Ann. Ist. Super. Sanità, vol. 32, n. 2 (1996), pp. 207-214

Quality assurance in occupational and environmental laboratory medicine

Antonio MENDITTO *(a)*, Pietro APOSTOLI *(b)* and Antero AITIO *(c)*

(a) Laboratorio di Biochimica Clinica, Istituto Superiore di Sanità, Rome, Italy
(b) Cattedra di Medicina del Lavoro, Università degli Studi, Brescia, Italy
(c) Finnish Institute of Occupational Health, Helsinki, Finland

Summary. - In a medical laboratory service, quality assurance (QA) concerns all those actions necessary to provide confidence that the results of laboratory tests will satisfy defined standards for quality. Taking into account the type of testing concerned and the techniques involved, quality assurance will encompass all steps taken to ensure that laboratory results are reliable. It covers the use of scientifically and technically sound practices for laboratory investigations, including selection, collection, transport, identification, storage, preparation and manipulation of specimens and recording, reporting and interpretation of the results. QA refers also to other activities designed to improve the reliability of investigations such as staff training and management, evaluation of the adequacy of the laboratory environment, maintenance and calibration of instruments and the use of technically validated and properly documented methods. All these activities should be described in a quality manual. This document is a prerequisite to obtain certification of the quality system or laboratory accreditation, according to the International Standard ISO 29000 series or the European Standard EN 45001, respectively.

Key words: quality assurance, quality system, certification, accreditation, laboratory medicine, occupational and environmental medicine.

Riassunto (*Garanzia di qualità delle analisi di laboratorio in medicina occupazionale ed ambientale*). - Nei laboratori di analisi cliniche, la garanzia di qualità (quality assurance, QA) comprende tutte le procedure e le operazioni necessarie ad assicurare che i risultati di test ed analisi raggiungano adeguati livelli di qualità. Tenendo conto del tipo di analisi e delle tecniche analitiche coinvolte, la QA considera tutti gli accorgimenti che devono essere presi per garantire la affidabilità dei risultati. Vengono presi in esame l'utilizzazione di pratiche di laboratorio (adeguate sia da un punto di vista tecnico che scientifico) per la selezione, la raccolta, il trasporto, l'identificazione, la conservazione, la preparazione, la manipolazione e l'analisi dei campioni, nonché l'archiviazione, la presentazione e l'interpretazione dei risultati. La QA comprende anche altre attività volte a migliorare l'affidabilità delle indagini di laboratorio, quali, tra l'altro, l'educazione ed il tirocinio del personale, la valutazione della adeguatezza degli ambienti, la manutenzione e la calibrazione degli strumenti e l'uso di metodi propriamente documentati e validati. Tutte queste attività devono essere descritte nel manuale della qualità. Questo documento è un prerequisito per ottenere la certificazione del sistema di qualità e l'accreditamento del laboratorio, rispettivamente secondo le norme internazionali della serie ISO 9000 o la norma europea EN 45001.

Parole chiave: garanzia di qualità, sistema qualità, certificazione, accreditamento, medicina di laboratorio, medicina occupazionale e ambientale.

Introduction

In the field of health care, the demand for quality - defined by the International Organization for Standardization (ISO) as the totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs [1] - by various components of society (including individual subjects, patients, physicians, researchers, administrations, governmental authorities and scientific organizations) is continuously increasing. The needs, stated or implied, which may be different for each component of society should be identified also by laboratories operating in the field of occupational and environmental laboratory medicine.

Society, in its broader sense, asks for tests which, being as safe as possible, guarantee both reliable and useful results and a good ratio between benefits and costs. The individual subject or the patient will not desire to undergo stressful or time-consuming investigative procedures; physicians will focus their attention on practicability (turn round time), sensitivity, specificity and predictive value of tests, while laboratory management and administration will look for safety of both workplace environment and procedures. The administration will also verify that tests generate an income, and national and international authorities will ask for information useful in the formulation of laws and regulations for the protection of both humans and the

environment. Finally analysts will have a particular attention on metrological aspects. Faced with all these needs, the laboratory has to ensure and demonstrate that the service provided is of adequate quality.

At present in the European Union (EU), recognition of the quality of services provided by a laboratory, and more generally, of the competence of a medical laboratory to perform analyses, is not needed by law. Formal recognition is obligatory only when good laboratory practice (GLP) is required for toxicological studies in animals and other biological systems. However, the increasing demand for quality in health care related activities and the competition among medical services in the EU will render the recognition of competence, in the form of certification or accreditation, a powerful marketing tool.

