Commutability assessments in practice at the JRC

Liesbet DEPREZ

Accurate Results for Patient Care Workshop 2019

A JCTLM Members' and Stakeholders' meeting

BIPM, 3 December 2019

European Commission

The European Commission's science and knowledge service

Joint Research Centre

European Commission

Mission statement of reference materials unit

"To perform pre-normative research, to provide science-based policy advice and to develop, disseminate and promote measurement standards in support of EU policies for biotechnology, health, environment, energy and engineering including advanced materials and nanotechnology"

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(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**

Accreditation to ISO 17034

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ISO 17034:2016

General requirements for the competence of reference material producers

7.2 Production planning:

7.2.3 The reference material producer shall address, during the planning stage, the following:

a)…

k) assessing commutability (where appropriate);

7.14 RM documents and labels:

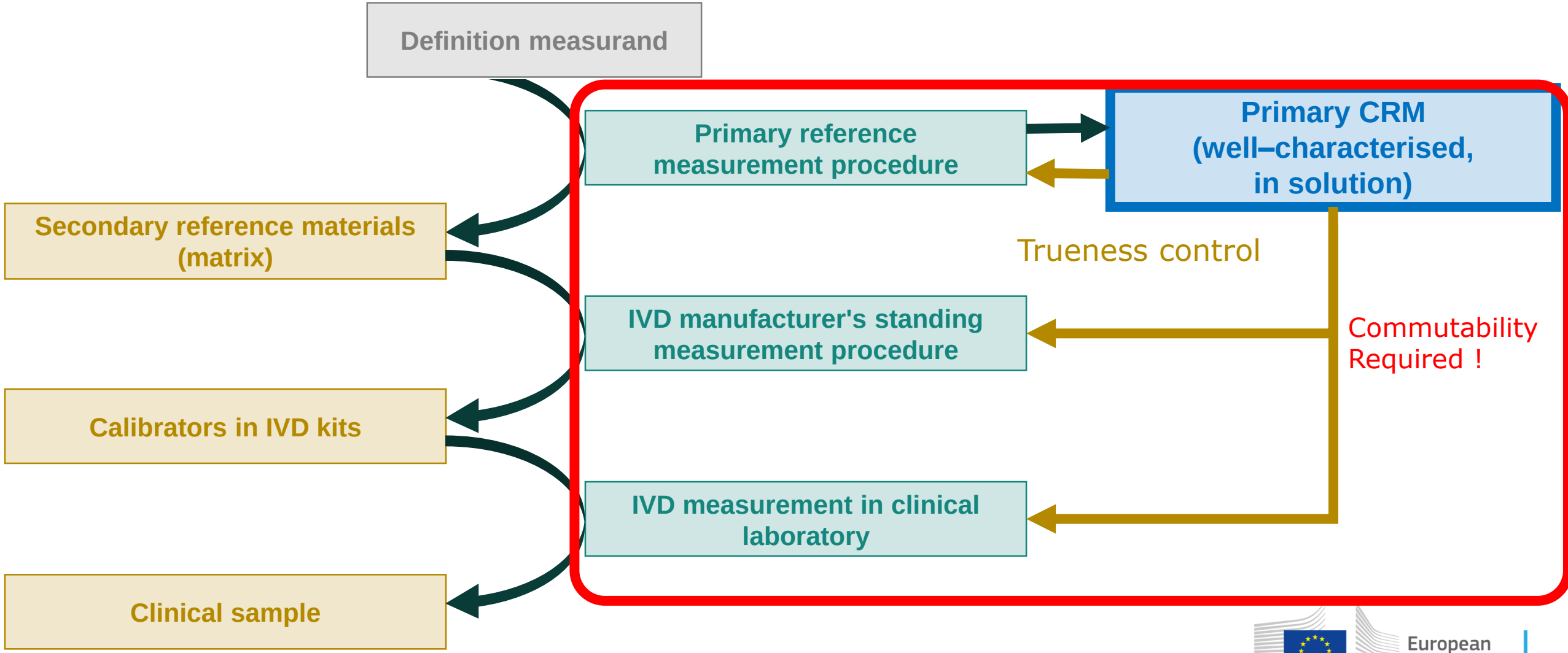
7.14.2 The contents of RM certificates and product information sheets shall include the following:

a)…

l) information on commutability of the material (where appropriate)

