The importance of commutability of biological CRMs

Vincent Delatour[1], Amandine Bœuf[1], Chiara Giangrande[1], Helene Vaneeckhoutte[1], Béatrice Lalere[1], Sophie Vaslin-Reimann[1]

[1]Laboratoire National de métrologie et d'Essais (LNE), 1 rue Gaston Boissier, 75724 Paris, France

Introduction

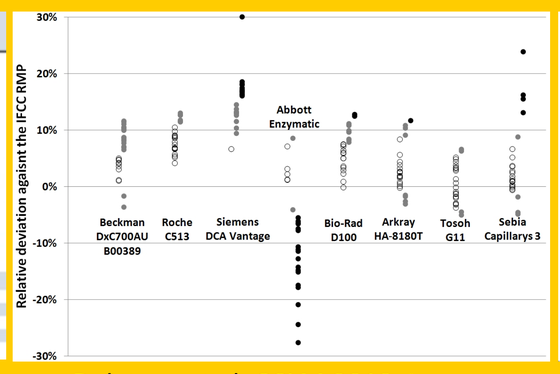
- ✓ Commutability is a property of a reference material (RM) that relates to the closeness of agreement between results for an RM and results for clinical samples (CSs) when measured by >2 measurement procedures (MPs).
- ✓ Commutability of RMs used in a calibration traceability scheme is an essential property for them to be fit for purpose.
- ✓ Commutability of trueness controls or external quality assessment materials is essential when those materials are used to assess trueness of results for CSs.

Why commutability matters?

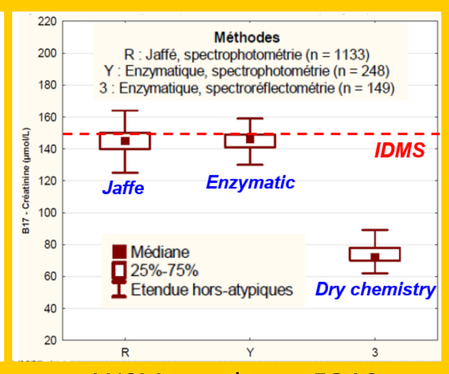
Table 3. Evaluation capabilities of PT/EQA related to scheme design.

	Sample characteristics			Evaluation capability: Accuracy: Individual laboratory: Absolute vs RMP or CRM	Relative to participant results: Overall	Relative to participant results: Peer group	Reproducibility: Individual laboratory intralab CV	Reproducibility: Measurement procedure interlab CV	Standardization or harmonization[b]: Measurement procedure calibration traceability: Absolute vs RMP or CRM	Standardization or harmonization[b]: Measurement procedure calibration traceability: Relative to participant results
Category	Commutable	Value assigned with RMP[a] or CRM	Replicate samples in survey							
1	Yes	Yes	Yes	X	X	X	X	X	X	X
2	Yes	Yes	No	X	X	X		X	X	X
3	Yes	No	Yes		X	X	X	X		X
4	Yes	No	No		X	X		X		X
5	No	No	Yes			X	X	X		
6	No	No	No			X		X		

Miller et al. Clin Chem. 2011;57(12):1670-80



Delatour et al. CCLM 2019, in press



ANSM mandatory EQAS

Quality control materials

- ❖ Non-commutability of EQA materials makes it impossible to :
  - ➢ evaluate trueness of assays
  - ➢ evaluate agreement of results from different peer groups
- ❖ Fully independant post-market vigilence is compromised

Calibration materials for standardization purposes

- ❖ Non commutability of calibrators breaks the traceability chain and results in the inability to standardize results

What are the different steps in a commutability study?

(1) Obtain Reference Material(s) (RMs) to be evaluated;

(2) Obtain representative clinical specimens (CSs);

(3) Select methods for which commutability should be characterized;

(4) Measure the RM(s) and CSs using the selected methods;

(5) Define acceptance criteria for commutability;

(6) Perform a statistical analysis of results to evaluate commutability of the RM(s)

(7) Make a conclusion for commutability of the RM(s) for each method involved

How to select patient samples?

