Commutability: Challenges in the harmonisation/standardisation of assays for autoimmune disorders

Evanthia Monogioudi

Joint Research Centre, European Commission

Workshop on Measurement Challenges: laboratory medicine

10 November 2021

JRC's mission

"As the science and knowledge service of the Commission our mission is to support EU policies with independent evidence throughout the whole policy cycle"

(Certified) Reference materials

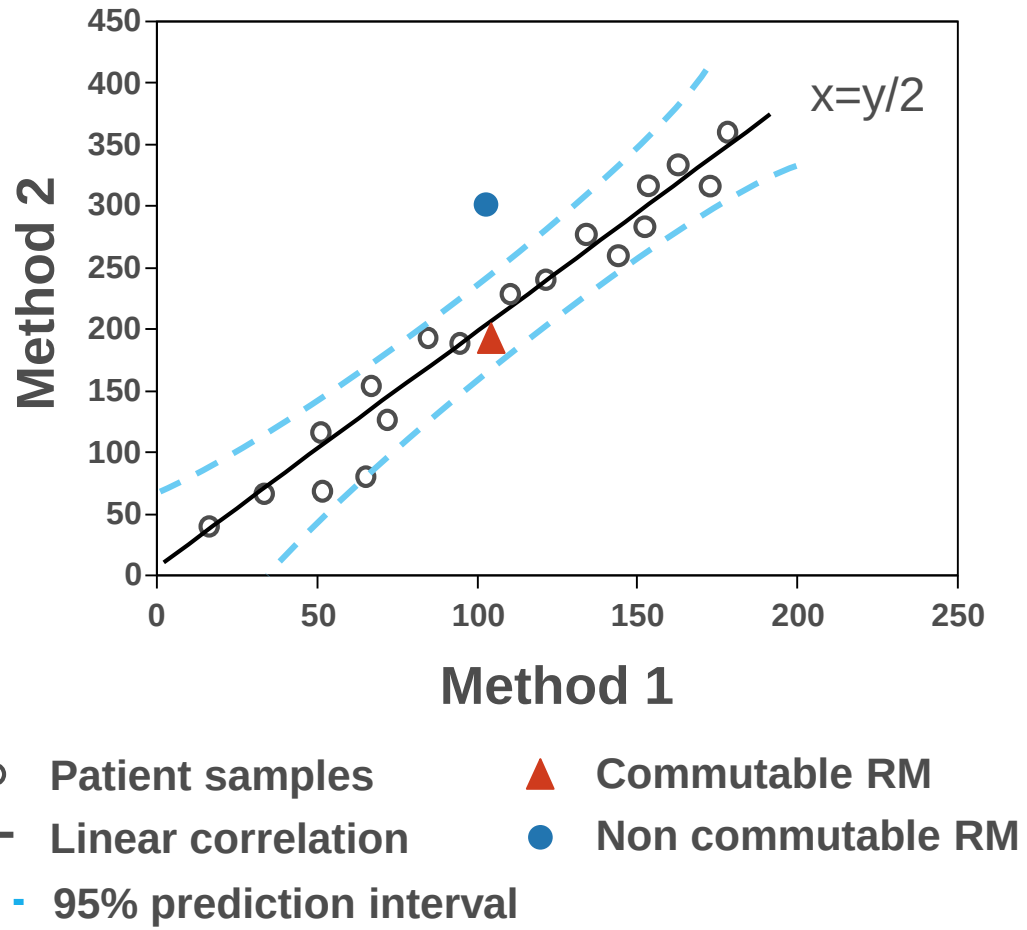
- Biomarkers for health monitoring
- Genetically modified organisms (GMOs)
- Food additives, contaminants, ingredients, residues
- Environmental pollutants
- Nanomaterials & industrial materials
- ~ **680 different materials available**

European Commission

Introduction: what is commutability

According to VIM, commutability is:

"a property of an RM, demonstrated by the closeness of agreement between the relation among the measurement results for a stated quantity in this material, obtained according to 2 given MPs, and the relation obtained among the measurement results for other specified materials"



JCGM. 3rd. Sevres, France: International Bureau of Weights and Measures; 2012. International vocabulary of metrology—basic and general concepts and associated terms (VIM)

IFCC working group on commutability

Clinical Chemistry 64:3
447–454 (2018)

Special Reports

IFCC Working Group Recommendations for Assessing Commutability Part 1: General Experimental Design

W. Greg Miller,[1*] Heinz Schimmel,[2] Robert Rej,[3] Neil Greenberg,[4] Ferruccio Ceriotti,[5] Chris Burns,[6] Jeffrey R. Budd,[7] Cas Weykamp,[8] Vincent Delatour,[9] Göran Nilsson,[10] Finlay MacKenzie,[11] Mauro Panteghini,[12] Thomas Keller,[13] Johanna E. Camara,[14] Ingrid Zegers,[2] and Hubert W. Vesper,[15] for the IFCC Working Group on Commutability