Intended use

ERM-AD456/IFCC: alfa-amylase



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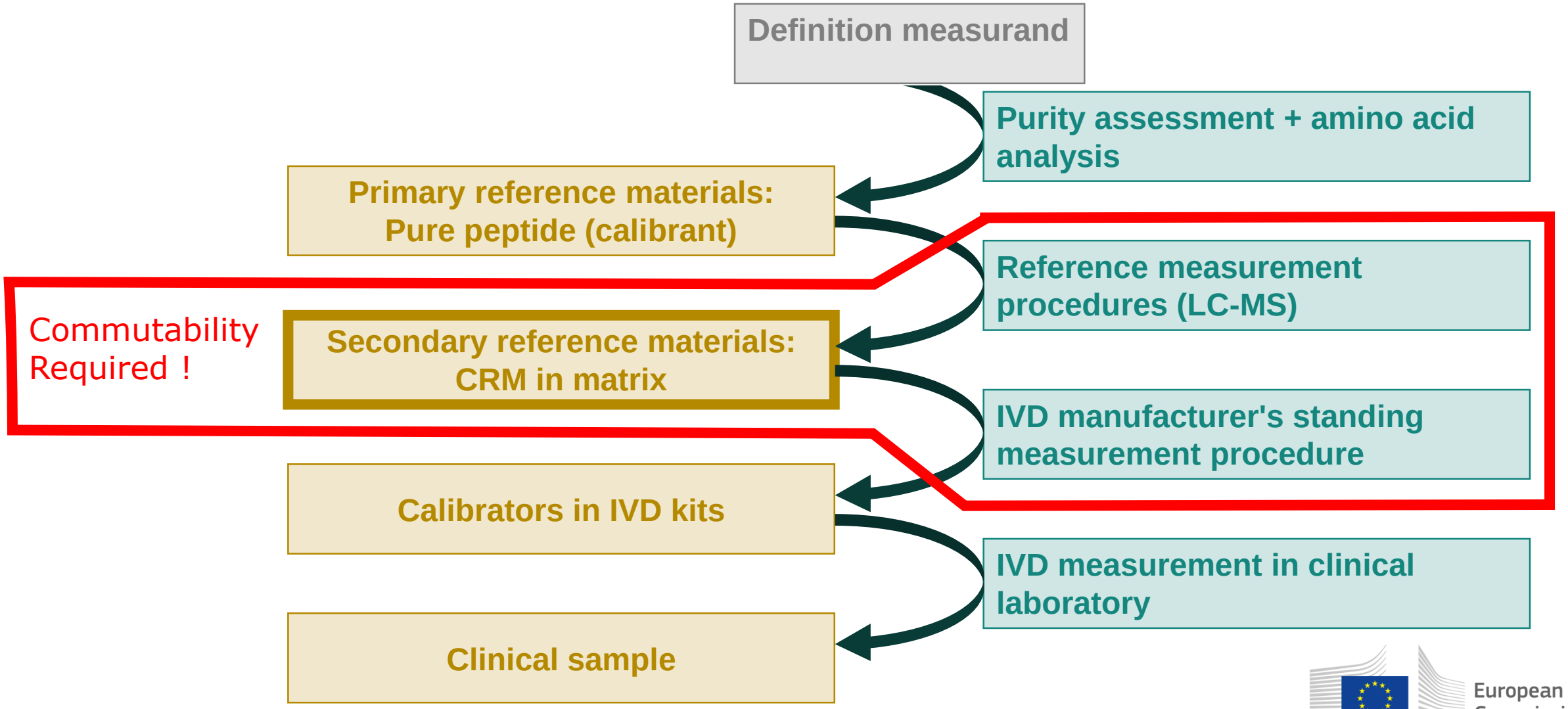
Intended use