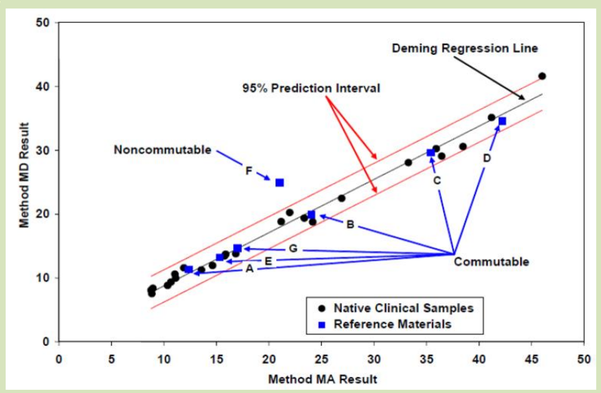
- ✓ Ideally, fresh single donations obtained from healthy volunteers and/or diseased patients
- ✓ Clinical specimens should not contain interfering substances or unusual molecular forms, such as found in less common pathologic conditions, when these affect all or most methods
- ✓ The interval of concentrations of the measurand in CSs must include that of the RM(s) but don't need to cover the entire measuring interval for the methods included
- ✓ Although individual CS are preferred, sufficient volumes of individual CSs cannot always be obtained to enable aliquotting for distribution and measurement by all involved methods. In this case, using pooled CSs instead of single donations is a practical solution that may reduce the cost and complexity of a commutability study (preliminary experiment needed!)

How many patient samples are needed?

- ✓ The number of CSs needed vary with the experimental design (eg. nb of replicates) and the performance characteristics of the methods involved (eg. precision)
- ✓ Although no fixed number can be given, a usual practice is to include at least 20-25 CSs
- ✓ For measurands with large differences in measuring interval for different clinical uses, commutability assessment may be restricted to one of the intended use intervals or require separate experiments for each interval. In this case, different sets of CSs are needed

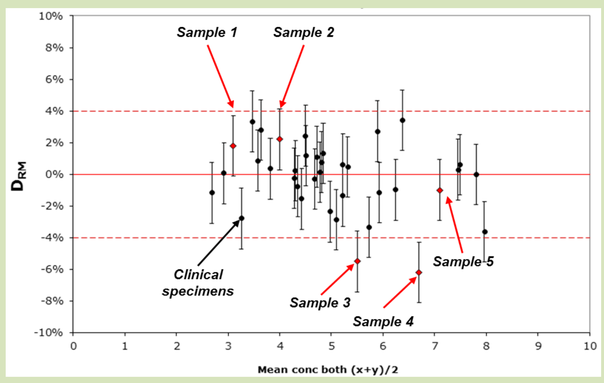
Statistical designs for commutability assessment

Conventional approaches (CLSI C53A & EP14)



- ✓ Linear regressions
- ✓ 95% prediction intervals
- ✓ Uncertainties are neglected : the hypothesis of non-commutability is tested on the 50% level of significance!
- ✓ The intended use is not taken into account

Difference in bias approach (IFCC WG-C)



- ✓ Difference plots
- ✓ Uncertainties are considered : some assessments will be inconclusive
- ✓ Acceptance criteria should be defined depending on the intended use of the material

IQC < EQA < trueness verifier < calibrator

Criteria based on statistical distribution of CS results between methods are less desirable and not recommended because they can produce different criteria for different combinations of MPs for the same measurand. Criteria based on statistical distribution of CS results may be unreasonably small or large compared to the intended medical use of laboratory test results

How to select methods?

- ✓ Include as many different methods as possible
- ✓ As it may not be possible to include all existing methods, including the most representative groups of methods will improve the likelihood of a RM being suitable for use with methods not included in the initial assessment. Considerations for inclusion include market share for commercially available methods and types of analytical measurement principles.
- ✓ Included methods should measure the same entity over similar concentration intervals
- ✓ Methods included in a commutability assessment should have adequate performance characteristics, e.g. sufficient precision and selectivity

How should measurements be conducted?

