Eurachem & CITAC

Co-Operation on International Traceability in Analytical Chemistry

EURACHEM / CITAC Guide

Guide to Quality in Analytical Chemistry

An Aid to Accreditation

Third Edition

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Eurachem

A focus for analytical chemistry in Europe

CITAC

Co-Operation on International Traceability in Analytical Chemistry

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Guide to Quality in Analytical Chemistry: An Aid to Accreditation

English edition

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Contents

Foreword

This edition is a revision of the CITAC/Eurachem Guide published in 2002. The 2002 edition was developed from CITAC Guide 1 (which in turn was based on the Eurachem/WELAC Guide).

This revision reflects changes that were introduced with the publication of the 2005 version of ISO/IEC 17025. The terminology has also been updated to take account of ISO/IEC 17000:2004, ISO 9000:2015 and the 3rd edition of the International Vocabulary of Metrology – Basic and general concepts and associated terms (JCGM 200:2012 – VIM).

The Guide focuses on the requirements of ISO/IEC 17025, however the content should also be of use to organisations seeking accreditation or certification against the requirements of standards such as ISO 15189 or ISO 9001, or compliance with the Principles of Good Laboratory Practice. Similarly, although the Guide has the title 'Guide to Quality in Analytical Chemistry' it is anticipated that it will also be of benefit to disciplines other than chemistry. For those working in microbiology, it should be noted that Eurachem has published a Guide specifically for microbiological laboratories.[†]

The Guide will also provide useful information both for laboratories that wish to establish a quality management system but are not seeking formal recognition, and for those involved in education and training.

The 2002 edition of the Guide contained an extensive reference and bibliography section. For ease of management, the bibliography section in this edition contains only literature cited in the text. Additional documents related to accreditation and quality assurance can be found in a 'reading list' under the menu item 'Publications' on the Eurachem website at www.eurachem.org.

[†]M. Eleftheriadou and K. C. Tsimillis (eds.), Eurachem Guide: Accreditation for microbiological laboratories (2nd ed. 2013), ISBN 978-91-87017-92-6. Available from www.eurachem.org.

Abbreviations and symbols

The following abbreviations, acronyms and symbols appear in this Guide.

AMC	Analytical Methods Committee of the RSC
AOAC International	a globally recognised standards developing organisation
BIPM	International Bureau of Weights and Measures
CITAC	Cooperation on International Traceability in Analytical Chemistry
CLSI	Clinical and Laboratory Standards Institute
CRM	certified reference material
EA	European cooperation for Accreditation
EC	European Commission
EQA	external quality assessment
EU	European Union
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GUM	Evaluation of measurement data – Guide to the expression of uncertainty in measurement
HPLC	high performance liquid chromatography
IEC	International Electrotechnical Commission
ILAC	International Laboratory Accreditation Cooperation
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JCGM	Joint Committee for Guides in Metrology
k	coverage factor (used in the calculation of expanded uncertainty)
LIMS	laboratory information management system
LOD	limit of detection
LOQ	limit of quantification
MLA	Multilateral Agreement
MRA	Mutual Recognition Arrangement
OECD	Organisation for Economic Cooperation and Development
OIML	International Organization on Legal Metrology
PCR	polymerase chain reaction
PVC	poly vinyl chloride
QA	quality assurance
QC	quality control
QMS	quality management system
RSC	Royal Society of Chemistry (UK)
PT	proficiency testing

RM	reference material
s	standard deviation
SI	international system of units
SOP	standard operating procedure
u	standard measurement uncertainty
U	expanded measurement uncertainty
UV	ultraviolet
VCM	vinyl chloride monomer
VIM	International vocabulary of metrology – Basic and general concepts and associated terms
WHO	World Health Organization

1 Notes for the reader

1.1 Aims and objectives

1.1.1 The aim of this Guide is to provide laboratories with guidance on best practice for the analytical operations they carry out. The guidance covers both qualitative and quantitative analysis carried out on a routine or non-routine basis. A separate Guide covers research and development work [1].

1.1.2 The guidance is intended to help those implementing a quality management system (QMS) in a laboratory, in particular those seeking accreditation against the requirements of ISO/IEC 17025 [2]. For those working towards accreditation it will help explain the meaning of the standard. The guidance will also be useful to organisations seeking accreditation or certification against the requirements of standards such as ISO 15189 [3], ISO 15195 [4] or ISO 9001 [5], or compliance with the Principles of Good Laboratory Practice (GLP) [6] or Good Manufacturing Practice (GMP) [7], and to those involved in the assessment of analytical laboratories against those requirements. The Guide should also be of value to those involved in education and training.

1.1.3 This Guide concentrates on the technical aspects of the quality management of a laboratory, with particular emphasis on those areas where interpretation is required for chemical testing or related measurements. The aspects of quality management not covered in detail by this Guide (for example contract review, records, reports and complaints) are fully addressed in other documents, such as ISO/IEC 17025 [2].

1.2 Terminology

1.2.1 In the revision of this Guide one of the main areas of focus has been the updating of terminology to reflect developments since the previous edition, published in 2002. The Guide follows, where possible, the terminology defined in ISO/IEC 17000 [8], ISO 9000 [9] and the 3rd edition of the VIM [10]. This has been supplemented, where necessary, with terminology used in ISO/IEC 17025 [2].

However, in some cases, it may be difficult to decide which term to use when several similar terms are in use. For clarity, it is considered important to use a term consistently throughout the Guide. One example is the term used to describe the document that gives a detailed description of the method used in a laboratory. For quantitative analysis VIM refers to the measurement procedure, in ISO/IEC 17025 this is referred to as the method, in ISO 15189 [3] it is the examination procedure and many laboratories refer to their standard operating procedure (SOP). In line with other recent Eurachem guides the Task Group has decided to adhere to ISO/IEC 17025 and use the generic term ‘method’. The term ‘concentration’ is used on its own (i.e. unqualified) when a generality is required. In the Guide this term should be taken to represent a family of terms which includes mass fraction, mass concentration, amount of substance concentration, etc.

The terms in VIM related to analytical chemistry are further explained in the Eurachem Guide ‘Terminology in analytical measurement’ [11].

2 Introduction

2.1 Every analytical measurement must produce a result that is sufficiently accurate to allow the user to make appropriate decisions; it must be fit-for-purpose. Every laboratory, no matter the field of analysis, is aware of the need for quality assurance of its results. Over the last decades agreement has been reached as to what is required to achieve quality. The starting point is to use a method that has been validated. The values for the key performance parameters (e.g. precision, bias) obtained during method validation provide a source of values to input into the measurement uncertainty evaluation of the results obtained using the validated method. This is still insufficient knowledge to enable the producer of the result to claim that this result can legitimately be compared to a result obtained in another laboratory or at a different time. To enable this assertion to be made one needs metrological traceability. Method validation, measurement uncertainty and metrological traceability are pivotal for achieving a reliable result and that is the reason they appear in ISO/IEC 17025 [2]. However they are essential in all laboratories (large and small) irrespective of accreditation requirements. To help laboratories there are guides available on the Eurachem website covering method validation, measurement uncertainty and metrological traceability [12-14]. This Guide indicates where method validation, measurement uncertainty and metrological traceability fit into quality assurance.

2.2 Appropriate quality management aims to enable a laboratory to show that it has adequate facilities and equipment for carrying out specific analyses and that the work was carried out by competent personnel in a controlled manner, following a documented validated method. Quality management should focus on the key issues which determine the quality, cost and timeliness of results, and avoid diversion of energies into less important issues.

2.3 Good quality management, including its formal recognition by accreditation, certification etc., helps to ensure that results are fit-for-purpose. However, it is important for both laboratories and their customers to realise that quality management cannot guarantee that 100% of the individual results will be reliable. There are two reasons for this:

i) Human errors can occur, where, for example, the results for two samples are mixed-up. In a well-run laboratory, the frequency of human errors will be small, but not zero [15].

ii) Random and systematic measurement errors also occur, leading to uncertainty in a measurement result. The probability of a result lying within the stated uncertainty range depends on the level of confidence employed, but again, even in a well ordered laboratory, deviant results will occasionally occur and very occasionally the deviation will be large.

The role of quality management is to put in place measures aimed at minimising the frequency of quality failures, and to identify and correct them before results are reported to the customer. As the effort taken increases, the number of quality failures is expected to reduce. It is necessary to balance the cost of quality management against the benefit in reducing quality failures to an acceptable (non-zero) level.