Clinical Chemistry 64:3
455–464 (2018)

Special Reports

IFCC Working Group Recommendations for Assessing Commutability Part 2: Using the Difference in Bias between a Reference Material and Clinical Samples

Göran Nilsson,[1] Jeffrey R. Budd,[2] Neil Greenberg,[3] Vincent Delatour,[4] Robert Rej,[5] Mauro Panteghini,[6] Ferruccio Ceriotti,[7] Heinz Schimmel,[8] Cas Weykamp,[9] Thomas Keller,[10] Johanna E. Camara,[11] Chris Burns,[12] Hubert W. Vesper,[13] Finlay MacKenzie,[14] and W. Greg Miller,[15*] for the IFCC Working Group on Commutability

Clinical Chemistry 64:3
465–474 (2018)

Special Reports

IFCC Working Group Recommendations for Assessing Commutability Part 3: Using the Calibration Effectiveness of a Reference Material

Jeffrey R. Budd,[1] Cas Weykamp,[2] Robert Rej,[3] Finlay MacKenzie,[4] Ferruccio Ceriotti,[5] Neil Greenberg,[6] Johanna E. Camara,[7] Heinz Schimmel,[8] Hubert W. Vesper,[9] Thomas Keller,[10] Vincent Delatour,[11] Mauro Panteghini,[12] Chris Burns,[13] and W. Greg Miller,[14*] for the IFCC Working Group on Commutability

Clinical Chemistry 66:6
769–778 (2020)

Special Report

IFCC Working Group Recommendations for Correction of Bias Caused by Noncommutability of a Certified Reference Material Used in the Calibration Hierarchy of an End-User Measurement Procedure

W. Greg Miller,[a,*] Jeffrey Budd,[b] Neil Greenberg,[c] Cas Weykamp,[d] Harald Althaus,[e] Heinz Schimmel,[f] Mauro Panteghini,[g] Vincent Delatour,[h] Ferruccio Ceriotti,[i] Thomas Keller,[j] Douglas Hawkins,[k] Chris Burns,[l] Robert Rej,[m] Johanna E. Camara,[n] Finlay MacKenzie,[o] Eline van der Hagen,[d] Hubert Vesper,[p] for the IFCC Working Group on Commutability

Real life example: RM for anti-glomerular basement membrane (anti-GBM) disease

- IFCC C-HAT request
- Rare autoimmune condition responsible for rapidly progressive glomerulonephritis and/or lung bleeding
- IgG autoantibodies / non-collagenous domain of the α3(IV) collagen chain
- IgA or IgM anti-GBM antibodies

