QUALITY ASSURANCE | Clinical Applications☆

A Taylor, Royal Surrey County Hospital, Guildford, UK; University of Surrey, Guildford, UK

Introduction

Clinical work is concerned with the understanding of disease, its diagnosis, and treatment. Those involved with clinical research or with patient care have a range of disciplines that may be applied to a problem under investigation. Most of these activities require the exercise of skill and expertise whether, for example, it is for surgery in heart disease, radiotherapy to treat cancer, or molecular biology to reveal the genetic basis for disease. Disciplines such as clinical biochemistry, hematology, immunology, will, therefore, focus on disease, diagnosis, and treatment but their application is largely (although not exclusively) associated with analytical procedures. They involve both quantitative and qualitative analysis of specimens of body tissues and fluids – and the interpretation of these results in the light of observations of the patient. The quality of analytical data is crucial to clinical science.

Clinical Analysis

Requirement for quality in laboratory medicine is best illustrated by one or two examples.

1. For healthy subjects, the concentrations of calcium in specimens of plasma will be within the narrow range of 2.2–2.6 mmol 1^{-1} (88–104 mg 1^{-1}). For any single individual the concentration will be maintained within an even narrower range, varying by less than 0.04 mmol 1^{-1}. A concentration increase of no more than 0.1 mmol l^{-1} (4 mg 1^{-1}) or ~4% is sufficient to indicate the presence of pathology of the parathyroid gland with the possible consequence of surgery being necessary for that individual. Thus, calcium in plasma has to be measured accurately and precisely within these ranges and without interferences.
2. Children with the inherited disease phenylketonuria are unable to metabolize a component of their diet (phenylalanine) and will develop irreversible brain damage unless they are provided with appropriate foods. This condition can be diagnosed soon after birth by examination of a small blood sample to detect the presence of phenylalanine. Tragic consequences ensue should there be an error in the test procedure and the diagnosis is missed. Regular inclusion of positive and negative controls is essential to demonstrate the reliability of the procedure.

Quality Management Systems

Clinical chemists were among the first to adopt the concept of analytical quality assurance in the late 1940s. Early studies were simply *ad hoc* distributions of specimens and comparisons of results among a few established laboratories, but they clearly demonstrated large differences in the values obtained. This work revealed for the first time the need for quality assurance, not

☆*Change History:* July 2013. A Taylor updated the section on technical components of quality assurance. Added Table 1.

just in clinical laboratories but also within all areas of analytical chemistry and various quality practices evolved over several years. To provide a common basis for nomenclature and application of quality assurance within hospital laboratories, the International Federation of Clinical Chemistry compiled a series of recommendations in the 1970s while practical procedures were described in several textbooks of clinical chemistry. Meanwhile, important features of management, particularly in the context of preclinical trial work were codified as Good Laboratory Practice. These different themes were eventually picked up in a systematic way in international standards. Thus, ISO 9001:2008 addresses generic issues of 'quality management systems', while ISO/IEC 17025:2005 focuses on the 'General requirements for calibration and testing laboratories'. The requirements of ISO/IEC 17025 were amplified and applied to clinical analysis in a document, 'Essential Criteria for Quality Systems of Medical Laboratories', prepared by the European Communities Confederation of Clinical Chemistry (EC4, www.uni-oldenburg.de/ec4/). A very similar document was published in 2003 as ISO 15189:2003 'Medical laboratories – particular requirements for quality and competence' (revised as 15189:2012). The valuable experience over more than 60 years of quality assurance in clinical analysis is effectively captured in this last standard.

Alongside these developments has been the issue of accreditation, i.e., 'a procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out specific tasks'. Those organizations responsible for accreditation of clinical laboratories draw extensively on the documents referred to above. ISO 9001 refers to a 'process based management system' in which elements of the quality management system (and, therefore, of the work or process being undertaken) are subject to review and improvement to meet the requirements and comments of the user/customer. This may be viewed as a cyclical process where the work of the laboratory is periodically assessed in the light of user statements to modify the way in which the laboratory is organized and managed. A diagrammatic representation of the process of laboratory organization and quality assurance in this way is shown in Figure 1. The components of the cycle can be linked to the standards in ISO 15189:2012 as indicated in Table 1.