ERM-DA480/IFCC: Amyloid β_{1-42}



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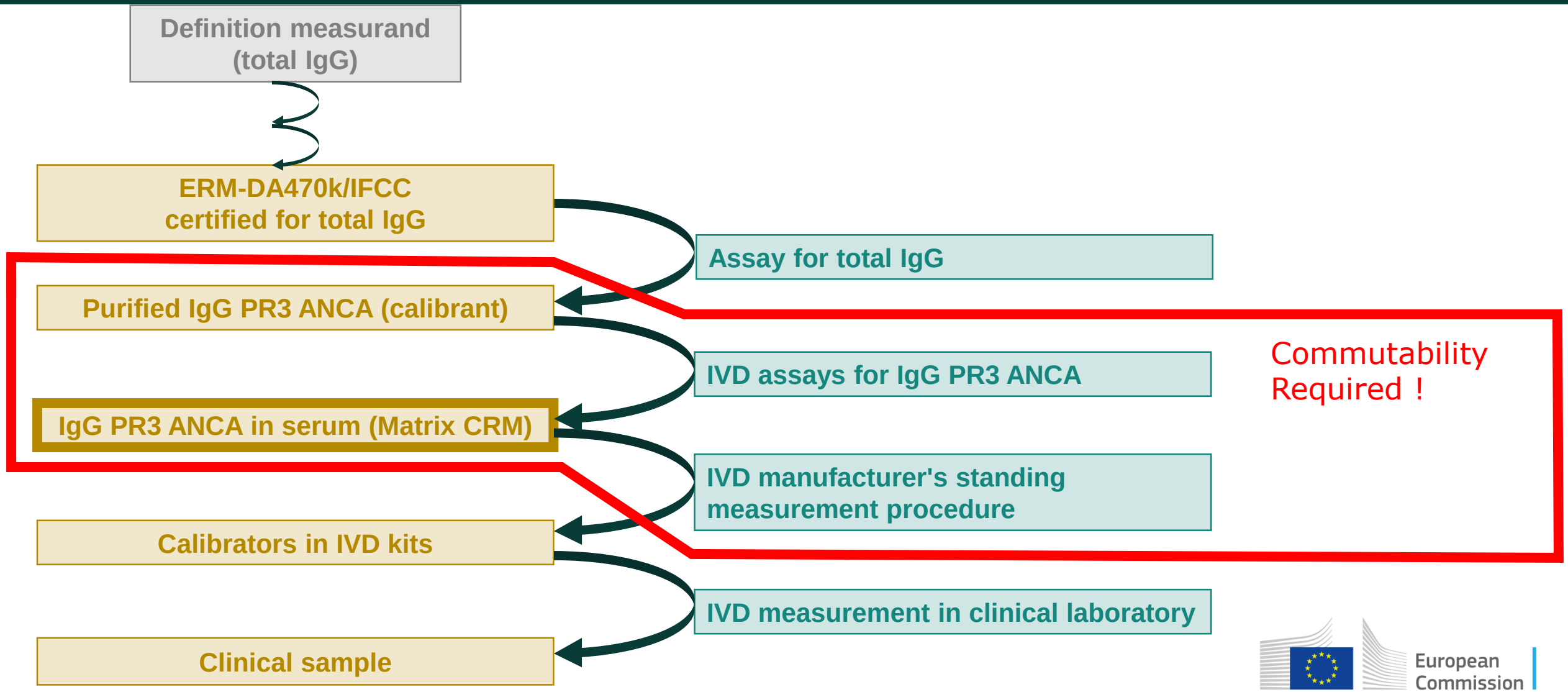
Intended use

