Challenges in the standardisation of non-targeted quantitative methods of analysis

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Increasing regulation and the demand for reliable quantitative measurement results, that are comparable over time and between different laboratories, have been major drivers for metrology in chemistry. These, along with the requirements of quality standards, such as ISO 17025, have fueled the development of many certified reference materials (CRMs). These materials can be highly purified substances, which are used as primary calibrators to support measurement traceability statements, or matrix reference materials that can be used in method validation or calibration. National Measurement Institutes (NMIs) currently assure the traceability of their measurement results for a small number of high priority measurands by conducting comparison studies to demonstrate their equivalence. Hence reference measurement procedures and materials produced by NMIs are important tools for assuring the global comparability of measurement results. The procedures used by the NMIs provide the best trueness and lowest measurement uncertainty. However, they are highly labour intensive and time consuming and therefore the number of such studies are limited. The methods used often quantify one, or a small group of similar measurands per campaign. Therefore, the production of CRMs to support multiparametric, "omic" or non-targeted methods are not ideally catered for using these approaches.

To address this issue the Organic Analysis Working Group (OAWG)[1] and Protein Analysis Working Group (PAWG)[2] of the Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM) co-ordinates studies that enable NMIs to back broader claims by looking at specific measurands that challenge particular analytical skills and that can be reasonably assumed to represent a wider group of measurands as agreed by the technical experts within the working group. This provides a mechanism for assuring the equivalence of measurement results provided by NMIs when assigning values to certified reference materials (CRMs) and when used as reference values for Proficiency Testing (PT) schemes.

The above approaches have worked well for materials with a small number of measurands and/or where the stability of the material has enabled its characterisation for an increased number of measurands over many years. For many sectors, the speed of development for these materials is not meeting the demand and CRM producers will have to alter their current practices to deliver the required materials in much reduced timescales. In this talk we will address the development of new highly automated reference method procedures for the provision of calibrators as wells as use of "beacon molecules" or generic calibrators that can be used to quantify molecules with similar properties. The estimated measurement uncertainty attained via these procedures, in comparison to the conventional approaches, will be presented. Finaly the requirement for more community-based approaches for the delivery of "fit for purpose" materials will be discussed.

[1] Teo, T.L., Lippa, K.A., Mackay, L. *et al.* Enhancing the accuracy of measurement of small molecule organic biomarkers. *Anal Bioanal Chem* **411**, 7341–7355 (2019)
[2] Josephs, R. D., Martos, G., Li, M., et al. Establishment of measurement traceability for peptide and protein quantification through rigorous purity assessment a review. Metrologia 2019, 56, 044006.
[3] Henrion, A., Arsene, CG., Liebl, M. *et al.* Label-free quantification of host cell protein impurity in recombinant hemoglobin materials. *Anal Bioanal Chem* **416**, 387–396 (2024)