2.4 The principles of quality management have been formalised in a number of published guidelines and standards. Those most widely recognised and used in analytical laboratories are:

2.4.1 ISO/IEC 17025 [2]. This standard is relevant to laboratories developing a management system for administrative, quality and technical operations. It addresses the technical competence of laboratories to carry out specific tests and calibrations and is used by accreditation bodies worldwide as the core requirements for the recognition of a laboratory's competence.

2.4.2 ISO 9001 [5]. This standard relates primarily to quality management for facilities carrying out production, or providing services.

2.4.3 ISO 15189 [3]. This standard was prepared specifically to cover medical laboratories carrying out the testing or examination of materials derived from the human body. The standard is based on ISO 9001 [5] and ISO/IEC 17025 [2] but specifies requirements that are particular to medical laboratories.

2.4.4 OECD Principles of Good Laboratory Practice (GLP) [6] and its national and sectoral equivalents. These guidelines are concerned with the organisational processes and conditions under which laboratory studies related to certain regulatory work are carried out.

2.5 Current standards such as ISO/IEC 17025 [2], ISO 9001 [5] and ISO 15189 [3] place emphasis on continual improvement. An organisation should continually improve the effectiveness of its QMS through activities such as setting quality objectives, reviewing audit results, and management reviews. ISO 9001 promotes the adoption of a process approach when developing, implementing and improving the effectiveness of a QMS. This approach is also referred to as 'Plan-Do-Check-Act':

- Plan – establish the objectives and processes necessary to deliver results in accordance with the customer's requirements and the organisation's policies;
- Do – implement the processes;
- Check – monitor and measure processes and products against policies, objectives and requirements for the product and report the results;
- Act – take actions to continually improve process performance.

2.6 The laboratory will select a standard according to its needs. However, central to this Guide is the contention that, at the technical level, good practice in quality management is independent of the formal QMS adopted.

2.7 A laboratory may decide to design its own quality management procedures or it may follow one of the established standards or guidelines. In the latter case it may claim informal compliance against the standard or protocol, or ideally may undergo independent assessment from an official expert body, with the aim of gaining independent endorsement of its QMS. Such independent assessment/endorsement is variously known as accreditation, certification or compliance depending on which standard or other document the assessment is made against. In particular areas of testing, accreditation is sometimes mandatory however, in most cases, the laboratory is free to decide what quality management measures it wishes to adopt. The independent assessment route has recognised advantages, particularly where the laboratory's customers require objective evidence of the technical competence of the laboratory. For clarification of the term 'accreditation' as used in this Guide, see Sections 3.4 and 4.

3 Definitions and terminology

There are a number of important terms used in quality management and conformity assessment whose meaning may vary according to the context in which they are used. It is important to understand the distinction between the various terms. The key reference is ISO/IEC 17000 [8]. Other terms can be found in ISO 9000 [9] and the VIM [10]. A selection of terms likely to be encountered in the laboratory are presented here.

3.1 ***QUALITY:*** Degree to which a set of inherent characteristics fulfils requirements (ISO 9000 [9])

3.2 ***MANAGEMENT SYSTEM:*** System to establish policy and objectives and to achieve those objectives (ISO 9000 [9])

3.3 ***QUALITY MANAGEMENT SYSTEM:*** Management system to direct and control an organisation with regard to quality (ISO 9000 [9])

3.3.1 In practice, the terms 'management system' and 'quality management system' are often used interchangeably. In ISO/IEC 17025 [2] 'management system' is used, however in ISO 15189 [3] 'quality management system' is the preferred term.

3.4 ***ACCREDITATION:*** Third-party attestation related to a conformity assessment body conveying formal demonstration of its competence to carry out specific conformity assessment tasks (ISO/IEC 17000 [8])

3.4.1 In the context of a laboratory making measurements, accreditation is a formal recognition that a laboratory is competent to carry out specific calibrations or tests. The mechanism under which accreditation is granted is described in Section 4 and the core requirements are documented in ISO/IEC 17025 [2].

3.4.2 Accreditation is also used in the context of ISO 9000 [9] based activities to describe the process whereby an accreditation body formally confirms a certification body as competent to certify organisations as being compliant with the ISO 9000 series of standards.

3.5 ***CERTIFICATION:*** Third-party attestation related to products, processes, systems or persons (ISO/IEC 17000 [8])

3.5.1 Certification, (sometimes known as registration) primarily differs from accreditation in that technical competence is not specifically addressed.

3.6 ***QUALITY ASSURANCE (QA):*** Part of quality management focused on providing confidence that quality requirements will be fulfilled (ISO 9000 [9])

The main requirements in a laboratory are:

- A QMS;
- A suitable laboratory environment;
- Educated, trained and skilled personnel;
- Training procedures and records;
- Specifications for reagents, calibrants and measurement standards (including reference materials (RMs));
- Equipment suitably maintained and calibrated;
- Procedures for sampling (where the laboratory is responsible for this activity);
- Procedures for sample handling;
- Documented and validated methods;
- Metrological traceability of results;
- Evaluation of measurement uncertainty;
- Internal quality control procedures;
- Participation in proficiency testing (PT)/external quality assessment (EQA);
- Procedures for checking and reporting results;
- Procedures for implementing preventive and corrective actions;
- Internal audit and review procedures.

3.7 ***QUALITY CONTROL (QC):*** Part of quality management focused on fulfilling quality requirements (ISO 9000 [9])

QC procedures relate to ensuring the quality of results obtained for specific samples or sets of samples and include:

- Analysis of QC samples;
- Analysis of measurement standards (including RMs);
- Analysis of blind samples;
- Analysis of sample blanks and reagent blanks [12];
- Analysis of spiked samples;

- Analysis in duplicate;
- Use of QC charts to monitor trends;
- Assessment of correlation of results obtained for different characteristics of a sample, provided that a known relationship exists.

More details on QC are given in Section 21.

3.8 ***AUDIT:*** Systematic, independent, documented process for obtaining records, statements of fact or other relevant information and assessing them objectively to determine the extent to which specified requirements are fulfilled (ISO/IEC 17000 [8])

3.8.1 In practice, quality audits take three forms. An audit carried out within the laboratory by its own personnel is often referred to as an 'internal audit' or 'first-party' audit. 'External audits' include 'second-party audits', conducted by an organisation having an interest in the laboratory (such as a customer), and 'third-party audits' which are undertaken by an independent external body, such as an accreditation body. A third-party audit carried out by an accreditation body, as part of the accreditation process, is known as an assessment.

In this Guide the term audit refers to an internal audit; assessment refers to a third-party external audit.

3.9 ***REVIEW:*** Verification of the suitability, adequacy and effectiveness of selection and determination activities, and the results of these activities, with regard to fulfilment of specified requirements by an object of conformity assessment (ISO/IEC 17000 [8])

3.9.1 A review checks all aspects of the QMS to ensure that it is still effective and achieves the set objectives. The review is carried out by senior management with responsibility for both the quality policy and the work of the laboratory. The review will include the results from internal audits.

More details on audit and review are given in Section 23.

3.10 ***MEASURAND:*** Quantity intended to be measured (VIM [10])

3.10.1 The specification of the measurand should be sufficiently detailed to avoid any ambiguity. It is important to remember that measurand is not an alternative for analyte [11].

3.11 ***STANDARD:*** This word has a number of different meanings in the English language. In the past it has been used routinely to refer both to written standards, i.e. widely adopted procedures, specifications, technical recommendations, etc., and to chemical or physical standards used for calibration purposes. In this Guide, to minimise confusion, standard is used only in the sense of written standards. The term measurement standard is used to describe chemical or physical standards, used for calibration or validation purposes, such as: chemicals of established purity and their corresponding solutions of known concentration; UV filters; weights, etc. Certified reference materials (CRMs) are one (important) category of measurement standards.

3.12 ***REFERENCE MATERIAL (RM):*** Material, sufficiently homogeneous and stable with reference to specified properties, which has been established to be fit for its intended use in measurement or in examination of nominal properties (VIM [10])

3.13 ***CERTIFIED REFERENCE MATERIAL (CRM):*** Reference material, accompanied by documentation issued by an authoritative body and providing one or more specified property values with associated uncertainties and traceabilities, using valid procedures (VIM [10])

3.14 ***MEASUREMENT PROCEDURE:*** Detailed description of a measurement according to one or more measurement principles and to a given measurement method, based on a measurement model and including any calculation to obtain a measurement result (VIM [10])

Note that in ISO/IEC 17025 [2] and this Guide the term 'method' is used (see Section 1.2.1).