Recognition of competence: certification of the quality system and laboratory accreditation

To obtain a certification of the quality system, the applicant laboratory should define the properties of its quality system within the framework of the International Standard ISO 9000 series or the European Standard EN 29000 series. The certification body recognizing the competence ensures that the requirements are fulfilled by means of external quality audit. The quality system includes all the procedures necessary to provide an appropriate service. The guidelines on quality management and quality system elements for services are outlined in the ISO 9004 part 2 [2], and in the EN 29004 part 2 [3] which are identical. In these standards - which define the principles and the elements of a quality system, i.e, the quality system itself, quality policy, quality management, quality control and quality assurance - medical laboratory services are considered and mentioned specifically among health care services. The objectives and the key elements of a quality system are: a) management responsibilities; b) personnel and material resources; c) quality system structure; and d) interface with the client. Management establishes a quality policy, identifies quality goals, establishes responsibilities and authorities for quality, provides the necessary structures, procedures, and material resources, and monitors the achievement of the quality goals, through quality audit. Personnel, one of the major resources in a medical laboratory service, should be motivated, e.g., through continual education and training. Knowledge and competence in the field of communication is particularly important. The quality system structure provides control and assurance over all processes and actions which may affect the quality of the service. The prevention of errors and feedback from suppliers, customers, and inspectors for quality audits are also stressed. The quality system must be described in the quality manual (see below).

Laboratory accreditation is defined by ISO [1] as the formal recognition that a testing laboratory is competent to carry out specific tests or specific types of tests. Test is defined as the technical operation that consists of the determination of one or more characteristics of a given product, process or service according to a specified procedure. The ISO/IEC Guide 25 [4] and the European Standard EN 45001 [5] formulate the general requirements for the competence of analytical laboratories. These standards give detailed instructions on the laboratory organization and management, and also on the main components of quality management, i.e., quality system, audit and review. The quality system is described in the laboratory quality manual and its attachments. Compliance to procedures specified in the quality manual is verified in audits at specified intervals and the appropriateness of the quality system adopted is reviewed at least once a year by the management. Some problems which may arise in chemical laboratories, and which are not envisaged in the EN 45001 [4] have been outlined in a document issued by the Western European Laboratory Accreditation and Cooperation (WELAC) and the European Association for Analytical Chemistry (EURACHEM) [6].

Concerning accreditation, the general criteria for the assessment of testing laboratories and the general criteria for laboratory accreditation bodies are outlined in the European Standards EN 45002 [7] and EN 45003 [8], respectively.

Needs and possibilities of quality assurance, accreditation and certification for clinical laboratories have been recently reviewed by Dybkaer [9].

Quality manual

According to ISO, the quality manual is a set of documents describing the organisational structure, responsibilities, procedures and processes by which the laboratory achieves its objectives and carries out the quality management [1]. A quality manual is an essential element for both quality management and accreditation, according to EN 29004 [3] and EN 45001 [5], respectively. The quality manual has three main sections: a) quality policy statement, i.e., a statement by the head of the laboratory, indicating the commitment to implement and maintain a high standard of quality in the laboratory; b) description of the organization and the responsibilities and authority of each component of the staff; c) work instructions, i.e., description of the actual measurement procedures and other detailed administrative and technical procedures which are necessary for the laboratory work. Compliance of the work done in the laboratory with the quality manual and the procedures described in it are verified at appropriate intervals by means of quality audit. Audits shall be carried out by trained and qualified

persons who are, wherever possible, independent of the activity to be audited. Review of the quality system shall be carried out at least once a year by the laboratory management in order to introduce the necessary changes or improvements so as to ensure a continuing suitability and effectiveness.

Guidelines for the implementation of a quality manual for the clinical laboratory have been proposed by Dybkaer *et al.* [10].

Quality assurance

Quality assurance (QA) is defined by ISO as all those planned and systematic actions necessary to provide adequate confidence that a product or a service will satisfy given requirements for quality [1]. Taking into account the type of testing concerned and the techniques involved in the field of laboratory medicine, QA will encompass all steps taken to ensure that laboratory results meet defined standard of quality and are reliable. It covers the use of scientifically and technically sound practices for laboratory investigations, including selection, collection, transport, identification, storage, preparation and manipulation of specimens and recording, reporting and interpretation of the results. QA refers also to other activities designed to improve the reliability of investigations such as staff training and management, evaluation of the adequacy of the laboratory environment, record keeping, maintenance and calibration of instruments and the use of technically validated and properly documented methods. Internal and external quality control are part of overall QA and deal with verification that errors in analytical data issued from the laboratory are of a magnitude appropriate for the specific requirements or needs of the user.