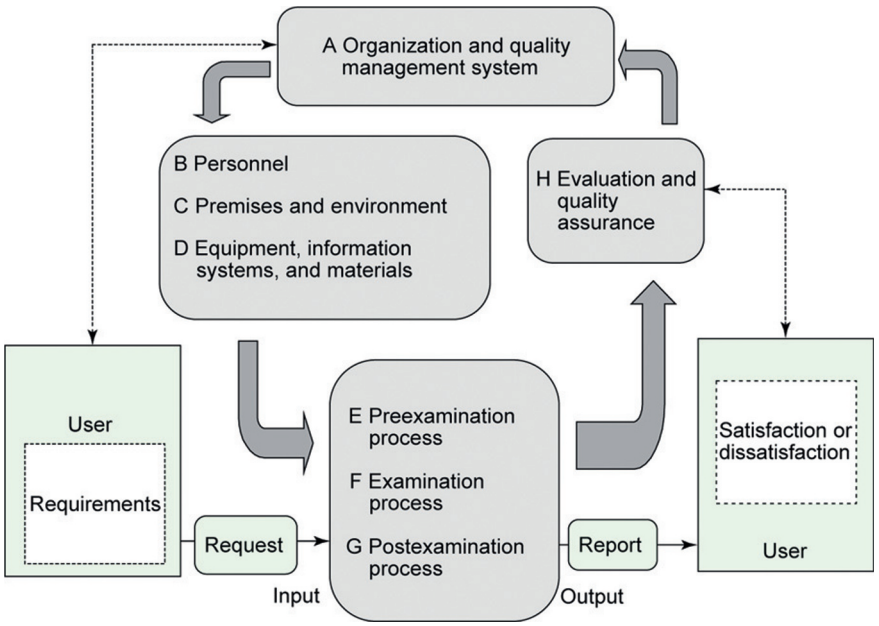

Figure 1 Relationship between a process-based quality management system and the ISO 15189:2012 accreditation standards.

Table 1 Relationship between ISO 15189:2012 standards and aspects of a clinical laboratory quality management system (Figure 1)

Components of quality management system	*Standards in ISO 15189:2012*
A: Organization and quality management system	4.1, 4.2, 4.3, 4.4, 4.13. 4.15, 5.4, 5.7, 5.8
B: Personnel	4.1, 5.1
C: Premises and environment	5.2, 5.3, 5.7
D: Equipment, information systems, and materials	4.6, 5.3, 5.10
E: Preexamination process	4.5, 4.7, 5.4, 5.5
F: Examination process	5.5, 5.6, 5.7
G: Post examination process	4.7, 5.4, 5.8, 5.9
H: Evaluation and quality assurance	4.8, 4.9, 4.10, 4.11, 4.12, 5.6

Practical Approaches to Quality Assurance

Introduction and Terminology

Analysts from different disciplines have adopted slightly different terms and also practical approaches to quality assurance. Recognizing this problem the international organizations for standardization have issued standards and guidelines addressing the definition of terms related to metrology, statistics, and analytical performances (International Vocabulary of Metrology, ISO Guide 99:2007; ISO Guide 30; ISO 3435, parts 1 and 2; ISO 5725, parts 1–6). In addition, a completely new concept has been introduced in 1993, with the ISO Guide on uncertainty of measurement, and, accordingly, the definition of terms related to analytical performances (namely within-run precision, between-run precision, and accuracy) have been revised to take into account this new development. Thus, the term 'accuracy' has been chosen to indicate the closeness of the agreement of an individual result with the 'true' value of the measurand. It is acknowledged that accuracy cannot be measured, but that the 'uncertainty' of measurement associated with a result, i.e., the interval of values that can be reasonably attributed to that measurand, may be determined. A new term, 'trueness', defines the closeness of the agreement of the mean of several results with an assigned value, and can be estimated as 'bias'. 'Precision' is a general term describing the closeness of the agreement between replicate measurements of the same sample by the same method. However, several different factors may affect estimates of precision and the terms 'repeatability' and 'reproducibility' are used to indicate two extreme conditions. Repeatability refers to measurements made under identical conditions, as far as possible (equivalent to within-run precision). Reproducibility is applied to estimates of precision that take account of all possible variables, including laboratories (more or less equivalent to between-laboratory precision). The term 'intermediate precision' refers to conditions lying between these extremes and it is recommended that the variables (time, operators, equipment, reagents, etc.) be indicated. As these terms are used in ISO/IEC 17025 and ISO 15189 it is important to become acquainted with them. The complete definitions of the terms are given elsewhere in this Encyclopedia.

