Application Note 8

Assessing commutability of reference materials

20.2.2020

Author: Liesbet Deprez
European Commission - Joint Research Centre
Retieseweg 111, 2440 Geel, Belgium
Email: liesbet.deprez@ec.europa.eu

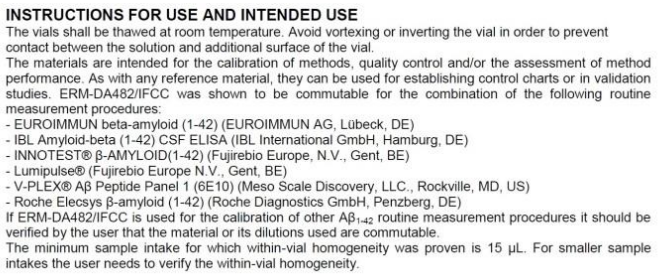
Commutability is a prerequisite for reference materials (RMs) intended to be used for calibration or quality control of different measurement procedures targeting the same measurand. This application note explains the concept of commutability and clarifies the commutability information provided on the ERM certificates. In addition, this note also describes the most crucial aspects of a commutability study.

INTRODUCTION

In several scientific fields (including clinical chemistry) the lack of agreement between results among different measurement procedures targeting the same measurand is a major concern. Efforts for standardisation or harmonisation of these measurement procedures often rely on the use of RMs for calibration or quality control. Commutability of the used RMs is essential to ensure that these efforts are successful.
The International Vocabulary of Metrology (VIM) defines the commutability of an RM as the property 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 the routine samples [1]. In more everyday language, commutability can be stated as a property of an RM that indicates how well an RM mimics the characteristics of a typical routine sample in various measurement procedures for a stated measurand.

COMMUTABILITY OF CRMs

According to ISO 17034 it is the responsibility of the RM producer to ensure that an RM is suited for its intended use. The commutability of an RM therefore needs to be assessed, where appropriate. For ERM®-RMs, the information concerning the commutability can be found on the certificates, under "instructions for use and intended use" (see Figure 1), or in the certification reports, under the header "commutability". The same RM may be commutable for some measurement procedures but non-commutable for others. A commutability statement is therefore only valid for the mentioned measurement procedures.
During the RM development efforts are made to include as many different measurement procedures as possible, especially if they are based on distinct analytical measurement principles. However, it may not be feasible to include all available measurement procedures or new measurement procedures might become available after the release of the RM. In addition, it should be kept in mind that substantial changes in the measurement procedure such as a changed reagent formulation can invalidate the commutability statement for a specific measurement procedure.
If a user intends to use an RM for calibration or quality control of a measurement procedure that was not included in the commutability assessment performed by the RM producer, it is the responsibility of the user to verify the commutability of the RM for the measurement procedure intended to be used.



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 $A\beta_{1\text{-}42}$ routine measurement procedures it should be verified by the user that the material or its dilutions used are commutable.
The minimum sample intake for which within-vial homogeneity was proven is 15 µL. For smaller sample intakes the user needs to verify the within-vial homogeneity.

Figure 1: Example of the instructions for use and intended use section of a certificate.

CRUCIAL ASPECTS OF COMMUTABILITY STUDIES

This list summarises the crucial aspects within the setup of a commutability study. In 2018, the IFCC working group on commutability (WG-C) published their guidelines on the general experimental design of commutability studies for clinical chemistry and these were used as a basis for this list [2].

Handling of the RM

The instructions for use, such as the reconstitution protocol, should be strictly followed when preparing the RM. If an RM is intended to be diluted (e.g. for the set-up of a

calibration curve) the diluted forms must be included in the commutability study. The matrix is known to have a major impact on the commutability of the RM so the choice of the diluent is crucial. In case of doubt, users are advised to contact the RM producer.

Samples representative for routine samples

The samples included in the commutability study should fulfil the following requirements:

- They should be representative for the routine samples that will be measured with the measurement procedure of interest in the real-life situation. Variations in matrix composition or various isoforms of the measurand that can be present in routine samples should be covered as much as possible. However, selectivity limitations of the measurement procedure should also be taken into account. Samples that contain known interfering substances or measurand isoforms that cannot properly be measured should be excluded.
  For practical reasons it might be necessary to treat the samples used in the commutability study differently than the routine samples. The effect of any modification (e.g. sample pooling, preparing aliquots, long time storage, freezing and the use of preservatives) on the commutability of the samples should be evaluated prior to the start of the commutability study.
- Concentrations of the measurand in the samples should cover a reasonable interval around the concentration of the RM.
- Sufficient samples should be included in the commutability to reliably establish the inter-assay relation of the routine samples. Therefore, a minimum of 30 samples are usually required.

The measurement procedures

A commutability assessment is based on the comparison among measurement results from two different measurement procedures. In addition to the measurement procedure of interest, a comparator measurement procedure should be selected. Ideally, this should be the measurement procedure (or one of the measurement procedures) used for the characterisation of the RM. Otherwise, another measurement procedure, for which the CRM has shown to be commutable, can be selected. The measurement procedures included in the commutability study must have a similar selectivity for the measurand. Measurement procedures with a different selectivity can be identified by the presence of excessive sample specific effects. In this case, it is not possible to establish reliably the relationship between the assays for the routine samples and therefore the commutability of the RM cannot be evaluated.

Measurement series

Both the RM and the samples should be measured in an adequate number of replicates. At least three replicates are recommended as it allows the removal of one replicate measurement in case of a technical error without the need to remove all results for that sample. Depending on the repeatability of the measurement procedures, more replicate measurements might be needed.
It is also recommended to perform all the measurements in one single run to minimise the effect of run-to-run variability. The presence of an analytical drift within the run can be covered by performing the replicate measurements on the RM at different positions in the measurement series.