ERM-DA483/IFCC: IgG proteinase 3 (PR3) anti-neutrophil cytoplasmic autoantibodies (ANCA)



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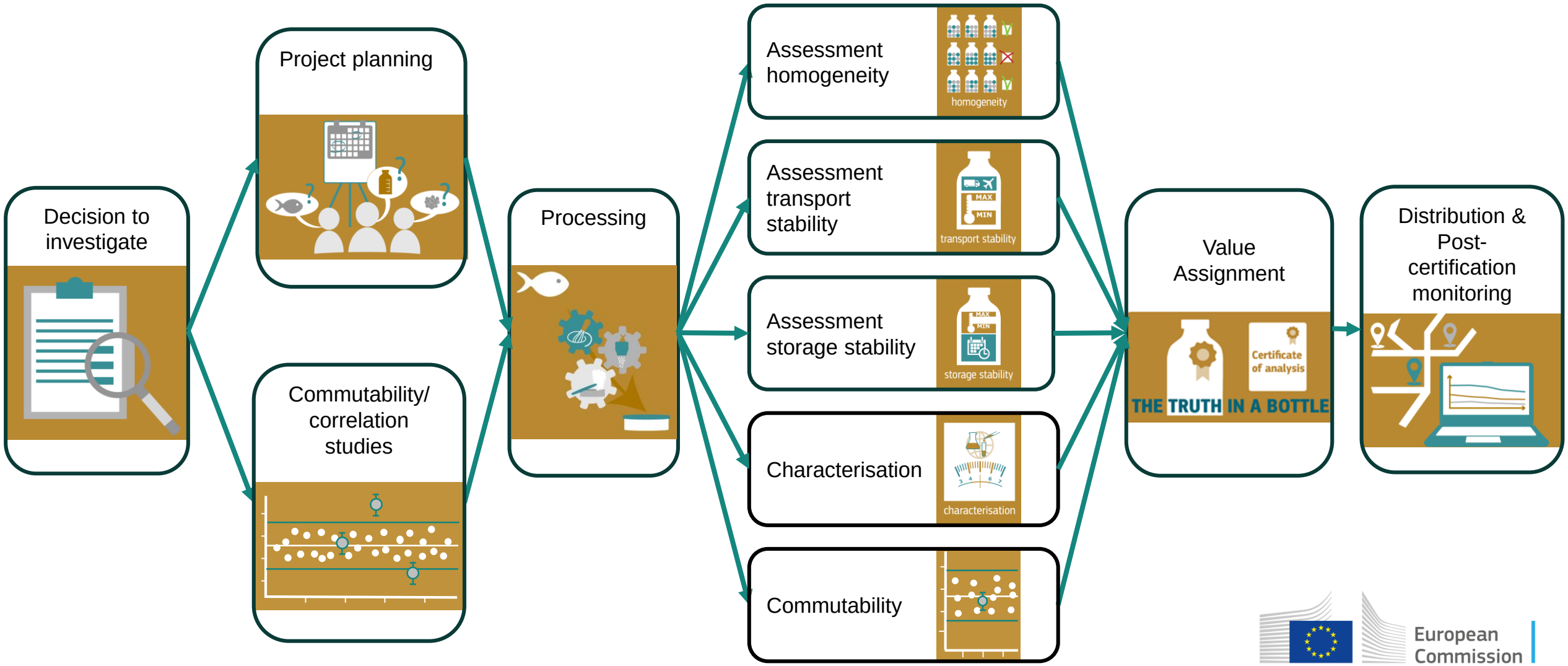
Commutability studies in production process



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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

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Commutability/correlation studies
Study design

Samples

- ≥ 30 samples
- Representative:
  - Consider subpopulations
  - Effects of freeze/thawing, aging and pooling
  - Avoid interfering substances
- Covering the measurement range

Methods

- Include reference measurement procedure
- Relevant IVD methods (as much as possible)