QA should not be viewed as an abstract concept and must be adapted taking into account the specific requirements of each type of measurement and testing procedure. Each analytical procedure implies a certain degree of accuracy and consequently different QA procedures are necessary. In addition, the inherent accuracy of an analytical approach may vary according to analyte levels, i.e., those found in the general population or in occupationally exposed subjects. Another important aspect is the context in which test results will be used. The quality requirements could be different depending on whether test results are used for diagnosis and prognosis of toxicity, procedures of risk assessment, epidemiological studies, research activities or for routine controls.

Measurement uncertainty: error, imprecision and bias

Measurement, at least in practice, cannot be free from imperfections which in turn give rise to an error in its result: the error is viewed as having two components namely random and systematic. The latter has mainly two levels-persistent bias and run effect. The persistent bias, when small in relation to random error, may be identifiable only after a long operation time and might be regarded as tolerable, provided it is kept within prescribed bounds [11]. The run effect is exemplified by a deviation of the analytical system during a particular run. When large, this effect will be identified by IQC as an out-of-control condition [11]. After correction for all recognized systematic errors, the residual errors generate the so called "uncertainty", which can be defined as the parameter, associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand. It reflects the lack of knowledge of the true value of measurand. The uncertainty must be estimated on the basis of the statistical distribution of the results of series of measurements and can be characterized by experimental variances. Since the variances of the true value and the persistent bias are both zero, in the absence of gross errors, the variance of the random error (within run) and the variance of the run effect and the value of the persistent bias fully describe an analytical system in control [11]. Estimates of other components can only be based on experience or other information, leading to assumed probability distributions that are also characterized by variances.

Imprecision is caused by slight variations during the analysis such as those related to weighing, volumetric delivery, variation in the timing of mixing for extraction or changes in instrument functioning. Imprecision is also affected to a great extent by the training and skill of the analyst. Imprecision is typically dependent on the concentration of the analyte being measured: it is highest at or near the limit of detection, decreases with increasing concentration, but tends to rise again, when the concentration becomes very high.

The analytical imprecision is not constant. It is smaller when replicate analyses are carried out in the same laboratory by the same person and instrument, using the same reagents and standards (repeatability conditions) and larger when the same methodology is applied in different laboratories by different operators and different equipments (reproducibility conditions). Analytical bias is caused by contamination or by shortcomings in specificity, recovery, or calibration [12]. Contamination is an inadvertent addition to the specimen of an amount of the analyte during the analysis and may be derived from reagents, as well as from pre-analytical and analytical procedures. Specificity is the ability of the analytical method to measure exclusively the analyte of interest. The specificity of any analytical method varies widely and may be achieved by specific detection (e.g., specificity of the mass of the molecule in mass spectrometric analysis), or by sample purification (extraction procedures, chromatographic methods) and it is strongly dependent on the matrix. Pretreatment may inadvertently decrease the specificity of an analysis. Recovery is the proportion of the analyte in the sample that reaches the

final step in the analysis and is measured. Recovery for standards prepared in pure solvents may be different from that observed in a biological matrix or also among different samples (e.g. urine specimens with different pH or osmolality).

Trueness of the end result is crucially dependent on the actual concentration of the calibration standard, which in turn depends on the purity of the chemical, on the accuracy of the dissolution and the dilution process and on the instability of the standard solution. Traceability of the standard chemical and the instruments to prepare the standard solution is a way to monitor the accuracy of the standard solutions.

Analytical methods

Definitive and reference methods are placed at the highest metrological level and are used for assessing the accuracy of routine methods. A definitive method is one which, after exhaustive investigations, is found to have no known sources of bias or ambiguity whereas a reference method is a method which shows negligible bias in comparison with its imprecision [13, 14]. The most striking differences between the definitive-reference level and the routine level are: a) method-dependency of the results; b) the sensitivity to matrix effects; and c) calibration by means of primary and secondary calibrators, respectively.

