples of the candidates, unprocessed bulk and where possible, (pseudo) clinical samples.
    - Requested to perform repeat tests on study samples, over a range of dilutions – intra lab repeatability, assay performance and precise potency estimates.
- In many case this limits the number of study samples. It is often impossible to include 30-50 clinical samples (normal and diseased, appropriate range) to fully assess commutability.

Traditional approach

- Include a limited number of additional samples in the collaborative study.
  - Choice will restrict the aspects of the reference material that can be characterised.
  - If there are no clinical samples then the commutability of the reference to clinical samples cannot be addressed.
- Assess (quantify) the improvement in inter-laboratory or inter-method agreement achieved.
- If use of the reference leads to an improvement, then it is valuable, even if it is not “perfect”.

Traditional approach

- Identify possible causes of non-commutability and investigate directly.
  - Pilot studies or Collaborative Study

- For example, including the liquid bulk along with a candidate standard in a collaborative study can assess directly any potential effect of freeze-drying.

- Main limitation of the current approach is the lack of truly representative clinical or pseudo-clinical samples.
  - Restrictions on number of samples possible to include in the study.
  - Availability/volumes of clinical samples.
  - Processing of samples for shipment in a study (e.g. freezing).

How else can we assess Commutability?

- Within a WHO collaborative study
- **In a separate commutability study**
- **Through an External Quality Assurance scheme**

Separate/EQA studies

- Separate commutability studies

  A commutable cytomegalovirus calibrator is required to improve the agreement of viral load values between laboratories. Caliendo AM, Shahbazian MD, Schaper C, Ingersoll J, Abdul-Ali D, Boonyaratanakornkit J, Pang XL, Fox J, Preiksaitis J, Schönbrunner ER. *Clin Chem*. 2009 Sep;55(9):1701-10.

- With an EQA scheme

  1st WHO International Standard for Diphtheria Antitoxin, Human. Stickings P with External Quality Assessment organised by C von Hunolstein (ISS, Rome) as part of ECDC/European Diphtheria Surveillance Network

- Partner with organisations such as IRMM, IFCC or AACC
  - International Consortium for Harmonization of Clinical Laboratory Results

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EQAS schemes to assess commutability

Proposed Diphtheria Antitoxin International Standard

- Immunity to diphtheria depends on the presence of

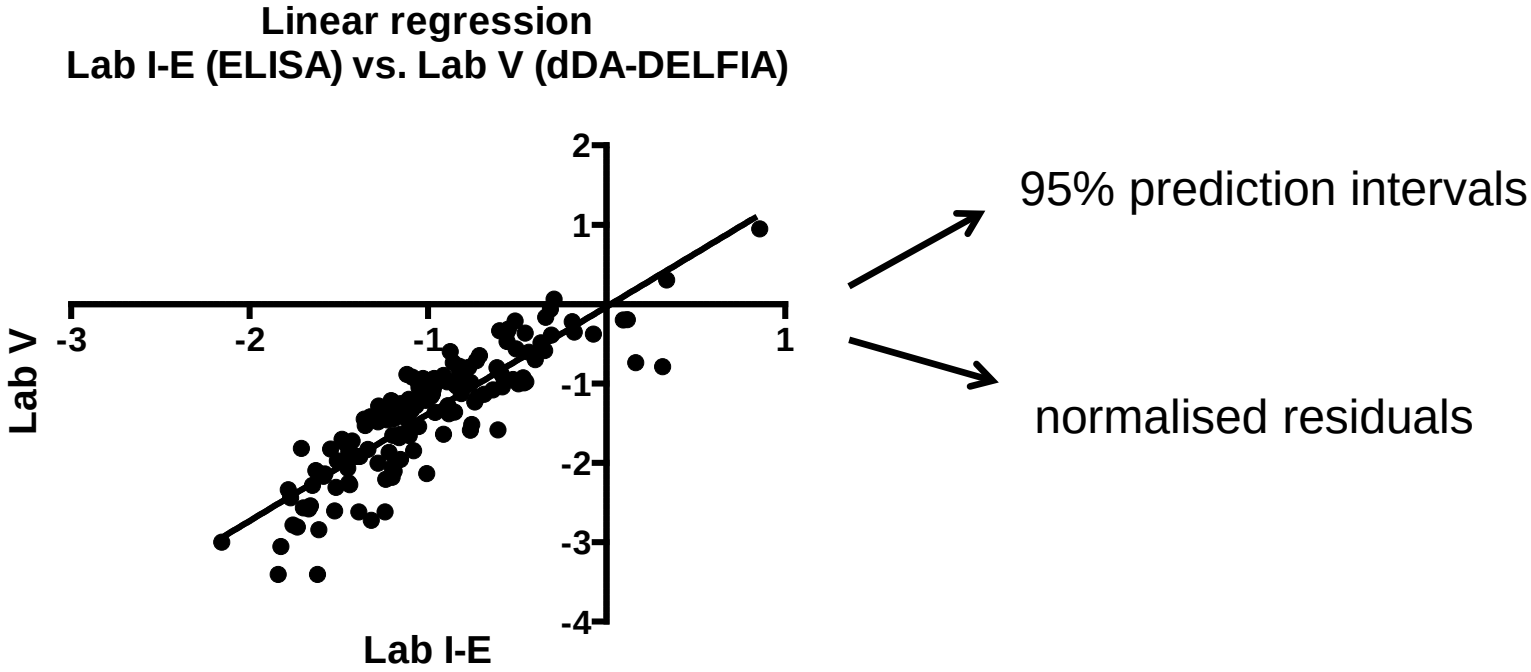
All participants tested a panel of 148 human serum samples