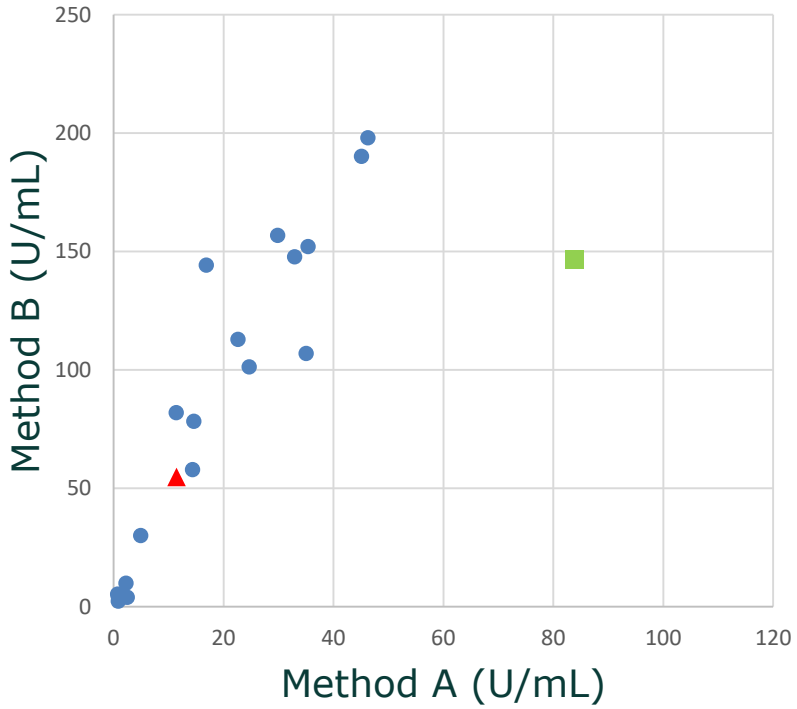
Commutability/correlation studies
Study design

Candidate RM

- Source of measurand
  - Single donation
  - Pools of several individuals
  - Recombinant protein
- Matrix
  - Serum versus artificial buffer
  - Effect of additives
- Format
  - Liquid frozen versus lyophilised
  - Dilutions: suitable diluents

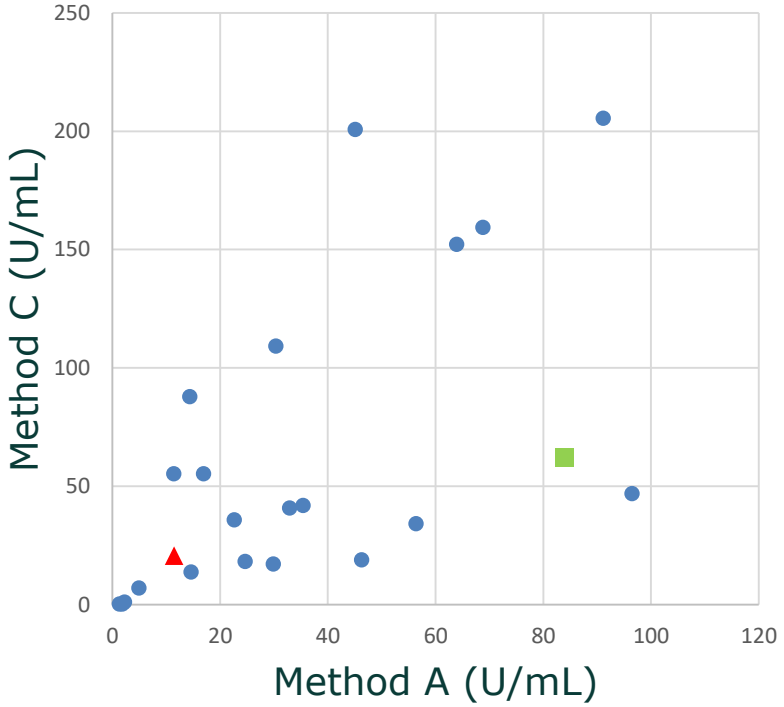
Evaluate correlation methods

Example IgG PR3 ANCA → will a commutable CRM make measurement results on patient samples comparable?