Although it is not universally adopted, most clinical laboratories now refer to 'quality assurance' with internal quality control (IQC) (intended to monitor precision and to detect significant changes in bias) and external quality assessment (EQC) (which can have a number of objectives including retrospective, independent supplementary checks on the effectiveness of the IQC procedures) as its major components. External quality assessment may also be called proficiency testing (PT), especially where laboratories are subject to licensing or approval by an external agency in order to undertake measurements.

Technical Components of Quality Assurance

Validation and Verification of Methods

Method validation is the confirmation, by examination of objective evidence, that analytical procedures are appropriate for their intended use. Performance characteristics to be determined as part of the validation procedure should include consideration of: measurement trueness, measurement accuracy, measurement precision including measurement repeatability and measurement intermediate precision; measurement uncertainty, analytical specificity, including interfering substances, analytical sensitivity, detection limit and quantitation limit, measuring interval, diagnostic specificity and diagnostic sensitivity (ISO 15189:2012). Validation is required where an entirely novel method has been developed, e.g., a procedure for the measurement by liquid chromatography of a new antibiotic agent in specimens of blood, where a validated method has been modified or used outside of the intended scope (e.g. a method for blood used for analysis of pleural fluid).

When a new instrument and/or reagent kit (*in vitro* device) is introduced or is a method taken from peer-reviewed texts or journals, or in international consensus standards or guidelines, or national or regional regulations, the performance characteristics should be independently verified prior to use. Verification programmes should be designed to demonstrate that claims of the manufacturer or authors of methods are replicated in the laboratory and relevant to the intended use of the test results.

While examining these topics further information relevant to necessary frequency of recalibration, suitable IQC protocol, and overall assay weakness will be obtained.

Precision

To measure repeatability one sample is repeatedly analyzed within a single assay batch. From the results given by this exercise the analyst can calculate the mean concentration, the standard deviation (SD), and the coefficient of variation (CV, sometimes referred to as the relative standard deviation, RSD). While there are no fixed number of replicates necessary for this measurement, it is usual to try and obtain at least 20 results, in order to ensure reliable statistics, and the number should always be stated in any description of the method's performance. The experiment should be repeated with further specimens having different concentrations of the analyte so that a clear indication is achieved of the precision over the range of concentrations that is measurable by the procedure (i.e., the precision profile). A similar series of measurements can be made to determine intermediate precision. Factors such as the preparation of reagents and calibration solutions, resetting of instrumental parameters, and the expertise of the analyst will contribute to the analytical variation. Therefore, these measurements should extend over several analytical episodes with changes to reagent batches and analysts. The influence of some of these variables can be critical and, unless great care is taken, the intermediate precision will be very poor. Inevitably, the CVs will be greater than the equivalent repeatability data.

Information derived from these experiments has two purposes. First, it can be decided if the methodological procedure is suitable for introduction into the repertoire of a laboratory. If the analytical variation is in excess of the resolution needed for clinical applications it will not be possible to detect significant changes in patient condition with any certainty or confidence. The method will have to be improved or discarded. This issue of clinical need is separate from quality assurance but can only be understood in the context of good analytical performance. Attempts to quantify the requirements of analytical methods for clinical purposes (quality specifications) have been developed for individual analytes, on the basis of normal intraindividual day-to-day (or hour-to-hour) variations, or as a function of their reference ranges. While these calculations can be helpful, in practice, the fundamental goal is to achieve as good precision as is practicable. Second, the data may be used for IQC protocols and for determination of measurement uncertainty (described later).

Limit of detection (LOD) and limit of quantitation (LOQ)