- An aliquot of the proposed new standard 10/262 and the current working standard (00/496) were included in the panel (total 150)

Diphtheria Surveillance Network

– Primary purpose of assessing performance of *in vitro* assays used for determining diphtheria antibody levels in human serum

Data analysis - Linear regression

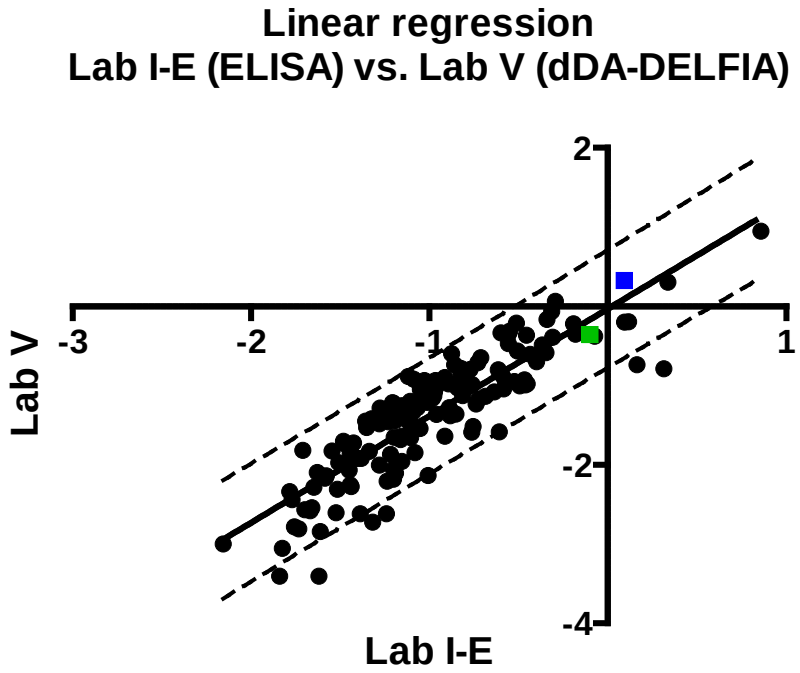


Data are estimates for individual serum samples (log IU/ml) n=148

Separate pair-wise comparisons for each method pair:
= (16^2)–16 = 240 individual comparisons

Paul Stickings, NIBSC

Commutability assessment
95% prediction intervals



Results for samples of interest are plotted and can be defined as “commutable” (within 95% PI) or “non-commutable” (outside 95% PI)

Data are estimates for individual serum samples (log IU/ml) n=148
Results for sample 230 (00/496 - green) and 231 (10/262 - blue) included

Commutability assessment
95% prediction intervals

Lab code	I	I-E	II	III	IV	V	VI	VII	VIII	IX	X	XII	XIII	XIV	XV	XVI
I		Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
I-E	Y		Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y
II	Y	Y		Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y
III	Y	Y	Y		Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y
IV	Y	Y	Y	Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
V	Y	Y	Y	Y	Y		Y	N	Y	N	Y	Y	Y	Y	Y	Y
VI	Y	Y	Y	Y	Y	Y		N	Y	N	Y	Y	Y	Y	Y	Y
VII	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y	Y	NR	Y	Y	Y
VIII	Y	Y	Y	Y	N	Y	Y	N		N	Y	Y	Y	N	Y	N
IX	Y	N	N	Y	Y	Y	Y	Y	N		Y	N	N	Y	Y	Y
X	Y	Y	Y	Y	Y	Y	Y	N	Y	N		Y	Y	Y	Y	Y
XII	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y		Y	N	Y	Y
XIII	Y	Y	Y	Y	N	Y	Y	NR	Y	N	Y	Y		N	Y	N
XIV	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y		Y	Y
XV	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y		Y
XVI	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	