- ✓ Clinical specimens and RM(s) which commutability is being characterized should be measured in the same conditions, ie. in the same analytical sequence (same analyzer, same reagent lot, same calibration lot, same period of time)
- ✓ A sufficient number of replicates should be performed depending on methods' precision

How should acceptance criteria be chosen?

- ✓ Acceptance criteria for commutability depend on the intended use of the considered RM(s): it is expected that more stringent acceptance criteria will be used to evaluate commutability of a RM used in a calibration traceability hierarchy than for trueness verifiers or EQA materials
- ✓ The criterion for a RM intended for use in a calibration traceability hierarchy should be a fraction of the allowable bias for an individual CS result
- ✓ The criterion for commutability should be a fraction of the bias component of the acceptance limits for evaluating an EQA or trueness control result.
- ✓ In some cases, practical limitations in study design (e.g. limited number of replicates or CSs) and / or the performance capability of methods (e.g. poor precision or selectivity) could produce large uncertainties that could limit the ability to make a decision about suitability of a RM. In such situations, use of less stringent acceptance criteria can be considered.

How to decide whether a RM is commutable or not?

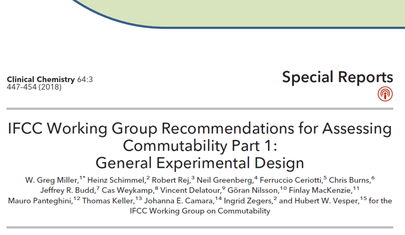
- ✓ Ideally, a pairwise comparison should be performed between of each method and a Reference Measurement Procedure. e.g. inclusion of 8 routine assays will result in 8 pair-wise comparisons
- ✓ If no reference method is available, pairwise comparisons will be established so as to cover all combinations of methods : e.g. inclusion of 8 methods will result in 28 pair-wise comparisons
- ✓ One or more pairs of methods may be identified for which a given RM is not commutable
- ✓ The decision is made based on the fraction of methods for which a RM is found commutable
- ✓ There are no simple recommendations for the fraction of methods for which a RM must be commutable that would qualify a RM as being fit for purpose. Considerations include the market share for methods and the number of tested individuals who may be affected

	Method 1	Method 2	Method 3	Method 4	Method 5	Method 6	Method 7	Method 8
Method 1		C	I	NC	C	C	C	C
Method 2			C	NC	C	C	C	C
Method 3				NC	C	I	I	C
Method 4					NC	NC	NC	NC
Method 5						C	C	C
Method 6							C	C
Method 7								C
Method 8								

	Method 1	Method 2	Method 3	Method 4	Method 5	Method 6	Method 7	Method 8
RMP	C	C	I	NC	C	C	C	C

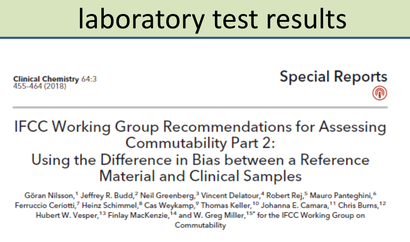
Conclusion

- ✓ Commutability is an important property of calibrators and quality control materials used to assess trueness of assays and between-method agreement
- ✓ A commutability assessment requires sourcing an appropriate number of clinical specimens in sufficient volume so that the same samples can be measured with all available assays. Involved assays should have sufficient precision or selectivity.


Clinical Chemistry 64:3 447–454 (2018) Special Reports

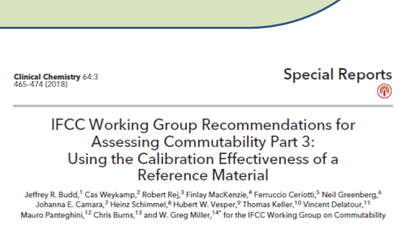
IFCC Working Group Recommendations for Assessing Commutability Part 1: General Experimental Design

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

vincent.delatour@lne.fr