If the analyte concentration is always at a level that is so high that sensitivity is not a problem, e.g., hemoglobin in blood, calculation of the LOD is unimportant. For a large number of other parameters the concentrations will always be very low. The LOD must be established so that a result can be quoted with an assurance that it has validity and does not represent an extreme of the background 'analytical noise'. With many investigations it is necessary to confirm whether or not a substance (e.g., HIV antibody) is present in the specimen. In these cases the minimum amount that can be determined must be known so that the sensitivity of the analysis can be considered when deciding if further action is necessary. The LOD is influenced by the inherent sensitivity of the instrumentation and by the methodological imprecision. To measure the LOD a specimen giving a reading close to that of the reagent blank should be analyzed with a large number (10–20) of replicates. The concentration equivalent to that of the reagent blank plus three times the SD of the series of results thus obtained represents the LOD. Although the LOD provides information on what can be distinguished from the blank, a high level of imprecision will affect the measurements of concentrations close to the blank. It is therefore sometimes useful to calculate the LOQ, i.e., the lowest concentration of an analyte that can be determined with acceptable precision (repeatability) under the stated conditions of the test. If the accepted level of repeatability is taken as 10%, the LOQ can be calculated from the same series of data as the concentration of the reagent blank plus 10-fold the observed SD.

Measurement interval

A simple experiment involving analysis of a series of standard solutions can provide valuable practical information and show how many calibration standards are needed for an assay, i.e., whether or not the calibration graph is linear, and at what point does the graph flatten out and it becomes necessary to dilute specimens with high concentration of analyte. Regression analysis is not sufficient to establish linearity and visual inspection or the analysis of residues will give more information (ISO 11095).

Analytical specificity and interferences

Most specimens of clinical importance have complicated and variable matrices. As a consequence there are many factors that can influence accuracy and have to be considered in the characterization of new or modified methods. Procedures to establish that a method is providing unbiased results will be considered in a later section but the features of biological systems and clinical specimens that can cause erroneous results include:

- Direct methodological interferences. Serum collected from patients with renal failure has increased concentrations of compounds such as urea while high levels of bilirubin are found in specimens from subjects with liver dysfunction. These are known to interfere (positively and negatively) with many analytical methods. Lipemic specimens cause light scattering that may produce aberrant results in spectrometric assays.
- Metabolites may be more or less active than the parent biomolecule, but a nonspecific methodology that is unable to differentiate between the various forms gives misleading results.
- A biological, protein-based matrix is more viscous and contains a high concentration of dissolved inorganic salts. The complex matrix can reduce the speed of pipetting and lead to differences in handling characteristics by tubing, syringes, etc., when compared with aqueous calibration solutions, and give erroneous results.
- Pathological conditions can give rise to sudden and unexpected large changes in the concentrations of a metabolite to be measured. Dilution of the specimen to allow quantification will adjust other components of the sample and may result in subtle changes to the measurement.
- Very many of the specimens collected for clinical investigation are from patients receiving drug treatment. Interferences associated with pharmaceutical agents or their metabolites are well recognized and documented.
- Measured concentrations can be influenced by characteristics of the methodology. It is usually unwise to rely entirely on data determined elsewhere to define the concentrations within normal populations or associated with particular clinical states. A series of investigations to confirm or establish reference ranges should be undertaken.

At the conclusion of these experiments the analyst should have a complete set of information to characterize the method, with relevant figures of merit, review of interferences, speed and costs of the procedure, and data to indicate more qualitative features such as robustness and the degree of technical skill required for regular use. Allied to this is the defining of information relevant to pre analytical factors such as the patient (e.g., fasting), sample collection (anticoagulants or other additives), sample stability.

Accuracy, Trueness and Measurement of Uncertainty

ISO 15189:2012 requires both the use of validated methods and the estimate of the uncertainty of measurement (i.e., the inaccuracy) associated with the individual results. To fulfill this requirement, determination of the method bias (trueness) is always necessary. In practice, trueness can be examined from two approaches. First, there is the estimate that should be part of the initial validation of the method (or a review if problems are found to have developed). An extension of this involves work with definitive and reference methods, primary standards, and reference materials and the traceability of results to SI units. A statement of the uncertainty of measurement should accompany each comparison and contribute to the estimate of the total uncertainty of measurement of the result. To this aim, manufacturers of *in vitro* medical diagnostic devices are now compelled to give information on the traceability of the results obtained using their products and further developments are to be expected in this field. The second approach to determination of trueness in the medical laboratory involves EQA. This has several synonyms, e.g., interlaboratory comparisons, round-robin exercises, or proficiency testing programs. In part, this work represents an ongoing surveillance of accuracy to supplement the laboratory's IQC program but EQA can fulfill a number of other functions including the provision of materials for which the concentration of analytes is known with reasonably good accuracy. These reference materials can subsequently be used for initial characterization or review of methods, or for the evaluation of instrument performance.