Y = result within 95% PI
N = result outside of 95% PI

NR = regression not significant (excluded)

Commutability assessment results

	% "Commutable"	
	Sample 231 Proposed 1st IS (10/262) Human IgG	**Sample 230 Working standard (00/496) Human serum**
95% Prediction intervals	96%	90%
Normalised residuals	96%	93%

Fortuitous timing of EQA study – establishment of the standard would have been significantly delayed had NIBSC organised the commutability study.

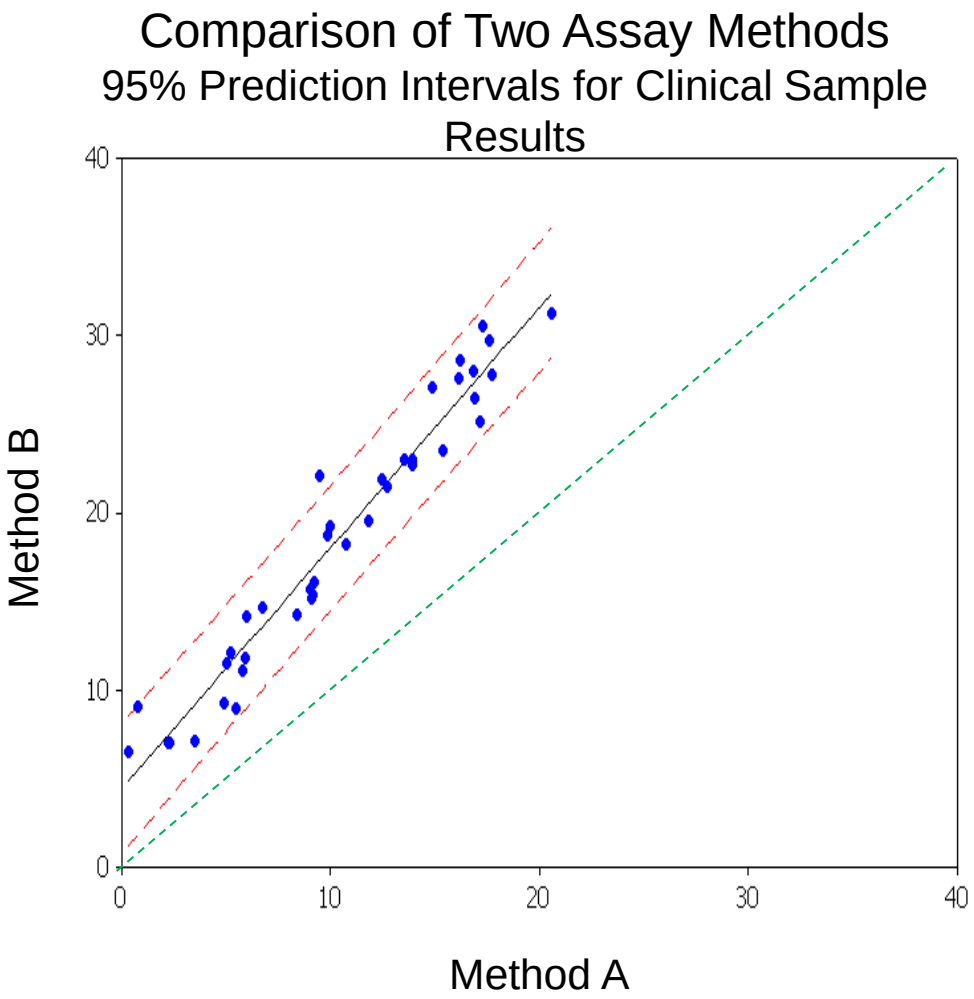
Commutability assessment

- This approach gives a ‘yes’ – ‘no’ assessment which is dependent on:

A reference material may be ‘non-commutable’ by the strict metrological definition, but still be more effective than not having any reference material.

- It does not give an assessment of how effective the reference material will be in controlling inter-method differences.