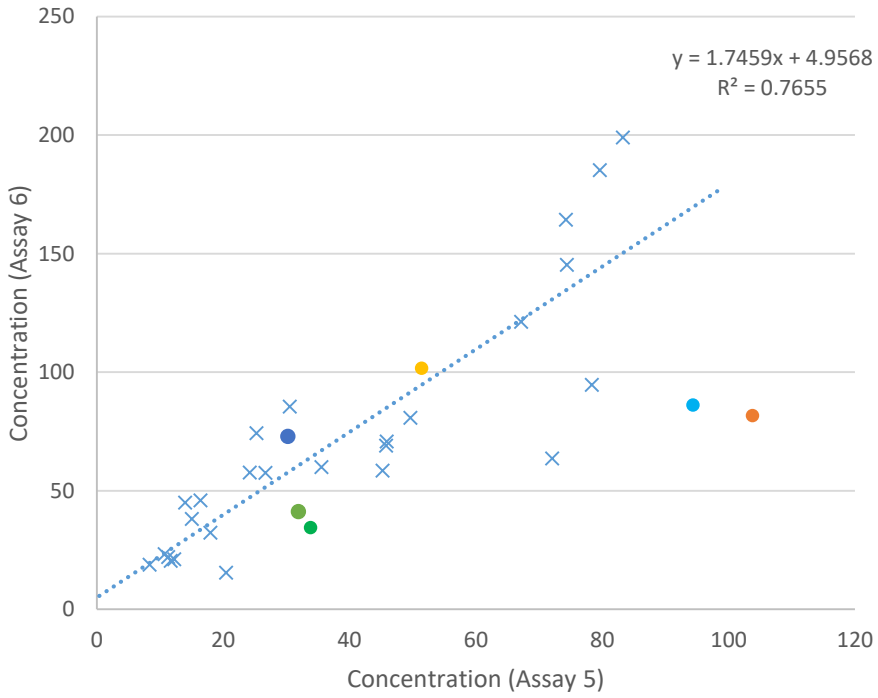
Challenges

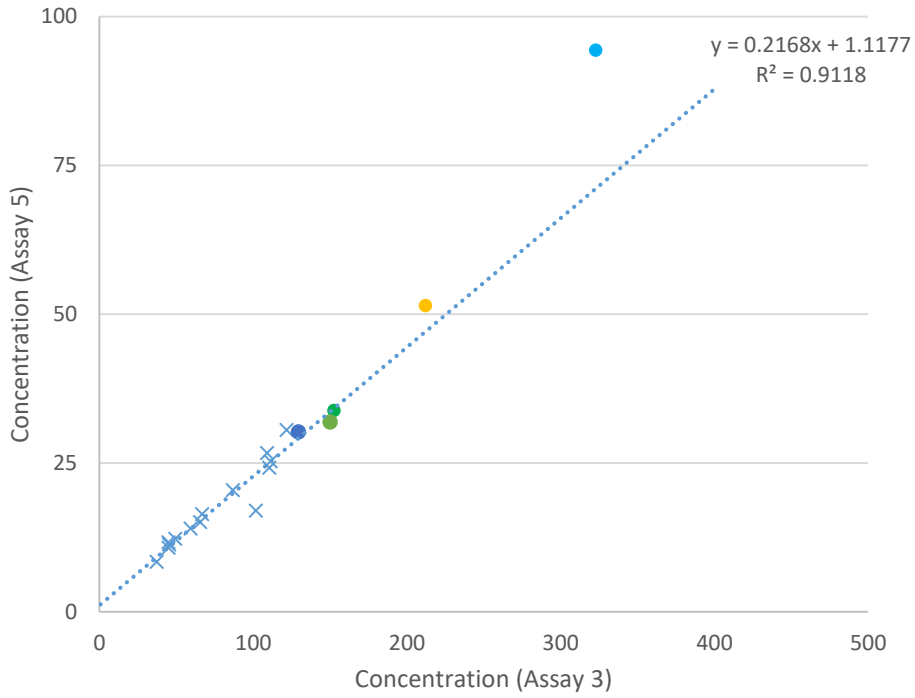
- Method correlation
  - Antigen complexity/specificity
  - Antibody response
- Starting material CRM
  - Pooling donations is too risky
  - Large single donations (>1L) after plasmapheresis
- Commutability study
  - Clinical sample availability limited
  - Concentration range (often dilutions required)

Real life example: commutability of a RM for anti-GBM IgG

- 7 routine methods
- 30 clinical samples
  - Without known interferences
  - 2 reps/plate, 4 reps/total
- 5 candidate RMs
  - 2 dilutions (5 reps/dilution)
- 5 purified anti-GBM IgG antibodies
  - 2 reps/plate, 4 reps/total
- Statistical approach: Difference in bias (IFCC)

Method correlation (anti-GBM IgG)





X **Clinical samples,** **RM A,** **RM B,** **RM C,** **pab RM A,** **pab RM B,** **pab RM C**

European Commission

Statistical analysis: difference in bias

Coverage factor:
depends on confidence level
and degrees of freedom

Standard uncertainty associated with average bias samples
Depends on number of samples
Variability among bias of individual samples (sample-specific effects)

$$U(d_{RM}) = k \times \sqrt{(u(B_{RM}))^2 + (u(\overline{B_S}))^2}$$

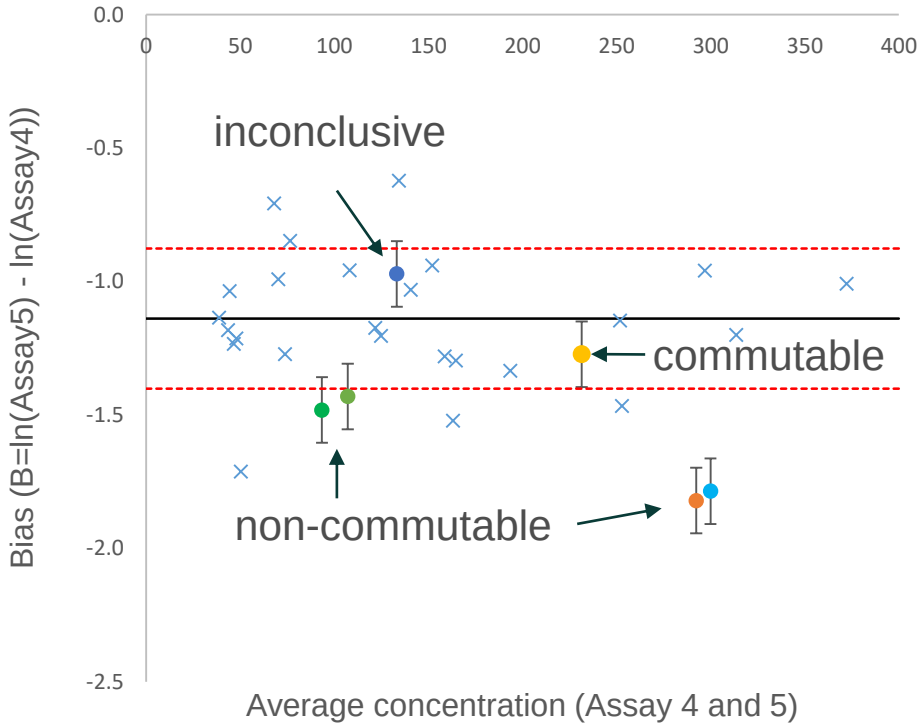
Standard uncertainty associated with bias RM:
Depends on repeatability of methods
and number of replicate measurements