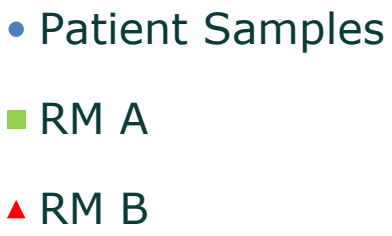
Pearson's r: 0.949

High degree correlation → Yes



Pearson's r: 0.617

Low degree correlation → No



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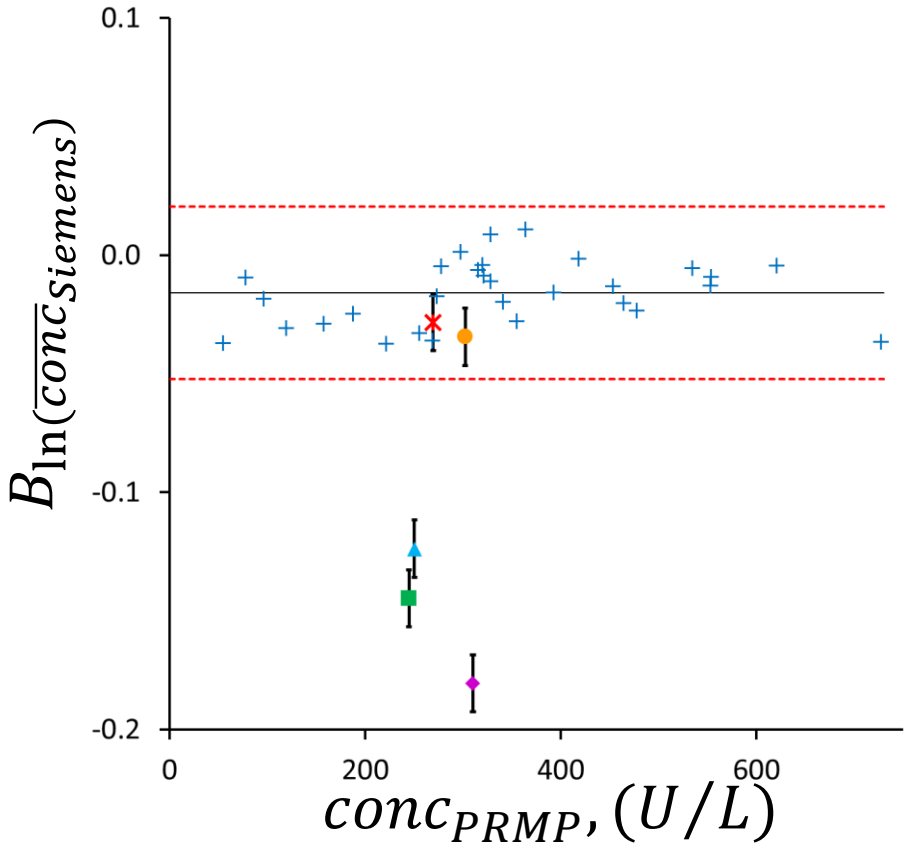
Evaluate commutability candidate RMs

Difference in bias approach

Example alpha-amylase



- Serum pools
- RM A: purified in buffer with HSA, lyophilised
- RM B: recombinant in buffer with BSA, lyophilised
- RM C: purified in buffer with BSA, liquid frozen
- RM D: purified in buffer with BSA, liquid frozen
- RM E: purified in serum, lyophilised
- $\bar{B}_S$: average bias of serum pools
- Expanded uncertainty on the difference in bias
- Commutability criterion, set at 3.7%

Publication: Deprez et al. 2018 Clin Chem. 64(9): 1296-1307

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Setting commutability criterion