3.15 ***METROLOGICAL TRACEABILITY:*** Property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty (VIM [10])

3.16 ***MEASUREMENT UNCERTAINTY:*** Non-negative parameter characterising the dispersion of the quantity values being attributed to a measurand, based on the information used (VIM [10])

3.17 ***METHOD VALIDATION:*** Confirmation by examination and the provision of objective evidence that the particular requirements for a specific intended use are fulfilled (ISO/IEC 17025 [2])

Note that the VIM [10] provides a different, but in principle similar, definition of validation. Further discussion of the terminology relating to method

validation can be found in the Eurachem guides on terminology [11] and method validation [12].

4 Accreditation

4.1 The references to accreditation in this and successive sections refer to ISO/IEC 17025 [2]. Its requirements form the basis for accreditation granted by an accreditation body and agreements are in place to support the equivalence of assessments (see Section 4.9). In the EU specific legislation applies for the establishment of national accreditation bodies (Regulation (EC) No 765/2008 [16]).

4.2 The standard ISO/IEC 17025 [2] contains two sets of requirements, one relating to management of the laboratory and the other dealing with technical issues.

4.2.1 Requirements relating to the management of a laboratory are very much in line with the requirements given in ISO 9001 [5]), i.e. ensuring that policy, procedures and appropriate documentation are in place for:

- Organisation and delegation of responsibilities;
- Establishment, assessment and improvement of the QMS;
- Control of documents and records;
- Ensuring customers are dealt with consistently (contracts, cooperation, feedback);
- Safeguarding the quality of supplies, services and any subcontracted work;
- Identifying and dealing with any nonconformities in relation to the established QMS;
- Confirming the management's current awareness of the effectiveness and appropriateness of the QMS.

These are the requirements found in Section 4 of the standard.

NOTE: This Guide does not deal specifically with any of these management issues – except for the requirements on internal audits and management reviews (see Section 23).

4.2.2 Requirements relating to the technical competence of the laboratory to carry out specific types of tests or calibrations are given in Section 5 of the standard. These are the subject of the more detailed recommendations found in the following sections of this Guide.

4.3 The requirements of the leading quality standards/protocols have many common or similar elements. For example, ISO/IEC 17025 [2] incorporates the ISO 9001 [5] management system elements which are applicable to laboratories. For laboratories within organisations who are seeking certification according to ISO 9001 (and therefore not looking to obtain a third-party evaluation of their technical competence as in the case of an accreditation), ISO/IEC 17025 and this Guide can still be recommended as useful tools for securing good quality work in that laboratory.

4.3.1 Laboratories who comply with the requirements of ISO/IEC 17025 [2] will operate a QMS that meets the principles of ISO 9001 [5]. They will not therefore require separate certification to the requirements of ISO 9001 for those activities covered by the ISO/IEC 17025 accreditation. However, the organisation may choose to obtain certification for non-technical activities which are not covered by the accreditation, such as finance, human resources or sales and marketing.

4.4 Accreditation is granted to a laboratory for a specified set of activities (i.e. tests or calibrations) following assessment of that laboratory by an accreditation body. Such assessments will typically involve an examination of the methods in use, the facilities/environment, equipment and personnel involved, and the means of controlling the procedures being performed. Furthermore, the QMS and the related documentation of the laboratory will be examined.

4.5 The methods will be examined to ensure they are technically appropriate for the intended purpose, that they have been validated and documented clearly and unambiguously, and that their performance is under control (e.g. through the use of QC charts). The performance of tests may be witnessed to ensure documented procedures are being followed and interpreted in a consistent way. The laboratory's performance in PT schemes or other interlaboratory comparisons will also be a focal point. Assessment may additionally include a 'performance audit' or 'measurement audit', where the laboratory is required to analyse specific samples and achieve acceptable levels of accuracy.

4.6 It is the responsibility of the laboratory to ensure that all procedures used are appropriate for their intended purpose. The assessment process

examines whether the procedures are fit-for-purpose.

4.7 Each accreditation body has established procedures against which it operates, assesses laboratories and grants accreditation. To ensure harmonised assessments, the accreditation bodies themselves must work in accordance with the requirements of ISO/IEC 17011 [17].

4.8 Assessors are chosen against specified criteria. The selection criteria for assessors appointed by accreditation bodies are specified in ISO/IEC 17011 [17]. These include the requirement for technical expertise in the specific areas of operation being assessed.

4.9 The benefit of accreditation is that it enables potential customers to have confidence in the quality of the work performed by the laboratory. Since the introduction of formal requirements for the competence of laboratories, the endorsement conferred by accreditation and other assessments has gained worldwide recognition and plays an important role in trade. Many laboratory accreditation bodies (who have been evaluated and found to satisfy relevant requirements, see Section 4.7) have signed a Multilateral Agreement (MLA) with European Accreditation (EA) members, and/or a Mutual Recognition Arrangement (MRA) under the International Laboratory Accreditation Cooperation (ILAC).

5 Scope of accreditation

5.1 A laboratory may apply quality management to all or part of its operations. Where a laboratory claims accreditation or certification to a particular standard, or compliance with the requirements of a specific regulation, it is important to be clear as to which activities the accreditation, certification or compliance applies. The formal statement of the activities which have been accredited against ISO/IEC 17025 [2] or certified against ISO 9001 [5], is known as the 'scope'.

5.2 The term 'scope' has a slightly different meaning in different standards. For example, for laboratories seeking accreditation to ISO/IEC 17025 [2] a clear statement of the activities to be accredited is required. The scope is typically defined in terms of:

i) the range of products, materials or sample types tested or analysed;

ii) the properties to be determined;

iii) the specification or method/equipment/ technique used.

Guidance on how to define the scope of accreditation for a testing, calibration or medical laboratory according to the relevant standards is given in ILAC G18 [18].

This type of scope is often referred to as a 'fixed scope'. The laboratory's accreditation schedule will contain the information indicated in i)-iii) above for the tests for which accreditation has been obtained. The range of values to be determined and the measurement uncertainty do not have to be stated in the scope of accreditation, however relevant documentation must be available to meet the requirements of ISO/IEC 17025.

5.3 Definition of scope in specific terms is clearly most easily applied to laboratories carrying out routine tests using established methods. However, the 'fixed scope' approach can be restrictive as it does not readily enable new or modified methods to be added to a laboratory's scope of accreditation, even where competence in a general area of testing has already been demonstrated. An alternative is for the testing laboratory to be granted a 'flexible scope'. A laboratory must maintain a list of the tests included under its flexible scope, but this approach allows the laboratory to include additional activities in its scope of accreditation on the basis of its own validations, without having to apply to the accreditation body for an extension to scope (as described in Section 5.4) [18-20]. Flexible scope can cover scenarios such as:

i) use of new or amended tests in accordance with a generic method;

ii) modification of existing methods to broaden their applicability (e.g. to deal with new sample types or analytes);

iii) inclusion of newly revised methods or standard methods that are technically equivalent to methods already covered by the laboratory's accreditation.

A flexible scope puts more responsibility on the laboratory in terms of demonstrating that methods are fit-for-purpose. Flexible scope also requires a laboratory to be able to demonstrate that it has procedures in place to adequately manage the accreditation of new or revised methods, and the updating of accredited methods. Although the concept of flexible scope is widely accepted, there are differences in its implementation in different countries.

5.4 Unless it has a 'flexible scope' accreditation (as described in Section 5.3) a laboratory wishing to change its scope, either by adding additional tests or changing the methodology of existing tests will require the approval of the accreditation body, who will have a specified policy for such situations. Typically, it is possible to grant simple changes by examination of documentation. For more complex changes, particularly where new techniques are involved, additional assessments may be required.

6 The analytical task

6.1 Analysis is a complex multistage activity which may be summarised by the following sub-tasks. Where appropriate the corresponding Section in this Guide is also listed. Note that analytical work is often an iterative process rather than the linear series of steps shown below, and that not every step will be required each time a routine measurement is performed. Those marked * are of more significance in the context of non-routine analysis.

- Specification of requirements (Section 7);
- Information review*;
- Creative thought*;
- Study plan* (Section 8);
- Sampling (Section 11);
- Sample preparation;
- Preliminary analysis*;
- Identification/confirmation of composition;
- Quantitative analysis;
- Data collection and review;
- Data interpretation/problem solving;
- Reporting/advice.

6.2 Although different standards emphasise different aspects of quality management and some of the above steps are not specifically covered, it is important that the quality management of each stage is considered, and where relevant addressed.

7 Specification of analytical requirement

7.1 The laboratory has a duty to provide an analytical service for its customers that is appropriate to solving the customers' problems.