Statistical evaluation

For the statical evaluation of commutability, several analyses have been described in the literature. For this list only three have been selected:

1. Regression analysis with 95% prediction interval

The guideline EP30-A from the Clinical and Laboratory Standards Institute (CLSI) [3] was published in 2010 and it has been broadly used in commutability assessment for several years. This guideline describes an approach in which a regression analysis is performed on the measurement results obtained for the routine samples with two measurement procedures. An RM is considered commutable if its data point falls within the 95% prediction interval defined by the routine samples (see Figure 2). However, this approach has several drawbacks. First, the width of the prediction interval is determined by the correlation among the sample results of the two measurement procedures. In case of a poor correlation, due to sample specific effects or assay variability, the prediction interval will be quite large and it becomes more likely that an RM is considered commutable. Second, the outcome is just a yes/no answer without taking into account the location of the data point of the RM within the prediction interval (in the middle versus close to the boundaries).

2. Difference in bias analysis

The "difference in bias" analysis is one of the two approaches recommended by the IFCC WG-C [4]. This approach quantifies the closeness of the systematic difference between the results of two measurement procedures (i.e. the bias) for the tested RM to the average bias for the routine samples. In addition, the uncertainty associated with the difference in bias is also estimated. An RM is considered commutable if the difference in bias and the associated uncertainty is smaller than a predefined commutability criterion (see Figure 3). The criterion should be based on application requirements. This analysis results in an inconclusive outcome when the associated uncertainty overlaps with the commutability criterion.

3. Analysis of the calibration effectiveness of an RM

The second approach recommended by the IFCC WG-C uses the calibration effectiveness of an RM to assess its commutability [5]. Two measurement procedures are calibrated using the RM and the RM is considered commutable if the bias among the results of the two measurements procedures for the routine samples is within a predefined acceptable level of equivalence based on application requirements. An RM is considered non-commutable in case that after calibration of the measurement procedures the results for routine samples do not agree. However, other reasons of disagreement, such as lack of calibration fit, should also be considered.

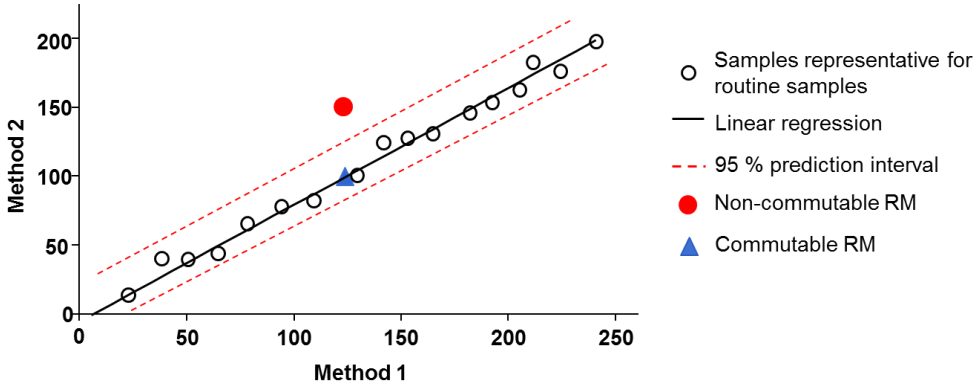


Figure 2: Schematic diagram showing the outcome of a commutability assessment according to a regression analysis with 95% prediction interval.

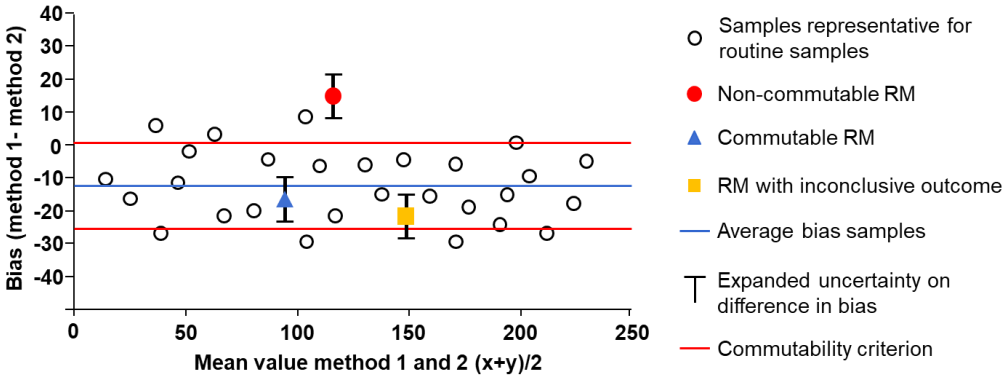


Figure 3: *Schematic diagram showing the outcome of a commutability assessment according to difference in bias approach.*

---

[1] International vocabulary of metrology - basic and general concepts and associated terms, 3rd ed. (VIM 3) available from http://www.bipm.org or as ISO/IEC guide 99-12:2007

[2] Miller et al. Clinical Chemistry 64 (2018):447-54

[3] Clinical and Laboratory Standards Institute (CLSI). Characterisation and Quantification of Commutable Reference Materials for Laboratory Medicine; Approved Guideline. CLSI document EP30-A (ISBN 1-5628-726-X)

[4] Nilsson et al. Clinical Chemistry 64 (2018):455-64

[5] Budd et al. Clinical Chemistry 64 (2018):465-74