Measurement of trueness

Wherever possible, investigations of the trueness of a method should include analysis of reference materials (RMs). The value of RMs for IQC is discussed below but for studies of trueness it is those RMs with previously determined and well-defined concentrations of analytes that are required. The essential features of RMs, stability, homogeneity, composition of matrix, etc., are reviewed elsewhere in this Encyclopedia, but it is important to indicate here how the concentrations of clinical RMs may be derived and the degree of confidence that can be attributed to the stated levels. Certified reference materials (CRMs) are those with concentrations defined with the smallest uncertainty and thoroughly documented. For clinical applications, however, the determinands that are present in CRMs are few in number and do not include most of those that make up the repertoire of clinical laboratories. Reliance has to be placed, therefore, on the 'assayed quality control' specimens (see below). Manufacturers of these specimens have different practices to determine the 'assayed values'. These include in-house measurements, results obtained by a limited number of expert laboratories, and distribution via an EQA scheme to a large number of laboratories to give consensus data. Almost certainly the assigned concentrations will be given together with an indication of the methodologies so that methodological biases can be taken into consideration. In addition to commercially available assayed RMs, the organizers of EQA schemes usually have specimens that are surplus to the requirements of the scheme. Organizers are generally willing to respond favorably to requests for one or more aliquots of the specimens and the relevant consensus data from the scheme.

A second experiment to investigate trueness is to calculate the recovery of a known amount of analyte added to a suitable specimen. Quantitative recovery from normal biological fluids must be followed by further experiments to determine whether there are interferences associated with pathological specimens. However, recovery experiments are not always possible in the clinical laboratory because many of the items that have to be measured, e.g., enzymes and immunoglobulins, are not available in a purified form.

Further studies on trueness are particularly valuable for newer work when the analyte under investigation is not included in any RM or EQA program. A series of specimens can be exchanged between laboratories and if the results obtained by the partners are not in good agreement the analysts must conclude that there are problems with trueness. This approach does not necessarily reveal interferences or biases associated with the technique and, therefore, it is desirable to take in addition a series of specimens for measurement by the method under investigation and by a method that involves an entirely different analytical technique.

Measurement uncertainty

The uncertainty of a measurement – the interval of values that can be reasonably attributed to that measurand, may be determined from data elaborated during validation or verification. Alternatively, results from internal quality control together with any analyses of certified reference materials or external quality assessment scheme specimens may be used. Worked examples of calculations applied to clinical assays are given in a guide from the National Measurement System Chemical and Biological Metrology Website, *Evaluating Measurement Uncertainty in Clinical Chemistry* (www.nmschembio.org).

External Quality Assessment

Many countries have authoritative, regular, structured provision for EQA for at least general clinical laboratory work (biochemistry, hematology, microbiology). There are also large numbers of specialist EQA schemes, often international, for those analytes measured in fewer laboratories. In addition, schemes to monitor laboratory activities that do not have a quantitative outcome, e.g., histological examination of tissue, the interpretation of analytical data, etc. are available.

As they play such an important role in the assessment of laboratory performance, a number of documents have been produced, suggesting minimal requirements for the managerial and technical aspects of EQA schemes. The issues addressed in these documents have been mainly integrated into ISO/IEC 17043:2010. The ISO standard for the accreditation of medical laboratories (ISO 15189:2012) also indicates that the laboratory should participate in EQA schemes that are substantially compliant with the requirements of the ISO standard.

Organization of EQA schemes consists of up to four components:

- management,
- data reduction,
- preparation of reports,
- assessment of laboratory performance.

Management of the EQA scheme is concerned with procurement and/or preparation and distribution of good quality specimens with analytes at concentrations appropriate for the needs of the participants, and at a volume consistent with usual laboratory routines. The number and frequency of distribution will be determined together with the time allowed for the analysis and return of results.

Data reduction involves the mathematical procedures applied to the results returned by the participants. Methods to determine the assigned values and their uncertainties, including robust statistics, are described in ISO 13528:2005. The consensus mean is most often taken as the assigned value but other approached may be employed. Ideally there should be a procedure to identify 'outliers' – results that are remote from the anticipated value, probably caused by a transcription error or analysis of a different sample. As inclusion of these results could distort subsequent calculations it is useful to apply a robust statistical routine to eliminate these data. Reports usually show the number and range of results, the mean, SD, and CV. In schemes where there are hundreds of participants, sub-routines are included to re-examine results and present these calculations for a specific method or other variable.