7.2 The key to good analysis is a clear and adequate specification of the requirement. This will need to be produced in co-operation with the customer who may need considerable help to translate their functional requirements into a technical analytical task. The analytical requirement may develop during the course of a commission but should have the agreement of both customer and laboratory. Each party should confirm they have the same understanding of the analytical problem and its solution. The specification of the analytical request should address the following issues:

- Analytical context;
- Information required;
- Criticality of test result;
- Time constraints;
- Cost constraints;
- Sampling;
- Metrological traceability requirements;
- Measurement uncertainty;
- Method requirements, including sample preparation;
- Identification/confirmation/fingerprinting;
- QA/QC requirements;
- Method development/approval.

7.3 The laboratory must have procedures in place for the review of requests, tenders and contracts, and maintain records of reviews including any significant changes. The review should also cover any work that is subcontracted by the laboratory. The level of documentation should be commensurate with the scale and criticality of the task and include the output of any 'information review' and 'creative thought'.

7.4 If a laboratory subcontracts work (either to meet a short term need or on a continuing basis) the customer must be informed and, when appropriate, their approval obtained. ISO/IEC 17025 [2] gives additional requirements in relation to the selection of subcontractors.

7.5 The laboratory should inform the customer about the significance of accreditation, and of the accreditation status of the tests and/or calibrations covered by the customer's request.

8 Analytical strategy

8.1 All analytical work should be adequately planned and documented. The level of detail required will depend on the complexity of the task.

8.2 Plans will typically indicate the starting and intended finishing point of the particular task together with the strategy for achieving the desired aims. Where, during the course of the work, it is appropriate to change the strategy, the plan should be amended accordingly. Any amendments should be documented and significant changes communicated to the customer.

9 Non-routine analysis

9.1 Non-routine analysis can be considered as:

- Tasks which are carried out infrequently, but where reliable methodology is already established;
- Tasks where every sample requires a different approach and methodology has to be established at the time.

The latter case is sometimes referred to as 'ad-hoc analysis'. Guidance on quality assurance for research and development and non-routine analysis is given in Eurachem/CITAC Guide CG2 [1].

9.2 The cost of measurements reflects the costs associated with method development, method validation, instrumentation, consumables, ongoing maintenance of equipment, input from personnel, calibration, QC, etc. Many of these costs are independent of the number of samples subsequently analysed using that method. Thus where a single method can be used for a large throughput of samples, the unit analytical cost will be comparatively low. Where a method has to be developed specifically for the analysis of a small number of samples, the unit analytical cost can be very high. For such non-routine analysis some of the costs can be reduced by use of generic methods, i.e. methods which are very broadly applicable. In other instances, subcontracting the work to a laboratory that specialises in the particular type of work would be the most cost-effective solution. When work is subcontracted, the requirements outlined in Section 7.4 apply.

9.3 A measurement can conveniently be described in terms of an isolation stage and a measurement stage. The purpose of the isolation stage is to simplify the matrix in which the concentration of the analyte is finally measured. Often the isolation procedure may vary very little for a wide variety of analytes in a range of sample matrices. A good example of a generic isolation procedure is the digestion technique used to extract trace metals from foods.

9.4 Similarly, once analytes have been isolated from the sample matrix and are presented in a comparatively clean environment, such as a solvent, it may be possible to have a single generic method to cover the measurement of the concentration of a wide variety of analytes (for example, gas chromatography or UV/visible spectrophotometry).

9.5 The documentation of such generic methods should be designed so that it can easily accommodate the small changes which relate to the extraction, clean-up or measurement of different analytes, for example by the use of tables. Parameters which might be varied include sample size, volume and type of extraction solvents, extraction conditions, chromatographic columns, separation conditions, or spectrometer wavelength settings.

9.6 The value of generic methods for non-routine analysis is that when a new analyte/matrix combination is encountered, it is frequently possible to incorporate it within an existing generic method with appropriate additional validation, measurement uncertainty calculations and documentation. Thus the additional costs incurred are minimised in comparison to the development of a whole new method. The method should define the checks which will need to be carried out for the different analyte or sample type in order to confirm that the analysis is valid. Sufficient information will need to be recorded in order that the work can be repeated in exactly the same manner at a later date. Where a particular analysis subsequently becomes routine, a specific method may be validated and documented.

9.7 It is possible to accredit non-routine analysis and most accreditation bodies will have a policy for assessing such methods and describing them in the laboratory's accreditation scope or schedule. Accreditation of a 'flexible scope', as described in Section 5.3, is one possible option. It is the laboratory's responsibility to demonstrate to the assessors that in using these techniques, it is meeting all of the criteria of the relevant quality standard. In particular, the experience, expertise and training of the personnel involved will be a major factor in determining whether or not such analyses can be accredited.

10 Personnel

10.1 The laboratory management has to identify the different functions within the laboratory and record them in an organisation chart (also known as an 'organogram').

10.2 The laboratory management should formulate the goals and job descriptions and, based on them, the required education, training and skills of the personnel appropriate for their functions. Present and anticipated tasks of the laboratory have to be considered in order to achieve continual quality improvement.

10.3 The laboratory management should normally define in procedures or in the quality manual, the minimum level of academic or vocational qualification and experience necessary for the key posts within the laboratory. Personnel who are required to perform specialist tasks, (e.g. particular types of test or sampling) or who issue test reports and/or provide 'opinions and interpretations', will need specific training appropriate for the task, including the prevention of human errors [15]. All analyses must be carried out by, or under the supervision of, a qualified, experienced and competent analyst. Other senior laboratory personnel will normally possess similar competencies. Lower formal qualifications may be acceptable when personnel have extensive relevant experience and/or the scope of their activities is limited. Personnel undergoing training or with no relevant qualifications may undertake analyses provided that they have received an acceptable level of training, have demonstrably achieved an appropriate level of competence and are adequately supervised. All education and training needs to be documented and maintained in a training record.

10.4 In certain circumstances, the minimum requirements for qualifications and experience of personnel carrying out particular types of analysis may be specified in regulations.

10.5 The laboratory management must ensure that all personnel receive sufficient training to enable the competent performance of the tests and operation of equipment. Where appropriate, this will include training in the principles and theory underpinning particular techniques. Where possible, objective measures (performance criteria) should be used to assess the attainment of competence during training. Only analysts who can demonstrate the necessary competence, or who are adequately supervised may perform tests on samples. A program of continuous training must be carried out and documented. Training and development plans for all personnel should be in place to support the attainment of appropriate competencies and ensure the future needs of the laboratory are met. Continued competence must be monitored, for example, by reviewing the performance achieved in QC and PT. The need to periodically retrain personnel must be considered, particularly (but not only) where a method or technique is not in regular use. Although the laboratory management is responsible for ensuring that adequate training is provided, it must be emphasised that a strong element of self-training takes place, particularly amongst more experienced analysts. Authorisation must be given before personnel can begin undertaking analysis on their own.

10.6 The laboratory management shall maintain an up-to-date record of the training that each member of staff has received. The purpose of these records is to provide evidence that every individual has been adequately trained and their competence to carry out particular tasks has been assessed. In some cases, it may be pertinent to state any particular limitations to evidence about competence. Typically the record for each person should include:

- Academic qualifications;
- External and internal courses attended;
- Relevant on-the-job training (and retraining as necessary).

Possibly also:

- Participation in QC and/or PT schemes, with associated data;
- Participation in intralaboratory comparisons;
- Cooperation in method validation;
- Technical papers published and presentations given at conferences.

10.7 In some cases it may be more appropriate to record competence in terms of particular measurement techniques rather than complete methods.

10.8 Access to training records will be necessary in the course of everyday work. Access to other personal details, usually held centrally, may be restricted by national legislation on data protection.

10.9 Appropriate procedures should be followed in the case of temporary staff, contractors, trainees and other newly employed personnel with regard to

their competence and awareness of the relevant QMS requirements.

10.10 Personnel must sign a confidentiality statement.

11 Sampling, sample handling and preparation

11.1 Measurement and test results may be required for a variety of reasons, including identifying the presence of a substance in a material, establishing an average analyte value across a material, establishing an analyte concentration profile across a material, or determining local contamination in a material. In some cases, for example forensic analysis, it may be appropriate to examine the entire material. In others, it is appropriate to take a sample. Clearly the way samples are taken will depend on the reason for the analysis.