Commutability assessment



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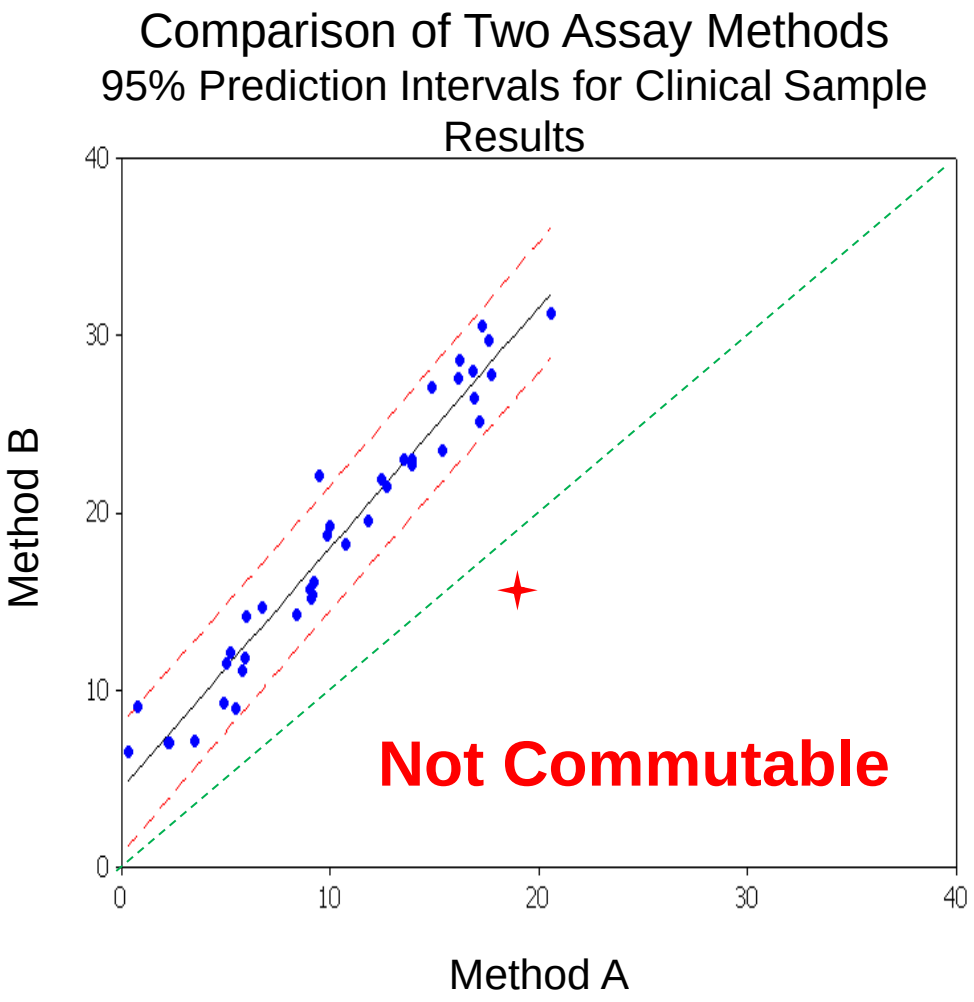