The operation of so many EQA schemes, with their own computer programs for the preparation of reports, makes it inevitable that reports will be very different in appearance. Most organizers are so familiar with what they are doing that they are certain that participants will immediately comprehend the significance of all the calculations and information that is laid before them. This is a rash assumption and a clear display, logically laid out on a page with the salient features prominently positioned, is required. Bespoke reports that identify the result from the individual laboratory and its relationship to other participants are preferred. Where schemes include a large number of analytes it is helpful to provide a simple summary of the participants' performance at the front of the report.

While a laboratory can review its own results against those of the other participants and decide if analytical performance is satisfactory, it has been shown that improvements are most effectively stimulated by a more formal independent assessment that includes some kind of measure or score. Scores allow laboratories to be compared and participants can look at their own performance relative to that of other colleagues. Changes in performance over time, within a single laboratory, are also revealed by regular calculation of a score.

As with report formats, performance assessments may be idiosyncratic to a scheme but some consistency in approach is recommended by ISO/IEC 17043:2010 with the use of the z-score, which is

$$z = \frac{x - X}{s}$$

where x is the laboratory result, X the target concentration, and s an appropriate estimate/measure of variability (often described as the standard deviation for proficiency testing) that is selected to meet the requirements of the scheme. The s-value can be determined from data derived from the results of the participants of a particular scheme or in other ways, e.g., the SD achieved by reference laboratories. Scoring systems have undoubtedly prompted enormous improvements in performance and in established schemes that have run for several years; results reported by most participants are in close agreement and indicate good accuracy.

A further step in the application of EQA to laboratory performance is to establish quality specifications, i.e., performance scores that are indicative of good and poor performances and to a degree of quality to which all participants should aspire. Performance assessments are prepared for the benefit of participating laboratories and their users. In addition, performance scoring can be employed to assess the competence of laboratories where licensing is required. Examples of scoring and guidance on how to establish the criteria for proficiency assessment are given in ISO 13528:2005.

The International Federation of Clinical Chemistry Working Group on Quality Control defined the functions of EQA schemes as:

- To supplement a laboratory's IQC procedures.
- To measure the performance of individual laboratories for comparison with other participants, or for changes with time (to which licensing and/or accreditation could be added).
- To obtain consensus concentrations for specimens.
- To investigate features within a laboratory that contribute to performance; e.g., method, size of laboratory, work load, test frequency, equipment, etc.
- To measure the 'state-of-the-art' for a test.
- To act as an educational stimulus.

The first three features in the list have been covered in the previous pages; the remaining aspects, especially that concerned with identification of reliable methods, etc., are relevant to laboratory management (see below).

It was emphasized at the beginning of this article that analytical accuracy is crucial to diagnosis and treatment of many clinical conditions. As with IQC, the laboratory must have a clearly defined policy to describe action taken on receipt of a report from an

EQA scheme. Those involved with organization of such schemes can provide many examples of horror stories where reports have been ignored or deliberately suppressed on receipt, rather than admit that a problem exists. This type of bad and potentially dangerous practice cannot occur if senior managers enforce the policy.

Internal Quality Control

The inherent imprecision of a method will have been determined as part of the validation, as it was implemented within the laboratory (intermediate precision). The information can then be applied to the IQC program that is designed to identify the intrusion of a bias and/or an alteration in the precision of the assay. Factors that can contribute to a bias or change in precision include:

- instrument stability or drift,
- deterioration of reagents,
- errors associated with the calibration material,
- problems with equipment, e.g., partial blockage within a dilutor or a shift in the monochromator calibration on a spectrometer,
- human errors, e.g., use of incorrect reagents, instrument settings, etc.

An IQC program can comprise several elements, but the most usual is to include a specimen(s) with known (or target) concentration/result within each batch, and to take that specimen(s) from a large stable pool so that it can be used in this way over a period of several months or longer. The precision of the method will show the analyst the allowable range of results to anticipate around the target concentration. An acceptance range of $\pm$2SD is usually applied but these limits should not be so wide as to deprive the analysis of useful clinical value, a point that should be evident at the time when the method is developed and introduced into the laboratory repertoire. The practical approach is to draw a Levey–Jennings chart with the results of the IQC specimen(s) plotted (**Figure 2**). A series of decision criteria or 'control rules' have been developed by Westgard (www.westgard.com) for use with this type of chart. Westgard rules guide the analyst as to the number and concentration of IQC specimens to be included, the frequency of inclusion within a test run, and how QC results can be applied to decisions as to whether a run should be accepted or rejected. Results determined for patients' samples should be reported only if the concentration of the IQC specimens satisfies preset criteria, whether the Westgard rules or those set internally by the laboratory.

