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Is commutability of a reference material always desirable?

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Commutability has been highlighted as one of the most fundamental requirements in the application of reference materials (RMs), particularly calibration materials and quality control materials, in laboratory medicine [1–4]. However, we believe it's also important to emphasize that commutability in a given *constellation* does not necessarily mean that an RM is suitable for its intended purpose.

Compromised selectivity and analytical specificity continue to be a major and widespread issue in many clinically applied laboratory tests today. In therapeutic drug monitoring (TDM), conventional ligand-binding tests often cross-detect conjugate metabolites of the actual target measurand, which is typically the active drug compound. Further, differential matrix effects on ligand binding present a recognized problem, especially for competitive immunoassays that employ only one test-antibody species. These effects are not confined to drug analyses, but also represent a fundamental issue in endocrine testing with ligand-binding assays, where both conjugate metabolites and structurally very closely related compounds are prevalent. MS-based analytical techniques offer features to overcome these limitations of currently used standard technologies, but their dissemination in clinical laboratories remains limited. Consequently, when applying reference materials such as calibration samples, external quality assessment samples, and general quality control samples, it is crucial to consider the selectivity issues of routine tests.

In this context, we would like to emphasize — in full agreement with the recent IFCC guidelines [2] — that prudent and correct use of the term and concept of *commutability* is essential, particularly given the potential shortcomings of ligand-binding-based TDM and endocrine assays. Indeed, commutability appears to be interpreted as a uniform quality label for reference materials among some members of the clinical laboratory community. Why is such a viewpoint inappropriate?

The International Vocabulary of Metrology, VIM [5], defines "*commutability of a reference material as the property of a reference material, 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 other specified materials*." The definition makes it clear that commutability is not an "absolute" or inherent property of a RM, but rather a "relative" property attributed in relation to a constellation of two or more individual measurement procedures. These procedures can vary greatly in their performance, especially regarding selectivity and specificity. Indeed, commutability to measurement procedures of inadequate selectivity may not be a desirable goal. This is described by the following thought experiment (visualized in Fig. 1), including two putative RMs (1 and 2) and two putative measurement procedures (A and B) applied in TDM:

- RM 1 contains the measurand – a drug compound - and its predominant conjugate metabolite (MEA, and MEA-G), manufactured from a human post-dose sample
- RM 2 merely contains the measurand (MEA) spiked into an albumin-matrix, no metabolites
- Method A shows a significant cross-reaction with the drug conjugate (MEA-G) (e.g., immunoassay)
- Method B *specifically* detects the drug measurand (MEA) with no cross-reaction (e.g., mass-spectrometry assay)

In this constellation, RM 1 would be characterized as non-commutable, while RM 2 would be considered commutable with respect to methods A and B. However, concluding that RM 2 is the "better" RM would be incorrect. In fact, RM 1 would be the more useful material for quality assurance because it could reveal a lack of specificity in a measurement method (such as Method A in this case). It's important

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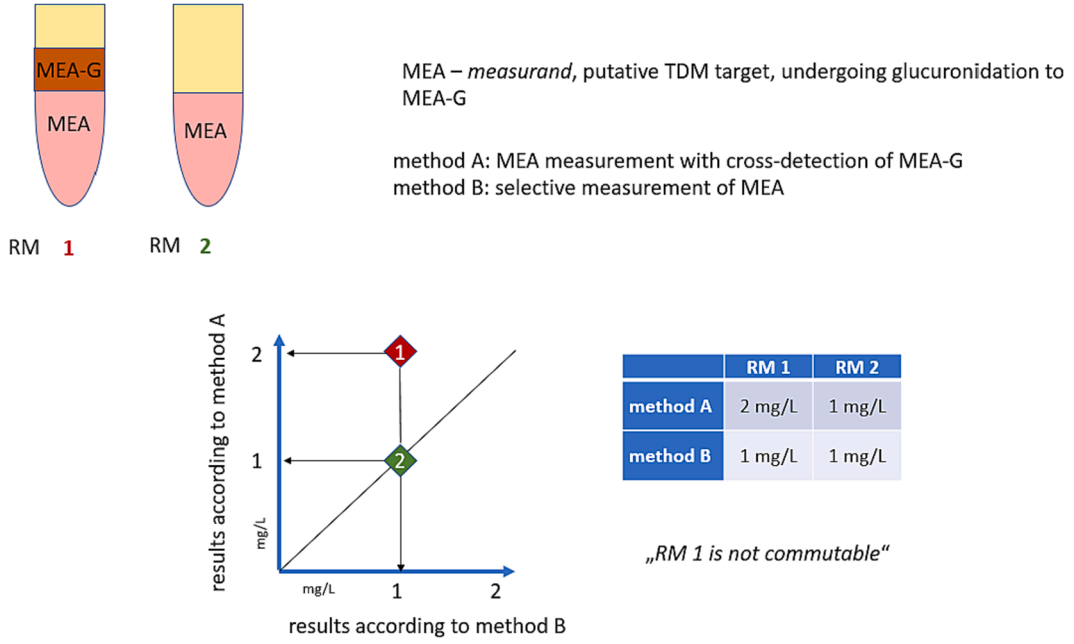

Fig. 1. Non-commutability of a putative reference material (RM, reference material).

to note that authentic single-donor post-dose serum or plasma is non-commutable in this constellation — even though this type of material is generally considered the gold standard for external quality assessment — in contrast to materials merely spiked with the measurand of interest.

We must conclude that commutability should indeed not be understood as a simple and uniform "quality label" of RMs. The use of commutable RMs for calibration and quality control is by no means a guarantee for reliable analyses; these properties are determined by a range of downstream characteristics and variables inherent to the applied measurement method. Commutability of a quality control material is convenient for both manufacturers and customers because a single target value, rather than method-specific target values, can be assigned for a range of routine analytical platforms. However, this could give the impression that these different analytical platforms also closely agree in real diagnostic samples, which is not necessarily the case.

There's no question that non-commutability of RMs can be a substantial and critical issue. Generally, this applies more to protein measurands than to small molecules, for example, due to conformational changes induced by the lyophilization of protein measurands. However, specifically for small molecules – as observed in TDM) – the pronounced susceptibility of methods to matrix effects appears to be the root cause of commutability issues in most cases.

Considering the context of this paper, it is important to note that the intended uses of RMs are not at all uniform. A material for internal quality assessment might primarily seek to verify the integrity of a single analytical system, while a material for external quality assurance could aim to detect systematic differences between the results of different assays on the market. The complexity of analytical specificity in connection to clinical diagnostic objectives should also be taken into account: For many assays, a high degree of specificity is indeed undesirable, such as when different isoforms of proteohormones need to be detected or "group tests" like the measurement of total serum protein concentration are applied. Accordingly, the relevance and meaning of commutability need to be thoroughly considered in relation to specific analytical constellations and diagnostic requirements.

Hopefully, the more widespread routine application of mass spectrometry, with its typically very high selectivity and specificity of detection in clinical laboratories, will increasingly overcome these commutability issues in the near future, particularly in TDM.

In summary, we believe that a differentiated perspective on the concept of commutability in laboratory medicine is crucial to fully understand and appreciate this concept's value.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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