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External Quality Assurance is mandatory for many laboratories but when used effectively it can provide many opportunities for improvement including the following:

- Characterize test bias and imprecision across multiple methods
- Identify interfering substances and quantify their effects across multiple methods
- Provide clinical laboratories with reliable information for replacing unsatisfactory methods
- Identify clinical laboratories that are at risk of poor performance
- Satisfy accreditation and regulatory requirements
- Assessment of method robustness to clinically relevant interference
- Assessment of individual laboratory performance
- Audit of wider aspects of analytical performance and educational activities.

However, because EQA schemes have access to large volumes of method specific data which can be used at a more global level they can assist in the harmonization of methods. This data can be used as a post market surveillance process. But EQA schemes are often tailored to and operate at local level rather than globally and this limits their ability to perform this key role. In this Newsletter's Special Report, Dr Tony Badrick shares his views on how EQA schemes can work together and provide much needed information on an aspect of traceability in laboratory medicine.

The role of EQA in monitoring metrological traceability – a personal view

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The primary role of EQA schemes are to identify poorly performing laboratories and poorly performing methods or a combination of these, for example a poorly performing method(s) in a laboratory with an otherwise history of good performance. Sometimes an EQA scheme will be structured to specifically target the identification of poorly performing laboratories as a component of a Regulatory programme. A categorization of different EQA schemes based on the presence of sample commutability, source of value assignment, and use of replicates has been published by Miller et al (1). Another significant difference between EQA schemes is how acceptable performance is assessed. Based on the primary aim of the EQA scheme both the EQA sample characteristics and the Acceptable Performance Specifications (2) differ, with programs that seek to identify (very) poorly performing laboratories generally having wider allowable limits and ranking at a higher category in Miller's table than schemes that aim to improve overall laboratory performance (aspirational schemes).

Traceability to what?

Metrological traceability is important to laboratories. Primarily a laboratory wants to ensure that they get the same result on a sample as another laboratory using the same sample method and instrument. In this case it doesn't matter if the sample is commutable or not, however it must be stable, reflect the concentrations seen in practice and as patient-like as possible (3). The frequency of EQA samples is also important. The fewer EQA samples there are the greater the impact of blunders (incorrect preparation of the EQA sample, EQA sample mix up/swap, incorrect data entry) or collusion as EQA samples will always be treated differently from patient samples. The fewer the number of samples, then statistically the less accurate is any measure of imprecision or accuracy. The fewer samples, the less of an external monitor of the impact in a method of changes in reagent or calibrator lots and the decreased opportunity to detect error in instrument processes which deal with patient samples and not on-board QC samples (e.g. some auto-dilution steps).

Metrological traceability is also important to the community as we need to ensure that ultimately a (correct) result for any test is the same no matter where or how it is measured. For this to be achieved, commutable samples need to be used and certified reference material (CRM)/reference measurement procedure (RMP) targets assigned. The measurand needs to be identified because in many cases different methods for the same analyte measure different measurands, for example isoenzymes and immunoassays where different antibodies, reagents or calibrators will give a different result for the same patient (3).

EQA and post-market surveillance

How can EQA schemes assist with monitoring metrological traceability? With any EQA scheme, participant results are compared against a measurand mean or median usually within a method group. Individual laboratories can see if they are obtaining the same results as their peers on an EQA sample. The expectation is that the EQA sample is commutable and hence reflects how a patient sample would perform. At this level there is traceability to a method group. If in fact all method subgroups (mean/medians) agree, then the manufacturers have traceability to a common 'standard' which may or may not be a CRM. If the method group means/median are not in agreement, and there is no EQA sample cause (non-commutability or matrix effect) for this effect, then there is a lack of metrological traceability with some or all the methods. If there is no CRM, and no EQA sample effect, then there may be a relationship between the mean/medians of different method groups caused by differences in standardization, antibody target or reaction conditions. These differences are often constant (or proportional to concentration) but will change if the standardization or reagent specificity of a method changes. These changes can be detected by carefully examining shifts in the relationships (mean/median) between these method groups. A change in standardization within a method group may also be detected by a gradual increase in imprecision in the method group as the new calibrator is distributed. Once everyone in the EQA program switches to the new calibrator, the imprecision will decrease and a new relationship with the other method group mean/medians may be established. At this level EQA programs provide a form of market surveillance (4) ensuring that manufacturers are delivering measurement systems that ensure metrological traceability or at least they can serve as a warning of changes in standardization or reagent specificity that may have an impact on patient safety (5).