11.2 If the test portion is not representative of the original material, it will not be possible to relate the analytical result obtained to the properties of the original material, no matter how good the analytical method is or how carefully the analysis is performed. Sampling plans may be random, systematic or sequential and they may be undertaken to obtain quantitative or qualitative information, or to determine conformance or nonconformance with a specification.

11.3 Sampling always contributes to the measurement uncertainty [21]. As analytical methodology improves and methods allow or require the use of smaller test portions, the uncertainties associated with sampling become increasingly important and can increase the total uncertainty associated with the measurement result. The measurement uncertainty introduced by subsampling etc. carried out within the laboratory should always be included in the test result measurement uncertainty, but the measurement uncertainty associated with the basic sampling process (carried out prior to submission of a sample to the laboratory, and often outside of its control) is commonly treated separately.

11.4 In many areas of testing the problems associated with sampling have been addressed and methods have been validated and published. Sampling procedures are sometimes prescribed in legislation as in, for example, the EU Regulation relating to certain contaminants in food [22]. Analysts should also refer to national or sectoral standards as appropriate. Where specific methods are not available, the analyst should rely on experience or adapt methods from similar applications. When in doubt, the material of interest, and any samples taken from it, should always be treated as heterogeneous.

11.5 Selection of an appropriate sample or samples, from a larger amount of material, is a very important stage in the measurement process. It is rarely straightforward. Ideally, if the final results produced are to be of any practical value, the sampling stages should be carried out by, or under the direction of, a skilled sampler with an understanding of the overall context of the analysis. Such a person is likely to be an experienced analyst or someone specifically trained in sampling. Where it is not practical to use such skilled people to take the samples, the laboratory is encouraged to liaise with the customer to provide advice and possibly practical assistance, in order to ensure the sampling is as appropriate as possible.

11.6 National accreditation bodies have their own procedures for the accreditation of sampling and can accredit sampling as a stand-alone activity.

11.7 It is important when documenting a sampling procedure to ensure that all of the terms used are clearly defined, so that the procedure will be clear to other users. Similarly it is important to ensure when comparing two separate procedures that the terminology used is consistent. For example, care should be taken in the use of the word ‘bulk’ since this can refer to either the combining of individual samples, or an undifferentiated mass.

11.8 One of the best treatments of sampling terminology is given in recommendations published by IUPAC [23], which describes the terms used in the sampling of bulk goods or packaged goods. IUPAC have also published separate guidance on terminology in soil sampling [24]. An overview of terminology relevant to sampling is provided by Eurachem [21]. In the case of sampling bulk or packaged goods, the sampling procedure reduces the original consignment through lots or batches, increments, primary or gross samples, composite or aggregate samples, subsamples or secondary samples to a laboratory sample. The laboratory sample, if heterogeneous, may be further prepared to produce the test sample. The laboratory sample or the test sample is deemed to be the end of the sampling procedure. Operations within this procedure are likely to be subject to sampling uncertainties. Activities undertaken after this step are generally considered to be ‘analytical operations’ which do not contribute to the uncertainty associated with sampling.

11.9 For the purposes of the guidance given below the following definitions, based on those proposed by IUPAC [23], have been used:

Sample: A portion of material selected to represent a larger body of material.

Subsample: This term may refer to: a portion of the sample obtained by selection or division; an individual unit of the lot taken as part of the sample or; the final unit of multistage sampling.

Laboratory sample: The sample or subsample delivered to the laboratory.

Test sample: The sample, prepared from the laboratory sample, from which test portions are removed for analysis.

Sample preparation: Procedures followed to select the test portion from the laboratory sample. They include: in-laboratory processing; mixing; reducing; coning and quartering; riffling; and milling and grinding.

Test portion: This refers to the actual portion of material removed from the test sample for the analysis.

Sample handling: Although not defined by IUPAC, this term is frequently used to refer to the manipulation to which samples are exposed after the selection from the original material through to the disposal of all samples and test portions.

11.10 The sampling process should be described in a detailed sampling plan. This should specify the number and size of the portions that need to be taken from the bulk material, and describe how the laboratory sample is to be obtained. The size and number of test samples to be taken from the laboratory sample must also be documented. Sampling plans should be designed in such a way that the resulting data will be representative of the parameters of interest and allow for all questions, as stated in the analytical requirement, to be answered.

11.11 There are important rules to be followed when designing, adapting, or following a sampling plan.

11.11.1 The problem necessitating the taking of samples and subsequent analysis should be understood and the sampling plan designed accordingly. The sampling strategy used will depend on the nature of the problem, for example whether:

a) the average analyte concentration in the material is required;

b) the analyte profile across the material is required;

c) the material is suspected of contamination by a particular analyte;

d) the contaminant is heterogeneously distributed (occurs in hot spots) in the material;

e) there are other non-analytical factors to consider, including the nature of the area under examination.

11.11.2 Care should be taken in assuming that a material is homogeneous, even when it appears to be. Where a material is clearly in two or more physical phases, the distribution of the analyte may vary within each phase. It may be appropriate to separate the phases and treat them as separate samples. Similarly, it may be appropriate to combine and homogenise the phases to form a single sample. In solids there may be a considerable variation in analyte concentration if the particle size distribution of the main material varies significantly, and over a period of time the material may settle. Before sampling it may be appropriate, if practical, to mix the material to ensure a representative particle size distribution. Similarly analyte concentration may vary across a solid where different parts of the material have been subjected to different stresses. For example, consider the measurement of vinyl chloride monomer (VCM) in the fabric of a PVC bottle. The concentration of VCM varies significantly depending on whether it is measured at the neck of the bottle, the shoulder, the sides or the base.

11.11.3 The properties of the analyte(s) of interest should be taken into account. Volatility, sensitivity to light, thermal stability and chemical reactivity may be important considerations in designing the sampling plan and choosing equipment, packaging and storage conditions. Equipment used for sampling, subsampling, sample handling, sample preparation and sample extraction, should be selected in order to avoid unintended changes to the nature of the sample which may influence the final results. The significance of gravimetric or volumetric uncertainties during sampling should be considered and any critical equipment calibrated. It may be appropriate to add chemicals such as acids, or antioxidants to the sample to stabilise it. This is of particular importance in trace level analysis where there is

a danger of adsorption of the analyte onto the storage vessel.

11.11.4 It may be necessary to consider the use and value of the remainder of the original material once a sample has been removed for analysis. Poorly considered sampling, especially if destructive, may render the whole consignment worthless.

11.11.5 Whatever strategy is used for the sampling, it is of vital importance that those performing it keep a clear record of the procedures followed in order that the sampling process may be repeated exactly.

11.11.6 Where more than one sample is taken from the original material it may be useful to include a diagram as part of the documentation to indicate the pattern of sampling. This will make it easier to repeat the sampling at a later date and also may assist in drawing conclusions from the test results. A typical application where such a scheme would be useful is the sampling of soils over a wide area to monitor fall-out from stack emissions.

11.11.7 Where the laboratory has not been responsible for the sampling stage, it should state in the report that the samples were analysed as received. If the laboratory has conducted or directed the sampling stage, it should report the procedures used and comment on any consequent limitations imposed on the results.

11.12 Once received into the laboratory, the laboratory sample(s) may require further treatment such as removal of extraneous material, subdivision and/or milling and grinding to make it suitable for analysis.

11.13 Unless otherwise specified the test portion taken for analysis must be representative of the laboratory sample. To ensure that the test portion is homogeneous it may be necessary to reduce the particle size by grinding or milling. However, if the laboratory sample is large it may be necessary to subdivide it first. Care should be taken to ensure that segregation does not occur during subdivision. In some cases it will be necessary to crush or coarsely grind the sample prior to subdivision into test samples. The sample may be subdivided using a variety of mechanisms, including coning and quartering, riffling, or by means of a rotating sample divider or a centrifugal divider. The particle size reduction step may be performed either manually (mortar and pestle) or mechanically using crushers or mills. Care must be taken during these processes to avoid cross contamination of samples, to ensure that the equipment does not contaminate the sample (e.g. metals) and that the composition of the sample is not altered (e.g. loss of moisture). Many standard methods of analysis contain a section that details the preparation of the laboratory sample prior to the removal of the test portion for analysis. In other instances legislation deals with this aspect as a generic issue.

11.14 The analytical operations begin with the removal of a known amount (test portion) from the laboratory sample or the test sample, then proceed through various operations to the final measurement.

11.15 Sample packaging, and instruments used for sample manipulation, should be selected so that all surfaces in contact with the sample are essentially inert. Particular attention should be paid to possible contamination of samples by metals or plasticisers leaching from the container or its stopper into the sample. The packaging should also ensure that the sample can be handled without causing a chemical, microbiological, or other hazard.