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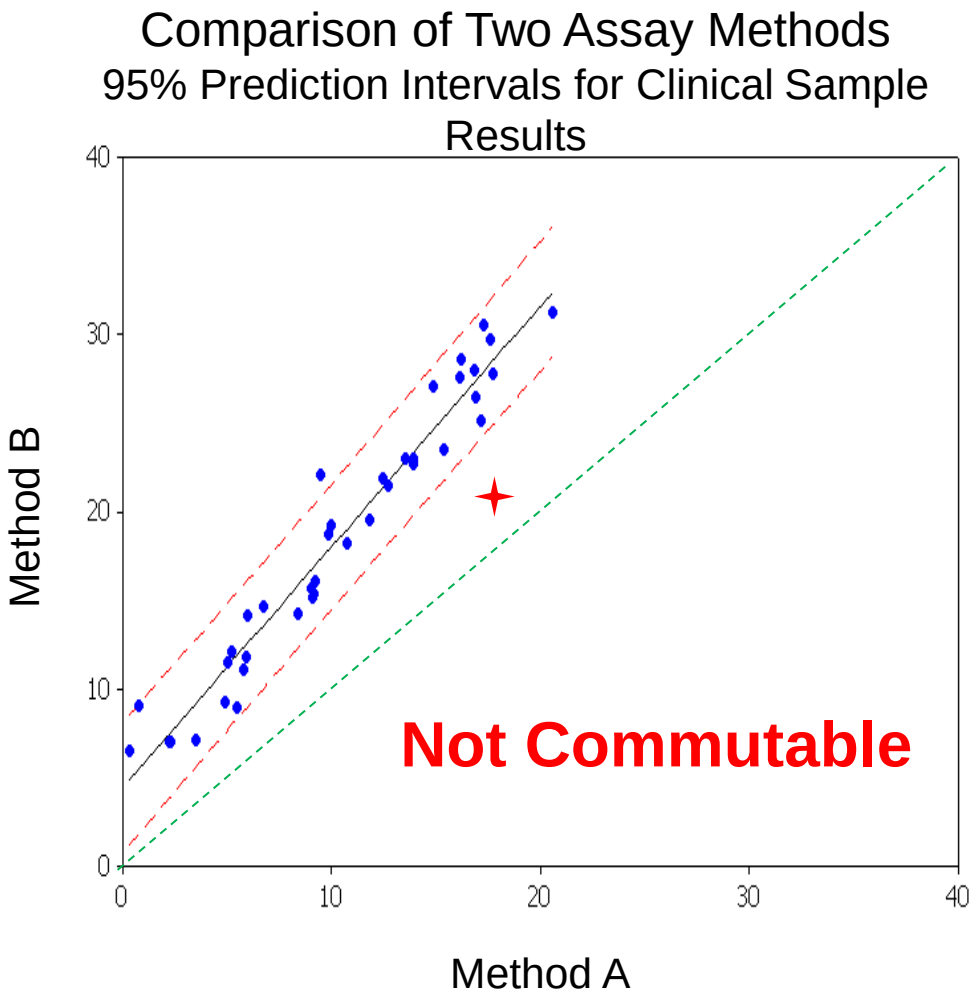

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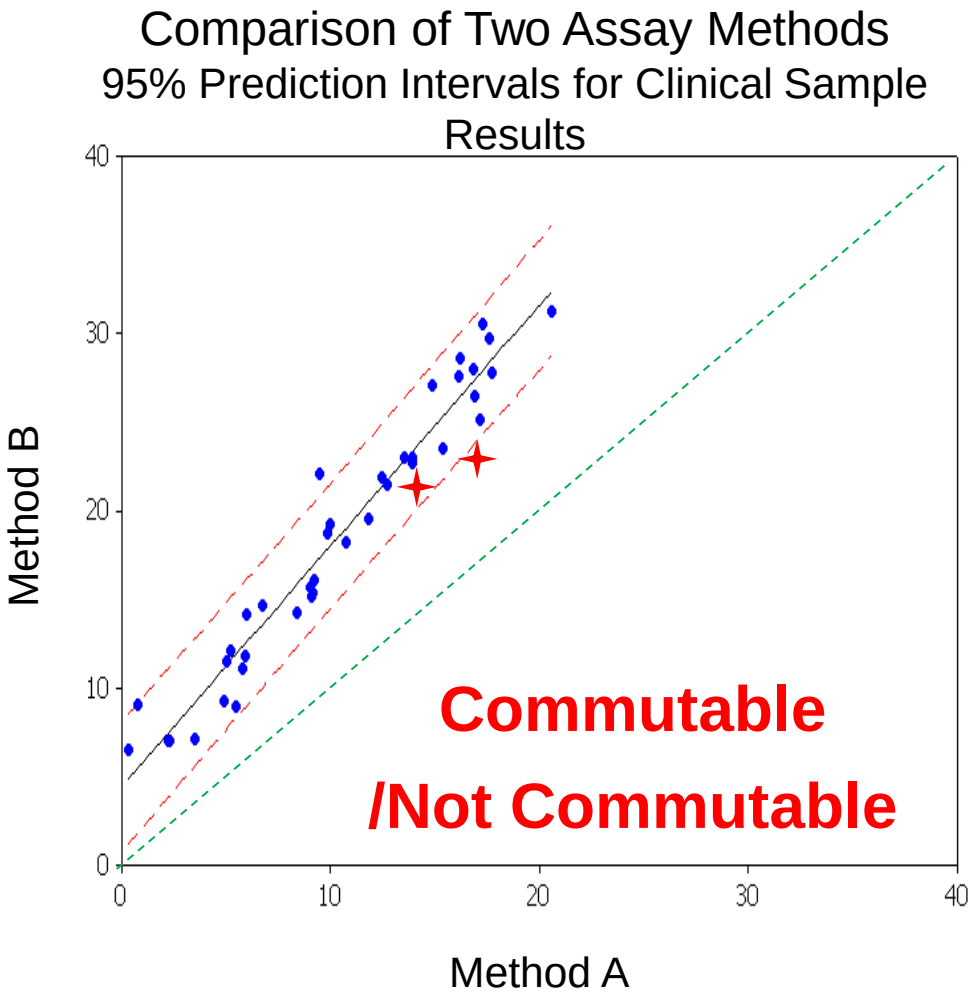