In addition to the systematic inclusion of quality control specimens as part of the analytical process there are other procedures that can be incorporated into the IQC program. These tests are usually applied to methods that are undertaken on a regular, almost daily, basis. They involve the carry-forward of specimens and the calculation of batch/day means. The sensitivity of daily mean plots is increased by the CUSUM technique.

Some analytical equipment include routines for calibration and quality control of analyses that are predetermined by the software developed by the manufacturers. In these circumstances, the principles and practices elaborated above may be unrealistic and analysts are forced to follow protocols as directed by the equipment.

No clinical laboratory should operate without an IQC program, but whatever approach is adopted the program will fail to have any impact unless it is accompanied by a well-defined policy for further action. The policy will form part of the quality management system and will describe the ways in which results of IQC specimens are to be recorded, the members of staff who should scrutinize these data, and the possible decisions that they can make. The outcomes of a properly implemented IQC program should be the early detection of errors or analytical problems, the maintenance of a known level of performance even if there are changes among staff, departmental routine, or even relocation of the laboratory, and prolonged experience of a procedure that can act as a 'benchmark' against which alternative methods can be compared.

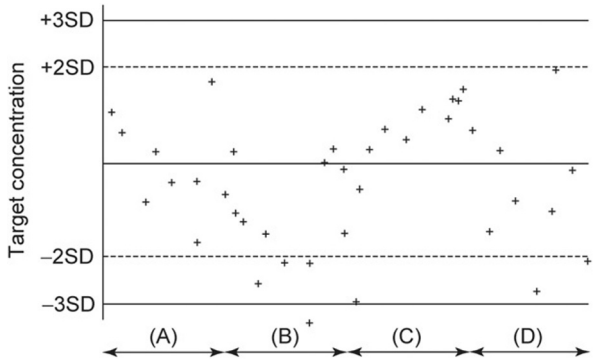

Figure 2 Results for an IQC specimen shown on a Levey–Jennings chart. This example presents four analytical scenarios: (a) good control where points are evenly distributed above and below the target concentration and ~95% are within $\pm$2SD; (b) a sudden shift in accuracy – perhaps the calibration material has become contaminated; (c) a gradual shift in accuracy – perhaps the substrate solution has exceeded the expiry date; (d) very poor precision – perhaps a valve is sticking and causing erratic transfer of sample. Other types of display are proposed from time to time, which are claimed to offer increased sensitivity to detect errors. The Levey–Jennings plot, however, is very widely used.

Managerial Components of Quality Assurance

Laboratory management is typically concerned with general organization and policy arrangements, all of which contribute to quality. This will include selection and training of staff, evaluation, purchase and maintenance of equipment, selection of analytical methods, document control, protocols for clinical investigation, and audit. Other management topics such as preparation and issuing reports, corrective actions, resolution of complaints, risk assessments, and health and safety are equally relevant to quality assurance and all should form part of the departmental quality management system but are outside the scope of this review.

Further Reading

1. Burnsett, D. *A Practical Guide to ISO 15189 Accreditation in Laboratory Medicine*; ACB Venture Publications: London, 2013.
2. International Federation of Clinical Chemistry. Expert Panel on Nomenclature and Principles of Quality Control in Clinical Chemistry. *Clin. Chim. Acta*. **1975**, 63, F25–F38; **1976**, 69, F1–F17; **1977**, 74, F1–F9; **1977**, 75, F11–F20; **1978**, 83, 189F–202F.
3. ISO 11095:1996, Linear calibration using reference materials.
4. ISO 13528:2005 Statistical methods for use in proficiency testing by interlaboratory comparisons.
5. ISO 15189:2012 Medical laboratories – Requirements for quality and competence.
6. ISO/IEC 17025:2005 General requirements for the competence of testing and calibration laboratories.
7. ISO/IEC 17043:2010 Conformity assessment – General requirements for proficiency testing.