11.16 The laboratory shall have procedures in place for the cleaning of all items used in sampling, including flasks and auxiliary equipment. Records of cleaning processes should be maintained.

11.17 The closure of the packaging should be adequate to ensure there is no leakage of sample from the container, and that the sample itself cannot be contaminated. In some circumstances, for example where samples have been taken for legal purposes, the sample may be sealed so that access to the sample is only possible by breaking the seal. Confirmation of the satisfactory condition of the seals will normally then form part of the analytical report.

11.18 The sample label is an important aspect of documentation and should unambiguously identify the sample to related plans or notes. Labelling is particularly important later in the analytical process, when the sample may have been divided, subsampled, or modified in some way. In such circumstances, additional information may be appropriate, such as references to the main sample, and to any processes used to extract or subsample the sample. Labelling must be firmly attached to the sample packaging and, where appropriate, be resistant to fading, autoclaving, sample or reagent spillage, and reasonable changes in temperature and humidity. In many laboratories, in particular those handling high sample numbers, samples are identified by means of barcodes linked to a

Laboratory Information Management System (LIMS).

11.19 Some samples, those involved in litigation for example, may have special labelling and documentation requirements. Labels may be required to identify all those who have been involved with the sample, including the person taking the sample and the analysts involved in the testing. This may be supported by receipts, to testify that one signatory (as identified on the label) has handed the sample to the next signatory, thus proving that sample continuity has been maintained. This is commonly known as 'chain of custody'.

11.20 Samples must be stored at an appropriate temperature and in such a manner so that there is no risk to laboratory personnel and the integrity of the samples is preserved. Storage areas should be kept clean and organised so that there is no risk of contamination or cross-contamination, or of packaging and any related seals being damaged. Extremes of environmental conditions (e.g. temperature, humidity), which might change the composition of the sample, should be avoided as this can lead to loss of analyte through degradation or adsorption, or an increase in analyte concentration (as in the case of mycotoxins, for example). If necessary, environmental monitoring should be used. An appropriate level of security should be exercised to restrict unauthorised access to the samples.

11.21 All personnel concerned with administration of the sample handling system should be properly trained. The laboratory should have a documented policy for the retention and disposal of samples.

11.22 To fully evaluate an analytical result for conformity assessment, or for other purposes, it is important to have knowledge of the sampling plan and its statistical basis. Sampling procedures for inspection by variables [25-29] assume that the characteristic being inspected is measurable and follows the normal distribution. In contrast, sampling for inspection by attributes [30-35] is a method whereby either the unit of product is classified as conforming or nonconforming, or the number of nonconformities in the unit of product is counted with respect to a given set of requirements. In inspection by attributes the risks associated with acceptance/rejection of nonconformities are predetermined by the Acceptable Quality Level and the Rejectable Quality Level, defined using appropriate statistical techniques.

12 Environment

12.1 Samples, reagents, measurement standards (including RMs) must be stored so as to ensure their integrity is maintained. In particular, they must be stored and used or tested in such a way that cross contamination is not possible. It is advisable that the reagents, measurement standards and samples are stored in different locations. The laboratory should guard against their deterioration, contamination and loss of identity, taking into account any specific requirements stated by the supplier or specified in the method (e.g. storage temperature).

12.2 The laboratory environment, services and facilities should be sufficiently uncrowded, clean and tidy to ensure the quality of the work carried out is not compromised. Where it is critical to the quality of its work, the laboratory shall maintain documented procedures and records relating to cleaning processes.

12.3 It may be necessary to restrict access to particular areas of a laboratory because of the nature of the work carried out there. Only authorised personnel may have access and this must be described in procedures and their names recorded. Restrictions might be made because of security, safety, or sensitivity to contamination or interferences. Typical examples might be work involving explosives, radioactive materials, carcinogens, forensic examination, polymerase chain reaction (PCR) techniques and trace level analysis. Where such restrictions are in force, personnel should be made aware of:

i) the intended use of a particular area;

ii) the restrictions imposed on working within such an area;

iii) the reasons for imposing such restrictions;

iv) the procedures to follow when such restrictions are breached.

12.4 Where incompatible activities are carried out in neighbouring work areas, provision needs to be made to ensure effective separation. The separation can be in terms of space (i.e. by carrying out the activities in different laboratory areas) or time (i.e. by scheduling work so that the incompatible activities happen sequentially with adequate cleaning procedures between the two).

12.5 When selecting designated areas for new work, account must be taken of the previous use of the area. Before use, checks should be made to ensure that the area is free of contamination. Decontamination procedures may be appropriate where the environment or equipment is subject to change of use or where accidental contamination has occurred.

12.6 The laboratory shall provide the appropriate environmental conditions and controls necessary for particular tests or operation of particular equipment. This should include consideration of the effects and required control of:

- Temperature;
- Humidity;
- Vibration;
- Airborne and dustborne microbiological contamination;
- Lighting.

In addition, the need for radiation screening and particular services (e.g. gas lines or demineralised water supply) should also be considered.

Critical environmental conditions must be monitored and kept within predetermined limits. Monitoring equipment needs to be adequately maintained, verified and/or calibrated.

12.7 A breakdown of critical environmental conditions may be indicated either by monitoring systems or by the QC results produced during the particular tests. The impact of such failures may be assessed as part of ruggedness testing during method validation (see Section 18.13) and, where appropriate, emergency procedures established. Any such event has to be followed up as a nonconformity in the QMS.

12.8 The correct disposal of reagents and samples does not directly affect the quality of sample analysis, however it is a matter of good laboratory practice and should comply with national environmental and health and safety regulations.

13 Equipment

(see also Appendix B)

13.1 Equipment qualification

13.1.1 Although not explicitly mentioned in ISO/IEC 17025 [2], the process of equipment qualification – defined as the process of ensuring equipment performance is appropriate for its intended use, from design to everyday use – is an underlying element of good equipment management. Equipment qualification is usually divided into four levels or stages, each dealing with different aspects of the equipment's history:

- Level I (Design Qualification, DQ) – Selection of an instrument and supplier;
- Level II (Installation Qualification, IQ) – Installation and release for use;
- Level III (Operational Qualification, OQ) – Periodic and motivated instrument checks;
- Level IV (Performance Qualification, PQ) – In-use instrument checks.

Level I deals with the initial stage of selecting the equipment and supplier. At this stage, key functions are specified and levels of performance are defined. In addition, requirements for other services, such as calibration, maintenance and training, are defined, according to the needs related to the intended use of the instrument and the laboratory's capabilities.

Level II addresses the operations to be performed and documented when the equipment is received and installed, before it can be released for routine use. Such operations will usually include checks that the equipment is received in good condition, as ordered, and assessment of its full functionality in the selected environment. This includes the start-up checks done by the supplier, followed by a full check of the equipment's key performance parameters, irrespective of any analytical method. Whenever required, calibration is performed as part of this stage. The release for use shall be documented and authorised by the person responsible for the instrument.

The checks performed before release also form the basis for periodic assessments of the instrument's functionality (Level III). These shall be performed at intervals which will depend on the frequency of use and knowledge of the stability of the instrument in the conditions of use. The checks shall also be performed if the instrument is moved to a new environment, or undergoes significant repair or maintenance operations. For measuring equipment, a process of 'metrological confirmation' (further explained in Section 13.2.2) shall be devised, to ensure that relevant metrological characteristics are kept under control. Acceptance criteria for the tested parameters should take into account the specification from the manufacturer of the instrument as well as the requirements for the intended use of the equipment.

Finally, checks of the performance of the equipment during routine use should be planned, to confirm, on a day-to-day basis, that the same quality level is achieved (Level IV). These are usually built into the analytical methods themselves, in terms of analytical response for blanks and calibration standards. Control charts for such responses, as well as for the QC samples used as part of the analytical methods allow the recording and monitoring over time of the equipment's performance. Further guidance and practical examples (e.g. for the qualification of spectrophotometers, mass spectrometers, HPLC) is available [36].

13.2 Categories of equipment

13.2.1 All equipment used in laboratories (including any associated software) should be of a specification sufficient for the intended purpose, and kept in a state of maintenance and metrological control consistent with its use (see Section 13.2.2). Equipment normally found in an analytical laboratory can be categorised as:

i) general service equipment not used for making measurements or with minimal influence on measurement results (e.g. hotplates, stirrers, non-volumetric glassware and glassware used for approximate volume measurements) and laboratory heating or ventilation systems;

ii) measuring instruments, including volumetric equipment (e.g. flasks, pipettes, pyknometers, burettes) and other instruments (e.g. hydrometers, U-tube viscometers, thermometers, timers, spectrometers, chromatographs, electrochemical meters, balances);

iii) physical measurement standards (weights, reference thermometers);

iv) computers and data processors.