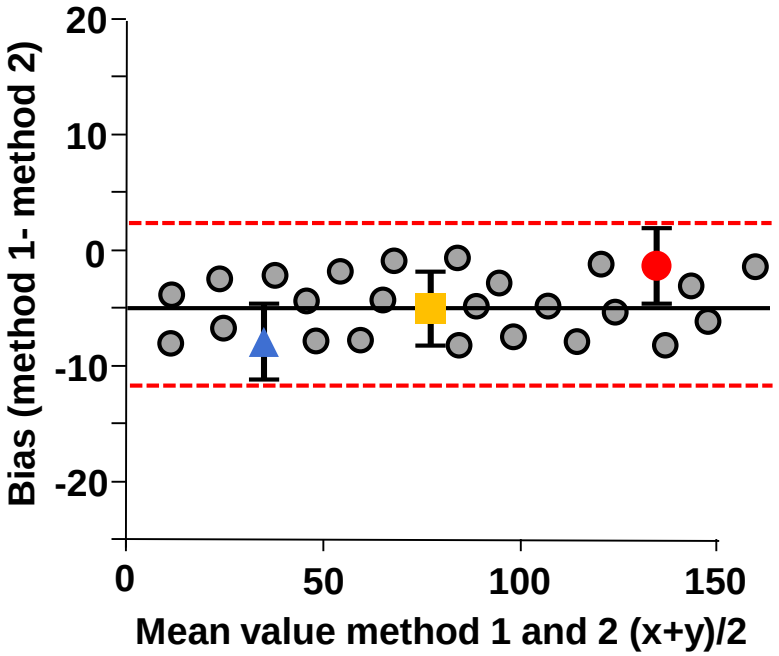
- Clinical performance criteria of the methods

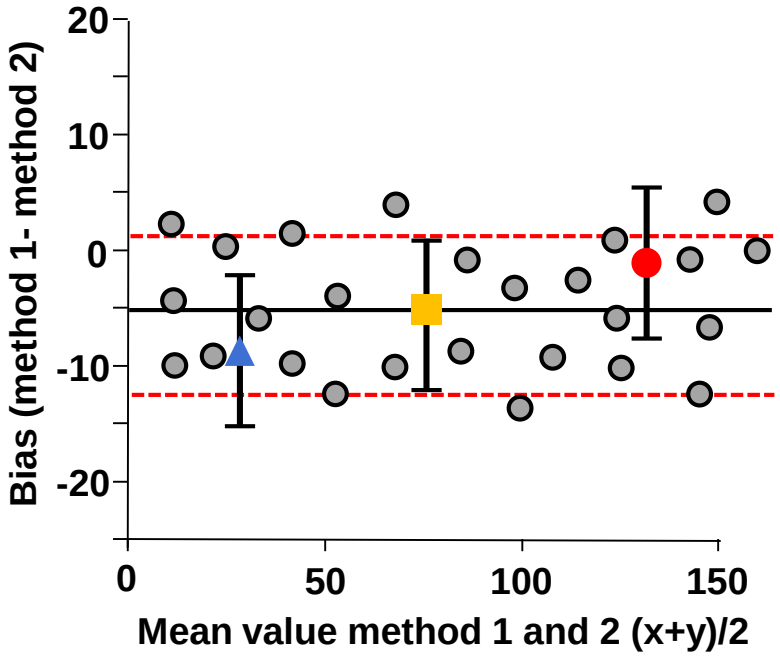
  Example: desirable specifications for IVD methods in Westgard database based on intra- and inter-individual biological variation