Traceability of reference method's accuracy to that of definitive method has to be guaranteed and continuously monitored through the use of certified reference materials (CRM, see below). Traceability of the routine method's accuracy to that of the reference methods may be assessed by using other reference and control materials. An important requisite of reference materials and in general of control materials is the commutability, i.e., the ability to exhibit the same properties (like bias) as that demonstrated by human specimens. Lack of commutability may result from the interaction of method sensitivity with the matrix or from matrix differences between the control material and biological specimen. Definitive and the reference methods are insensitive to the matrix and can be expected to give reliable results when applied to different materials whereas for the routine method the commutability of the control materials has to be demonstrated.

Reference materials (RM)

According to ISO, a RM is a material or substance, one or more properties of which are sufficiently well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials [15]. A CRM is a RM one or more of whose property values are certified by a technically valid procedure, accompanied by, or traceable to, a certificate or other documentation which is issued by a certifying body [15].

RMs and CRMs are available from many national and international organizations. Concerning trace elements in body fluids, freeze-dried urine, blood, and human serum are available from the National Institute of Standard and Technology (NIST, USA); lyophilized bovine blood is available from the European Community Standards Measurement and Testing (SM&T, EU, formerly Community Bureau of Reference, BCR); lyophilized animal blood is available from the International Atomic Energy Agency (IAEA, Austria); bovine blood, lyophilized human urine and bovine serum are available from the Laboratory of the Government Chemist (LGC, UK); lyophilized human urine, bovine blood and bovine serum are available from the National Research Centre for Certified Reference Materials (NRCCRM, Peoples' Republic of China); lyophilized bovine blood, human blood and urine are available from Kaulson Laboratories, Inc (USA); lyophilized human blood, serum and urine are available from Nycomed Diagnostica (Norway); lyophilized human blood is available from Referensmaterial AB (Sweden); bovine blood is available from Trace Laboratories Ltd (UK). A RM for trace elements and some organic compounds (ALA, hippuric acid, mandelic acid, pentachlorophenol, phenol and trichloroacetic acid) is available from Bio-Rad, ECS Division (USA).

CRMs may be used to verify the precision and trueness of analytical methods and their use is an important part of the initial assessment of analytical methods. Best information from the use of a CRM is obtained, when the CRMs have an identical matrix, and are available in a concentration range similar to that appropriate for samples that will be analyzed using the method under study.

Concerning RMs, it is often difficult to know, how well the stated concentration value estimates the true value, and therefore, these reference materials are best suited for precision studies, their analysis may only give a rough estimation of the trueness of the analysis.

Quality control (QC)

The ISO definition of QC is "the operational techniques and activities that are used to fulfil requirements for quality". As a part of their quality system, and to monitor analytical performance, laboratories should operate systematic internal quality control (IQC) checks and participate wherever possible in external quality assessment (EQA) schemes. All these operations should be clearly defined in the quality manual.

Internal quality control (IQC). - IQC is defined as the set of procedures undertaken by laboratory staff for the continuous monitoring of operation and the results of measurements in order to decide whether results are reliable enough to be released [11]. IQC primarily monitors the accuracy of results on quality control materials, and precision on independent replicate analysis of test materials. Internal quality control procedures

depend mainly on repetitive analysis of samples designed for IQC purposes. In the simplest form, the differences of results from duplicate samples are continuously monitored. The range of the results gives an indication of the imprecision of the method. More information may be derived from several replicate analyses of the same homogeneous control specimens; they provide information in addition to imprecision, also on changes in bias. As a minimum, one such analysis should be included in every analytical run.

The material used for IQC should have a matrix similar to that of the routine samples. For a number of analyses in biological monitoring, e.g., head-space analyses of volatile solvents in the blood, stable quality control materials with an appropriate matrix are not available. In these cases, a formulated aqueous control specimen can be prepared and used separately from the calibration standards. For some analytical methods, commercial RMs are also available and may be used in internal quality control. One purpose for the internal quality control is to give an alert when an analysis is no longer functioning as expected. This alert is based on the finding that a result obtained in a control analysis does not belong to the random variation of the method. In addition, unacceptable variation between the duplicates of a specimen, or lack of linearity of the calibration curve may be used as an indication of abnormal analytical performance. It is mandatory that quality control charts are developed for each analysis (with established criteria of acceptability for control analyses) and continuously updated.

External quality assessment (EQA). - EQA is also a part of the quality system and aims at checking laboratory performance by means of interlaboratory comparisons. Such activities have their roots in informal exchange of specimens among laboratories in order to verify and improve laboratory performance, and in a large number of *ad hoc* comparative studies of laboratory performance, usually on a specific analysis.

