Editorial

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The central role of external quality assurance in harmonisation and standardisation for laboratory medicine

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Harmonisation of the total testing process is fundamental to the delivery of quality pathology [1]. Although this goal is not new, advances in information technology, the move towards electronic health recording and the recognition of patients as part of the global health village have led to an appreciation that discordance in results between laboratories and between methods is no longer accepted practice. Often, the first step in the recognition of discordance between results is through assessment against an external quality assurance (EQA) scheme. As such, EQA is recognised as a pillar in the overall process of standardisation with the other four pillars being: certified reference materials (CRM); reference measurement procedures (RMP); reference laboratories; and reference intervals and decision points [2].

Inter-laboratory comparisons are a mandatory requirement for accreditation to the international standard applicable to medical testing laboratories (ISO 15189:2012) [3]. EQA programmes offer an organised approach for these appraisals, allowing large-scale statistical comparisons to be made. In themselves, EQA programmes are required to "substantially fulfill the relevant requirements of ISO/IEC 17043" [3]. However, where programmes for specific analytes are not available, an alternative approach is required for comparison under ISO15189:2012 and may include the use of (1) a CRM, (2) samples previously examined, (3) material from cell or tissue repositories, (4) exchange between laboratories and/or (5) control materials that are tested daily in inter-laboratory comparison programmes [3]. Each of these alternative options usually does not provide the same rigorous review as the peer comparison process of EQA.

To demonstrate comparability, EQA programmes provide "blind" samples for analysis, the laboratory returns their results to the EQA organiser for statistical analysis and a report is subsequently provided back to the laboratory. Although all EQA programmes aim to improve the quality and agreement of laboratory tests, not all programmes are the same. Variations include frequency of the challenge, the approach to define central tendency (e.g. median, mean or target values) and the allowable dispersion of results (e.g. central 95% of results, two standard deviations on either side of the mean, evidence-based clinical decision limits or based on biological variation data). Ideally, the EQA programme material should be commutable, but in practice, this is not always demonstrated [4]. In addition, to pilot and then fully establish an EQA programme, a sufficient number of laboratories need to participate in order to form a comparison.

There are a number of groups worldwide, including major entities such as the Centers for Disease Control and Prevention (CDC) in the USA and the Cooperation in Science and Technology (COST) in Europe, that include in their objectives the harmonisation of analytes in laboratory medicine [5–9]. As an example, the CDC Vital programme offers a free EQA scheme to support standardisation of nutrient testing for developing economies [9], which is an important process for analytes with a defined clinical decision point such as serum vitamin A [10]. Each of these groups incorporates EQA into the fabric of their harmonisation initiatives. All view EQA as essential for the ongoing assessment of the quality and reliability of testing services, through the calculation of imprecision and bias (systematic error) of the method and the determination of comparative performance. Hence, EQA is not just a pillar but is the central support for on-going harmonisation.

In this issue of *Clinical Chemistry and Laboratory Medicine,* a collaborative process is described for the development of an EQA for serum dihydrotestosterone (DHT), thus forming the first of the five pillars in the quest for harmonisation, standardisation and assay trueness. This analyte is clinically important for the assessment of disorders of sex development. The new EQA provides the first peer comparison of serum DHT measured by mass

spectrometry and immunoassay laboratories. The authors state that, "in the absence of an EQA program, agreement between methods is unknown", and the outcomes of this pilot project demonstrate a clear difference between analytical methods [11]. The paper concludes with the statement that the introduction of this EQA is a significant step in the process of harmonisation as the establishment of this programme provides the first objective worldwide assessment of analytical performance for this important steroid [11].

As DHT is a well-defined molecule, it can potentially be fully standardised with established trueness through a traceability chain. This requires the other four pillars to be implemented. For three of these pillars, the Joint Committee for Traceability in Laboratory Medicine (JCTLM) maintains a database to recognise the pillars of CRM, RMP and reference laboratories [8]. One of the important aspects of the JCTLM is that it provides an independent peer review process and central repository for these reference materials, reference methods and reference laboratories. As part of this review process, EQA participation is deemed essential for reference measurement procedures and reference laboratories. Indeed, ISO 15193 indicates a mandatory requirement for "inter-laboratory comparisons (external quality assessment, proficiency testing)" for reference measurement procedures in clauses 4.16 and 4.18 [12].

Over time, EQA programme participation can improve the quality of laboratory testing [13]. Collectively, information from programmes can be used to (1) reduce bias and improve imprecision of the methods, (2) confirm the quality of analysis, (3) increase the confidence of the laboratory, (4) support the goals of harmonisation and standardisation and (5) provide evidence to confirm best testing practice. This latter point is exemplified in the European COST Action BM1303 – working group 3's "Harmonisation of Laboratory Assessment" to support the "Elucidation on Differences of Sex Development" [5, 11]. In addition to the importance of harmonisation for clinical decisions and ongoing patient care, this COST Action also identifies significant benefits for research through the promotion of optimised serum DHT (and other) assays. This aspect of harmonisation will allow for the pooling of data from different research studies, thus enabling a more rapid translation and implementation of laboratory findings into patient care.

With the globalisation of medical testing, medical diagnostic laboratories can no longer consider result discordance for routine testing. Such harmonisation is not however necessarily true for research or translational research laboratories where method development may be a principle activity. In fact, there is a crisis in translational research with only 20% of findings being found to be reproducible [14, 15]. From the information presented, key stakeholders have not appeared to be aware of processes well applied by diagnostic laboratory medicine that have been developed, including the use of sample exchange or EQA when available. Some contend that there is insufficient funding to do this, but in reality, it is missing from the budget of many funding submissions. In turn, grant reviewers may presume quality without the requirement of objective evidence. Acceptable performance in available EQA would help verify bias and imprecision, which ultimately will support reproducibility and objectivity.

Quality is the way forward. Better quality leads to better medical science, which in turn leads to better patient care. The pilot EQA programme presented in this edition of *Clinical Chemistry and Laboratory Medicine* highlights the importance of incorporating an EQA as an intrinsic part of the laboratory method. Participation in EQA, or at least sample exchange when EQA is not available, should be given high priority for both method validation and on-going harmonisation. This process of result comparison should apply for all laboratories engaged in medical testing, be it diagnostic or translational research.

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