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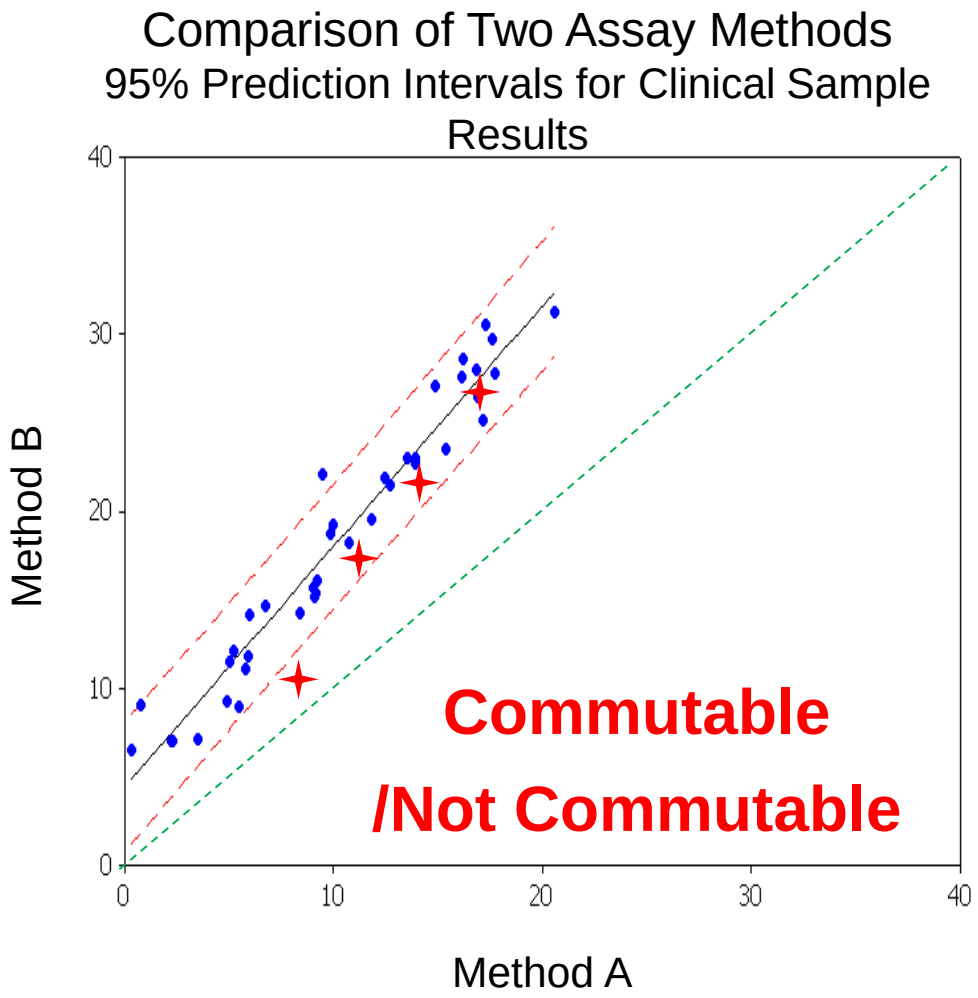

Points for consideration

- How much is enough?
  - Can never prove that a material is completely commutable.
- What do we report? What do we do if we find a particular commercial method non-commutable to a WHO reference?
  - Statement or disclaimer in IFU?
  - ECBS report or publication?
- Is it a commutability issue or a need to define the measurand more precisely?
- Whose responsibility is it to investigate the commutability of new methods or assay kits?

Potential ways forward?

- Recognise restrictions on what can be done in a WHO collaborative study, and be pragmatic.
  - Can’t delay the establishment of a new IS to allow full commutability study.
- Reach a consensus between standards organisations and clinical chemistry and clinical virology organisations.
- Collaborate with other groups and/or EQA schemes.
  - Access to clinical samples and participating laboratories.

WHO, Geneva, April 2013

- WHO Consultation on Commutability of WHO Biological Reference Preparations for in vitro Detection of Infectious Markers.