13.2.2 Laboratories can obtain guidance on managing measurement processes and the metrological confirmation of measuring equipment used from ISO 10012 [37], which can help with developing effective metrological processes. According to the definition given in that standard, 'metrological confirmation' typically includes calibration and checks of the calibration status; maintenance and/or repair, followed by re-calibration as necessary; a comparison with the metrological requirements for the intended use; and sealing and/or labelling as required. Typical examples of characteristics for which metrological requirements should be established are: measuring interval, resolution, repeatability and trueness.

13.3 General service equipment

13.3.1 General service equipment will typically only be maintained by cleaning and safety checks as necessary. Metrological controls will be necessary where the setting can significantly affect the test or analytical result (e.g. the temperature of a muffle furnace or constant temperature bath). Such checks need to be planned, documented and recorded.

13.4 Measuring instruments

13.4.1 The performance of some volumetric (and related) glassware is dependent on particular factors, which may be affected by cleaning methods etc. As well as requiring strict procedures for maintenance, such equipment may require more regular and scheduled metrological control, depending on use. For example, the performance of pyknometers, U-tube viscometers, pipettes, and burettes is dependent on 'wetting' and surface tension characteristics. Cleaning procedures must be chosen so as not to compromise these properties. Such scheduled maintenance and metrological control activities need to be documented and recorded.

13.4.2 Attention should be paid to the possibility of contamination arising either from the fabric of the equipment itself, which may not be inert, or from cross-contamination from previous use. In the case of volumetric glassware, cleaning procedures, storage, and segregation of equipment may be critical, particularly for trace level analyses where leaching and adsorption can be significant.

13.4.3 Correct use combined with periodic servicing, cleaning and calibration will not necessarily ensure an instrument is performing adequately. Where appropriate, periodic performance checks should be carried out (e.g. to check the response, stability and linearity of sources, sensors and detectors, the separating efficiency of chromatographic systems, or the resolution, alignment and wavelength accuracy of spectrometers) – see Appendix B. Laboratories need to ensure that the test and calibration equipment (and any associated software) are protected against unauthorised adjustments, and have a systematic approach to transferring correction factors. Additional controls may be required when the equipment has been used outside of the laboratory, for example when performing field tests.

13.4.4 The frequency of such performance checks may be specified in manuals or operating procedures. If not, then it will be determined by experience and based on need, type and previous performance of the equipment. Intervals between checks should be shorter than the time the equipment has been found to take, in practice, to drift outside acceptable limits.

13.4.5 It is often possible to build performance checks – system suitability checks – into test methods (e.g. based on the expected detector or sensor response to RMs, the resolution of component mixtures by separation systems, or the spectral characteristics of measurement standards). These checks must be satisfactorily completed and recorded before the equipment is used.

13.4.6 In some cases, a test and its performance is actually defined in terms of a particular piece of equipment and checks will be necessary to confirm that the equipment conforms to the relevant specification. For example, the flashpoint value obtained for a particular flammable sample is dependent upon the dimensions and geometry of the apparatus used in the testing.

13.5 Physical measurement standards

13.5.1 Wherever physical parameters are critical to the correct performance of a particular test, the laboratory shall have or have access to the relevant measurement standard, as a means of calibration.

13.5.2 Measurement standards should be stored and used in a manner consistent with preserving their calibration status. Particular consideration should be given to any storage advice given in the documentation supplied with the measurement standard. Certificates and other relevant documentation should be stored in such a way as to be readily available until the measurement standards are in use and afterwards, filed for as long as deemed necessary to document the metrological

traceability of the measurements linked to them. Checks on the calibration status should be performed at regular intervals and laboratories should establish acceptance criteria for the results of their metrological control.

13.6 Computers and data processors

13.6.1 Requirements for computers are given in Section 22.

14 Reagents and consumables

14.1 The quality of reagents and other consumable materials must be appropriate for their intended use. Consideration needs to be given to the selection, purchase, reception and storage of reagents.

14.2 Suppliers of critical reagents and consumables should be evaluated and approved; relevant documentation and records should be maintained. The purpose of such evaluation is to prevent possible deviations from the expected quality of the measurement results that may arise from failure of any critical supply to meet the requirements. The process should be based on a risk assessment for the reagents and materials supplied. Key questions to be asked include:

- What may happen and why, should a given product fail to match the relevant specifications?
- What would be the consequences for the laboratory work?
- What is the chance of such a failure occurring?
- Are there any factors that may reduce either the probability of the failure or its consequences? Is the level of risk acceptable?

Further guidance on risk assessment and management is provided in ISO documents [38-40].

14.3 Documents referring to the purchase of reagents and other items affecting the quality of laboratory operations must contain an adequate description of the order. The order must clearly identify the specification required and the purpose for which the reagent is purchased. These documents should be reviewed and approved as appropriate prior to release.

14.4 Where the quality of a reagent is critical to a test, the quality of a new batch should be verified against the outgoing batch before use, provided that the outgoing batch is known to be still serviceable. However, in all cases, the reagents and other consumables should be inspected and verified as complying with set specifications.

14.5 Reagents received into the laboratory should be labelled with the dates of receipt, opening and expiry, plus the name of the person opening the reagent. The laboratory must ensure compliance with the expiry dates of reagents. For this purpose, the rule of FIFO (First In-First Out) or of FEFO (First Expired-First Out) should be applied.

14.6 The grade of any critical reagent used (including water) should be stated in the method description, together with guidance on any particular precautions which should be observed in its preparation, storage and use. These precautions relate to toxicity, flammability, stability to heat, air and light; reactivity to other chemicals; reactivity to particular containers; and other hazards. Reagents and RMs prepared in the laboratory should be labelled to identify substance, concentration, solvent (where not water), any special precautions or hazards, restrictions of use, and date of preparation and/or expiry. The person responsible for the preparation shall be identifiable either from the label or from records.

15 Metrological traceability

15.1 The formal definition of metrological traceability is given in 3.15. Practical guidance is provided by Eurachem/CITAC [14] and IUPAC [41]. Traceability is essential because it provides the linkage that ensures that measurement results obtained in different laboratories or at different times are comparable. To achieve this it is necessary to link all the individual measurement results to some common, stable reference. Such reference points can be a measurement unit (preferably those included in the internationally recognised system of units, the SI), a measurement procedure (e.g. a standard method) or a reference material. A complete traceability chain is achieved through a calibration hierarchy consisting of primary measurement standards (or other high level measurement standards) which are used to establish secondary measurement standards that can be used to calibrate working level standards and related measuring systems. Laboratories normally purchase their measurement standards from commercial producers. These are supplied with certificates demonstrating their traceability to higher level measurement standards. ILAC document P10 [42] describes the ILAC policy with regard to the metrological traceability requirements of ISO/IEC 17025 [2] and ISO 15189 [3], and provides laboratories with guidance on how to address the traceability issue. It has to be noted that every step in the traceability chain adds further uncertainty. Whenever possible, traceability to SI units through suitable measurement standards should be documented, in order to support the comparability of measurement results across space and time. It is acknowledged that some measurement results (e.g. pH, concentrations of some biological substances, hardness) have no SI units but even these can be defined. Such measurement results should be traceable to internationally agreed references (e.g. pH scale, WHO reference materials or Mohs scale). Therefore although traceability to SI is the ideal, it is not the only option for the start of a metrological traceability chain.

15.2 The results from chemical measurements are generally obtained by calculating the value of the measurand from a measurement model (or equation) that involves the values of other quantities, such as mass, volume, concentration of measurement standards etc. For the measurement result of interest to be traceable, all the quantity values in the equation must also be traceable. Other quantities not present in the measurement equation, such as pH, temperature etc. may also significantly affect the result. Where this is the case, the results of measurements used to control these quantities also need to be traceable to appropriate references. For other measurements (e.g. percent of fat in food), comparability of measurement results can only be achieved by the use of agreed methods. In such cases the measurand is then defined by the method and traceability is established as described in Section 15.5.