Structure of different EQA schemes

EQA schemes aiming to improve overall performance rather than identify worst performers will have tighter allowable limits, usually more samples and at a wider measuring range. Identifying best performance means lowest imprecision and bias from a target value (6). Where possible the target value is based on a CRM and RMP and the EQA sample should be commutable. However, not all measurands have CRM or RMP or reference laboratories available despite the ongoing activities of the JCTLM (7). Using RMP and CRM is an expensive process and yet the value of a program in measuring analytical imprecision is dependent on the number of samples measured and the number of participants in the program, which impacts on the cost per sample. Therefore, to achieve the objectives of these 'aspirational' EQA programs will inevitably involve some compromise. It is the need to meet all of these variables that is a challenge for EQA providers.

Role of EQA schemes

There has been great progress with the standardization of assays because of the efforts of manufacturers and professionals (8). The benefits of this work are not only that patients can receive the same result no matter where the sample is assayed, but it allows the possibility of harmonized reference intervals (9, 10) and decision points (11). However, there are real consequences to the lack of standardization of measurement systems now (12). This role of EQA schemes in monitoring the metrological traceability of an assay is vital, but not yet well recognized, let alone implemented (13). In some EQA schemes (14) this role is promoted, but very few schemes are global, and thus their effectiveness is limited. The next step in developing this role requires EQA schemes to co-operate and share results. This is difficult, not only because of the use of different sample materials, but also different measurement classification systems, making comparison complex. However, organizations such as the EQALM (15) are actively working with their member organizations to address these problems (16).

EQA schemes are one of the pillars of 'the temple of laboratory standardization' (17), playing a role just as important as reference laboratories. However, this role should be bigger and is currently restricted by the cost, sample material, frequency of challenges and level of collaboration. The sample material needs to be commutable and have target values set by a reference laboratory where possible. In the medium term this will only cover a small range of measurands, so we will need to accept that the best we can achieve in the short term is harmonization of method results. Disease produces abnormal patient's results, so we can be deluded if we only send EQA samples with results in the reference interval or not at a clinical decision point. Cost will preclude many EQA schemes from being able to produce these types of samples, so collaboration between EQA schemes is essential. Perhaps the best that we can achieve in the short term are some common samples sent to a broad range of instrument groups. Harmonizing EQA Acceptable Performance Specifications is another barrier to global improvement of diagnostic methods. The definition of poor performance needs to be agreed upon. The other variable in EQA schemes is the frequency of EQA samples. The basis and value of conventional QC is being questioned (18) and it may be that patient based real time quality control will finally find a role in clinical chemistry process control (19). With this change in the way assays will be controlled in a laboratory, there is a need to carefully consider how EQA can be used to improve the metrological traceability of results. EQA sample frequency should be related to patient risk just as QC processes must be.

Conclusion

EQA schemes provide strong opportunities for laboratory improvement and staff education about assay variation and the concepts of Quality Control. Many schemes are also an essential component of the Regulatory framework in a country, identifying poor laboratory practice. But EQA schemes can do more both in terms of market surveillance and harmonization efforts. The real power of EQA is that it provides an independent snapshot of the performance of many laboratories and methods regularly. The role of EQA globally as well as locally, is to reduce the risk of the production of erroneous results. This has not been fully realized yet.

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