Recently, guidelines for the optimal operation of proficiency testing schemes have been published [10, 11]. According to IUPAC, ISO and AOAC [11] the ideal structure of an external quality assessment scheme should be as follows:

1) coordinator organises preparation, homogeneity testing and validation of test material;

2) coordinator distributes test samples (analyte concentration unknown to the participant) on a regular schedule;

3) participants analyse test portions and report results centrally;

4) results are subjected to statistical analysis, and the performance of the individual laboratories is assessed;

5) participants are notified of their performance;

6) advice is made available for poor performers, on request;

7) coordinator reviews performance of the scheme.

The test material used in EQA must be similar to the materials that are routinely analysed as far as the matrix, and concentrations of the analyte are concerned. It must be homogeneous, stable, and preferably non-infective; in any case the coordinator should consider any hazard that the test material might pose and take appropriate action to advise any party that might be at risk of the potential hazard involved [11].

The exact chemical identity of the analyte must be carefully considered in relation to the analysis performed and the aim of the analysis: the analyte in the control material used for the quality assessment of the biological monitoring method of exposure to phenol, should be in the form that it appears in the urine of workers exposed to phenol, i.e., phenylglucuronide and phenylsulphate.

The frequency for the distribution of samples in a scheme depends on the availability of suitable materials in large amounts, consistency of results from previous rounds, cost/benefit ratio of the scheme, laboratory turn-round time of analyses and difficulty in executing analytical quality control. According to IUPAC, ISO and AOAC [11], the optimal frequency is probably between once every two weeks and once every four months. A frequency greater than once every two weeks would be not cost effective and would also encourage replacement of IQC by the EQA. A frequency lower than once every four months will cause unacceptable delays in identifying and correcting analytical problems and will not allow to monitor meaningful trends in laboratory's performance.

The target (assigned) values for control samples can be established by means of four different approaches: a) consensus values from expert laboratories; b) directly by formulation, i.e., by adding a measured amount of the analyte into a base matrix which does not contain it at all; c) direct comparison with appropriate CRMs; d) consensus values obtained by participating laboratories, provided that the number of laboratories is large enough [11].

External quality assessment schemes in occupational and environmental laboratory medicine. - Concerning countries outside Europe, various organizations run EQA schemes for inorganic and organic compounds. The Centre de Toxicologie du Quebec operates an interlaboratory comparison programme for cadmium and lead in blood; aluminium, selenium, copper and zinc in serum; arsenic, fluoride, mercury, cadmium and chromium in urine [16].

In Japan, biological monitoring is obligatory for all workers exposed to lead, toluene, xylene, trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane, styrene, dimethylformamide or n-hexane. Since 1980, the Japan Federation of Occupational Health Organization has been running an EQA scheme (one round per year). In 1991, 36 to 67 laboratories participated in EQA schemes for Pb and FEP in blood, and ALA, hippuric acid, methylhippuric acid, total trichlorocompounds, TCA, mandelic acid, monomethylformamide, and 2,5-hexanedione in urine [17].

The EQA schemes operating in various countries in Europe are described in detail in various papers published in this issue [18-28].

Standardization

The aim of measurement standardization is to ensure that the measurement of the same analyte in the same samples, made at different places or at different times, can be readily compared. Standardization is essential not only for diagnosis and monitoring of the individual, but also for epidemiological studies. Standardization is especially desirable for analytical techniques such as immunoassays in which the EQA schemes have shown great variability. Theoretically perfect comparability is achieved when the true value of the analyte in the sample can be measured, within known limits of confidence. This ideal goal can be achieved in a small number of cases, when extremely accurate methods and reliable RMs are available. In most cases this goal can only be approached. This is the reason why the target value is usually reached by consensus.

Since for the majority of analytes neither definitive nor reference methods are available, the consensus can be achieved by applying a method to the same samples containing the analyte (calibrators and specimens). In this case at least one well studied common calibrator must be distributed.

When considering complex substances, such as biological molecules and especially macromolecules, the definition as analyte may not be so clear, because of their potential intrinsic or acquired heterogeneity. For example an enzyme, in most instances, is assayed by determining its catalytic activity. However, different isoenzymatic forms may be present which may or may not have the same quantitative catalytic activity. From the user's point of view, these different isoenzymes may not be considered equivalent. In immunoassays, a wide variety of molecules with similar immunoreactivity may coexist in samples, but they may have a very different diagnostic significance.