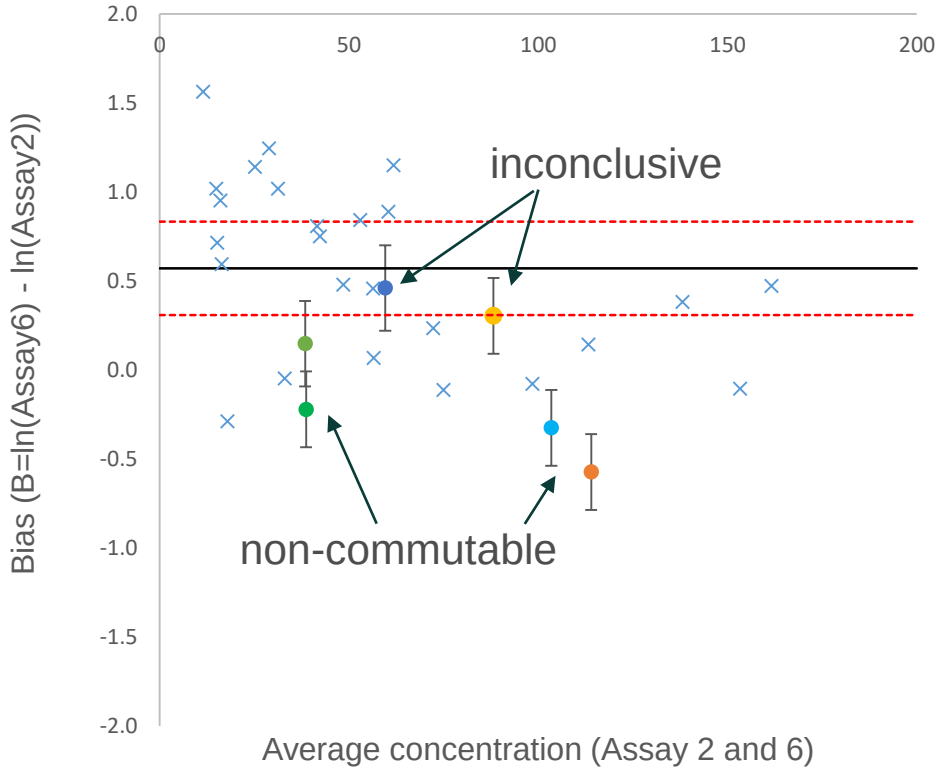
Commutability Criterion

"the maximum accepted difference between the bias of the RM and clinical samples"

1. $d_{RM} \pm U(d_{RM})$ is within $C \pm 0$ ⟶ Commutable
2. $d_{RM} \pm U(d_{RM})$ is outside $C \pm 0$ ⟶ Non-commutable
3. $d_{RM} \pm U(d_{RM})$ is overlapping with $C \pm 0$ ⟶ Inconclusive

IFCC approach: Difference in bias





X **Clinical samples,** **RM A,** **RM B,** **RM C,** **pab RM A,** **pab RM B,** **pab RM C**

Average bias **Commutability criteria** **Expanded uncertainty, difference in Bias**

European Commission

Conclusions

- Criterion
  - Same for each method comparison
  - Linked to intended use of CRM
- Sample-specific differences are rather large
- Too high uncertainty →Inconclusive results
- Large number clinical samples and measurements needed for conclusive results
- If several RM: difficult in one run

Conclusions

Possible solution: two step approach

Phase 1: study with many RM and large uncertainty

Phase 2: extended study with selected RM and smaller uncertainty

Keep in touch

You can find me at evanthia.monogioudi@ec.europa.eu

EU Science Hub: https://ec.europa.eu/jrc

Our reference materials catalogue: https://crm.jrc.ec.europa.eu

@EU_ScienceHub

EU Science Hub – Joint Research Centre

EU Science, Research and Innovation

Eu Science Hub

Thank you

European Commission