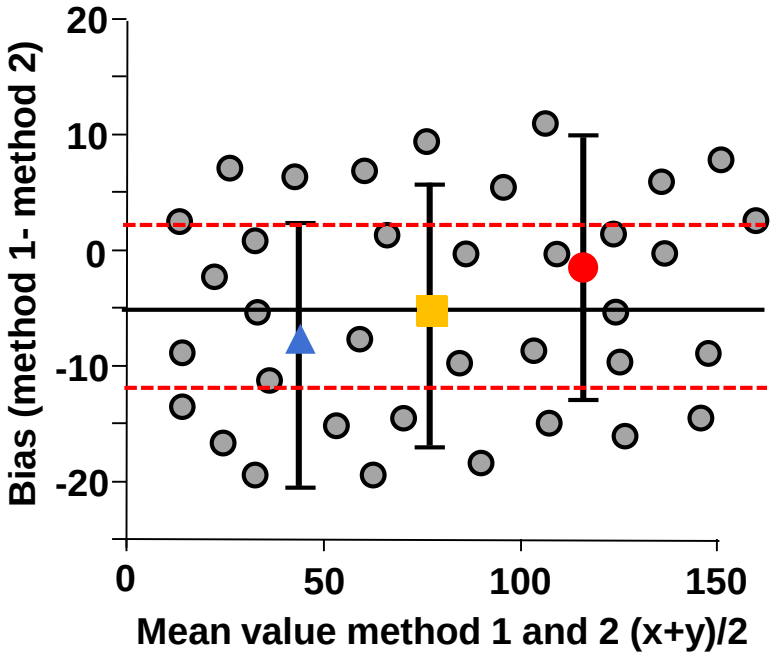
- Intended use CRM

  Calibrant versus trueness control

Commutability citerion versus spread samples







Clinical samples
RM A
RM B
RM C
Average bias clinical samples
Commutability criterion

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Information on commutability for CRM users

On the certificate

INSTRUCTIONS FOR USE AND INTENDED USE

The vials shall be thawed at room temperature. Avoid vortexing or inverting the vial in order to prevent contact between the solution and additional surface of the vial.

The materials are intended for the calibration of methods, quality control and/or the assessment of method performance. As with any reference material, they can be used for establishing control charts or in validation studies. ERM-DA482/IFCC was shown to be commutable for the combination of the following routine measurement procedures:

- EUROIMMUN beta-amyloid (1-42) (EUROIMMUN AG, Lübeck, DE)
- IBL Amyloid-beta (1-42) CSF ELISA (IBL International GmbH, Hamburg, DE)
- INNOTEST® β-AMYLOID(1-42) (Fujirebio Europe, N.V., Gent, BE)
- Lumipulse® (Fujirebio Europe N.V., Gent, BE)
- V-PLEX® Aβ Peptide Panel 1 (6E10) (Meso Scale Discovery, LLC., Rockville, MD, US)
- Roche Elecsys β-amyloid (1-42) (Roche Diagnostics GmbH, Penzberg, DE)

If ERM-DA482/IFCC is used for the calibration of other $A\beta_{1-42}$ routine measurement procedures it should be verified by the user that the material or its dilutions used are commutable.

In the certification report

Annex D: Commutability

Laboratory	Method Name	Method Principle
L1	Varelisa™ PR3 ANCA	ELISA
L2	Wieslab® Anti-PR3 ELISA	ELISA
L3	anti-PR3-hr-hn ELISA (IgG)	ELISA
L4	QUANTA Lite PR3 IgG	ELISA
L5	ORG 518 Anti-PR3 (cANCA)	ELISA
L6	DIASTAT anti-PR3 (cANCA)	ELISA

Table D1: Laboratories that participated in the commutability studies and the methods for which pilot batches processed in the same way as ERM-DA483/IFCC were found to be commutable.

European Commission

Acknowledgements

Team at JRC

IFCC Scientific Division

Committee on Harmonization of Autoimmune Tests (C-HAT)

Working group on CSF-Proteins (WG-CSF)

Working group on Pancreatic Enzymes (WG-PE)

Working group on Commutability (WG-C)

European Commission

Thank you

Questions?

You can find me at **liesbet.deprez@ec.europa.eu**

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

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