Then in immunological determinations, the analyte is an epitope rather than a molecule.

Interpretation of data

A variety of information may be necessary for a correct interpretation of laboratory data. For each biological marker, apart from some indications on the uncertainty of analytical results, reference, permissible and intervention values, and specificity, sensitivity and predictive values should be established.

The most frequent statistical evaluation of data is carried out by means of descriptive statistics. Mean and its confidence interval, variance, standard deviation, skewness and kurtosis are used to fully describe a normal distribution. For analytes showing an asymmetric distribution, median and its exact confidence interval, and centile are often used; however it would be preferable to operate a log-normal transformation of data in order to derive the geometric mean and the geometric standard deviation. These approaches are useful for the establishment of reference values in non-exposed subjects and in the establishment of permissible and intervention values.

Descriptive statistics provide valuable information but are often not sufficient to characterize the behaviour of biological indicators; in these cases a multivariate approach may be adopted. Multiple regression evaluates the inter-dependence of variables (independents and dependent) according to a given fitting (usually linear) model, using the information contained in the correlation matrix of data. The analysis can be performed according to two categories of method of different complexity: discriminant analysis, where the objects are classified into known prototype classes, and cluster analysis, where the unknown classes are also identified through an iterative process of refinement.

The "yes/no" classification is frequently adopted in assessing the significance of effect indicators. In this procedure the results are given directly by the untransformed analytical signal (analytical and biological information coincides). In most cases continuous variables are transformed into dichotomous variables through the adoption of a cut-off point. This qualitative expression of results involves both some ambiguity of classification (reactive/non reactive, positive/negative, pathological/normal) and a loss of information content of analytical data. In a binary classification, the comparative evaluations and trend analyses become more difficult. For example the repeatability and reproducibility are not very informative, in respect of the estimation of results in quantitative assays. However the "yes/no" classification allows establishment of the sensitivity, predictive values and specificity of a test.

A laboratory test may be evaluated by means of several cut-off points. Hence it may be useful to compare the sensitivity and specificity of alternative laboratory tests over a range of possible cut-off points. The receiver operating characteristic (ROC) curve plots the rate of true-positive tests versus the rate of false-positive tests at different cut-off points [29, 30].

By plotting the ROC curves of each of several alternative tests, one can determine which test is best in discriminating the effect by the non effect. When two or more laboratory tests are so plotted, the test whose ROC curve is further up and to the left is best as discriminant because for any given true-positive rate, it has the lower false-positive rate and vice versa.

ROC curves are also helpful in making an estimate of optimum cut-off points for required values of sensitivity and specificity. The cut-off point for which the sum of sensitivity and specificity reaches a maximum is called "point of maximal information".

Conclusions

Laboratory measurements are widely used and are essential in the practice of occupational and environmental medicine. Laboratory data have a key role in the field of prevention (for exposure assessment and risk assessment, and health surveillance) and in the diagnosis and prognosis of toxicity. In spite of this, adequate procedures of quality control and programmes of external quality assessment are available for only a few determinants. Analytical methods are often not rigorously characterized, documented or validated and for some tests, e.g. measurement of biomarkers of effect, interlaboratory comparisons have shown that the analytical performances are far from being optimal.

A laboratory which provides data in the field of occupational and environmental medicine is faced every day with a series of complicated and often new problems. Advanced technologies and methods which allow the solution of challenging analytical problems require stringent QA and QC. Owing to this, procedures and actions used for QA need to be improved and continuously updated. Over the last few years the theoretical and methodological aspects of QA have been greatly developed and the production of documents related to: definition of terms and standardization, operation of testing laboratories, harmonized protocols for interlaboratory comparisons and external quality assessment schemes has greatly increased.

The laboratory service should demonstrate and document its QA procedures and aim at a recognition of its competence by means of certification of the quality system or accreditation. The director and the management of the laboratory may proceed in a step by step manner, having previously acquired a licence by national institutions. The first step should be participation in external quality assessment schemes for as many analytes as possible. Then should be the production, implementation, periodic review and audit of the quality manual, taking into account the guidelines issued in international and European standards. The final step will be obtaining an official ISO 9000 certification of the quality system, the formal recognition by an accreditation body or an official accreditation according to the European standard EN 45001.

Submitted on invitation.
Accepted on 1 February 1996.

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