15.3 Establishing the traceability of physical quantities such as mass, volume, etc., is readily achieved, at the level of uncertainty needed for analytical measurements by calibration, according to established procedures, of the relevant equipment using measurement standards. The problem areas for analysts are usually calibration and validation of methods. Calibration is generally based on the repeated measurement of suitable calibrants having values with demonstrable traceability (e.g. pure substances or solutions of pure substances). Identity and purity of the chosen RMs are important issues, the former being more of a problem in organic chemistry, where much higher levels of structural detail are often required and confusion with similar components can readily occur. The uncertainty of the purity of the substance used as a RM, as well as the contributions from the preparation of a set of standards, will be part of the uncertainty budget for the measurement results, together with the uncertainty of the calibration itself (see the Eurachem/CITAC Guide [13] for a more detailed treatment of this issue). However, only in the case of some organic materials, where purity and stability problems can be severe, or where low uncertainty is required, will purity be a significant problem. A major issue in chemical analysis is the different analytical behaviour of atoms and molecules depending on their surrounding environment, i.e. a substance in pure water will behave differently from the same substance in a sample of food, waste water or blood. This is known as ‘matrix effect’. Therefore, beside calibration of measuring equipment, the traceability of measurement results in analytical sciences also relies on validation, to establish that the method actually measures what it is intended to measure (e.g. the mass fraction of methyl mercury in fish) and confirmation that the measurement equation used to calculate the results, including appropriate ‘recovery’ factors, if necessary, is valid. In addition, validation provides important information on the

performance of the method, which can be used to estimate the uncertainty of the measurement results [13, 43]. A more detailed discussion on method validation is given in Section 18.

15.4 For many chemical analyses, where extraction, digestion, derivatisation and/or saponification are commonly required, the main problem can be gaining good knowledge of the amount of analyte in the original sample relative to that in the sample presented to the end measurement process. Bias can arise due to incomplete recovery of the analyte from the sample matrix, processing losses, contamination or interferences. A detailed description of the issue is provided by IUPAC [44]. The strategies available to address method bias include:

- Use of primary or reference methods of known and small bias;
- Comparisons with closely matched matrix CRMs;
- Measurement of spiked samples and blanks;
- Study of losses, contamination, interferences and matrix effects;
- Collaborative studies according to ISO 5725 [45-50].

Establishing the traceability of measurement results for samples undergoing extensive pre-treatment requires relating the measurement bias to appropriate stated references, such as the values carried by matrix matched RMs. It should be noted that the measurement of the recovery of spiked samples does not necessarily completely simulate the extraction of the native analyte from the samples. Typically, problems can occur with the extraction of solids. For example, a spiked analyte may be freely available on the surface of the sample particles, whereas the native analyte may be strongly bound within the particles and therefore much less readily extracted. Problems may also occur, in certain circumstances, with liquid or even digested samples. For example, in biological samples, association with carrier biomolecules may be responsible for a reduction in the amount extracted compared to the extraction of the same analyte spiked into a sample. It is important to note that recovery factors, if applied, become part of the measurement model and, as such, will always contribute to the measurement uncertainty of the final measurement result.

In other cases the limitation in achieving traceability to SI derives from difficulty in evaluating bias and its uncertainty, such as the recovery of the analytes from complex matrices. One option is to define the measurand by the method and establish traceability as described in Section 15.5. Such measurements have a 'lower level' of traceability, but also have a smaller measurement uncertainty, relative to the stated references. Alternatively, the bias can be estimated and corrected for and the uncertainty due to the bias estimated and included in the overall uncertainty evaluation. In many cases bias is left uncorrected, but taken into account in the estimate of the measurement uncertainty [43].

15.5 Most measurement results from chemical analysis can, in principle, be made traceable to the mole. However, when the measurand is defined in operational terms, such as extractable fat or protein based on a nitrogen determination, then establishing traceability of these measurement results to the mole is not feasible. In such cases the measurand is defined by the method and variations in the protocol (e.g. a different solvent or a different conversion factor) lead to a different measurand. When using such methods traceability is to the agreed method (e.g. standard method), which shall be followed exactly, as well as to the corresponding SI units for the quantities used to calculate the result, e.g. mass and volume, the values produced by the method and/or the values carried by a RM. Such methods are called empirical methods.

16 Measurement uncertainty

16.1 Measurement uncertainty is formally defined in 3.16. Good practice in the evaluation of measurement uncertainty is described in an international guide [51] and recommendations for the harmonisation of uncertainty evaluations are given by EA [52]. An interpretation for analytical measurements, including a number of worked examples, is given in a Eurachem/CITAC Guide [13]. Measurement uncertainty characterises the range of values attributable to the measurand with a specified level of confidence. Every measurement result has an uncertainty associated with it, deriving from errors arising in the various stages of sampling and analysis and from imperfect knowledge of factors affecting the result. For measurement results to be of practical value it is necessary to have some knowledge of their uncertainty. A statement of the uncertainty associated with a result conveys to the customer the 'quality' of the result.

16.2 ISO/IEC 17025 [2] requires laboratories to evaluate the measurement uncertainty of their results. There is also a requirement to report measurement uncertainty under specific circumstances, for example, where it is relevant to the interpretation of the test result (which is often the case) or when it is requested by the customer.

16.3 The estimation of measurement uncertainty provides several advantages to both accredited and non-accredited laboratories, including:

- Improved knowledge of the (overall or individual) factors that affect the measurement result. This may provide key information for improving/optimising the method and for identifying efficient and cost-effective corrective measures, when necessary;
- A clear and quantitative statement of the quality of measurement results;
- Competitive advantage due to the added value the uncertainty estimation can provide for customers, particularly when assessing compliance with specifications;
- Less stringent control on influence quantities (e.g. environmental temperature, pH value of the sample) shown by the uncertainty evaluation to provide a negligible contribution to the overall uncertainty of the measurement result.

16.4 A wide variety of factors affect the result obtained from an analytical measurement. For example, temperature effects on volumetric equipment, reflection and stray light in spectroscopic instruments, variations in electrical supply voltages, an individual analyst's interpretation of the method and incomplete extraction of the analyte, all potentially influence the result. As far as reasonably possible such errors must be minimised by external control, or corrected for by applying a suitable correction factor. The exact effect on a single measurement result is, however, impossible to obtain. This is because the different factors vary from measurement to measurement, and because the effect of each factor on the result is never known exactly. The likely range of deviation must therefore be estimated.

16.5 Each step of the measurement process – such as sample preparation, extraction, clean-up, concentration or dilution, instrument calibration (including RM preparation), instrumental analysis and raw data processing – will contribute to the measurement uncertainty. The primary task in obtaining an estimate of the uncertainty of a measurement result is the identification of the relevant sources of uncertainty and the assignment of a value to each significant contribution. The separate contributions must then be appropriately combined in order to give an overall value (see [13] for guidance). A record should be kept of the individual sources of uncertainty identified, the value of each contribution, and the source of the value (for example, repeated measurements, literature reference, CRM data).

16.6 The component uncertainties can be evaluated individually or in convenient groups [43, 53]. For example, data from a precision study during method validation may provide an estimate of the total contribution of random variability, due to a number of steps in a measurement process. Similarly, an estimate of overall bias and its uncertainty may be derived from the analysis of matrix matched CRMs and spiking studies.

16.7 Where uncertainty contributions are estimated in groups, it is nonetheless important to record the sources of uncertainty which are considered to be included in each group, and to record individual uncertainty component values where available as a check on the group contribution.

16.8 If information from interlaboratory trials is used, it is essential to consider uncertainties arising

outside the scope of such studies. Further guidance on this issue can be found in ISO 21748 [54].

16.9 The uncertainty contributions for each source must all be expressed as standard deviations or relative standard deviations [51]. In some cases, this will require conversion of data. An uncertainty expressed as a standard deviation is known as a 'standard uncertainty' and has the symbol *u*. Details of how to calculate standard uncertainties from different types of data can be found in the Eurachem/CITAC Guide [13]. The summation of the components to obtain a combined standard uncertainty is also explained.

16.10 In order to express the uncertainty of a result with a particular level of confidence the overall uncertainty should be expressed as a multiple of the calculated combined standard uncertainty (this multiple is known as the expanded uncertainty, *U*). The recommended multiplier (coverage factor, *k*) is 2, that is, the expanded uncertainty is equal to 2*u*. Where the contributions arise from normally distributed errors, this value will correspond approximately to a 95% confidence interval.

16.11 It is often not necessary to evaluate uncertainties for every test and sample type. It will normally be sufficient to investigate the uncertainty over the scope of the method, and to use the information to estimate the measurement uncertainty for the results obtained with that method during routine use.

16.12 The uncertainty of a measurement result should be reported in such a way as to allow customers to interpret results unambiguously, taking into account the level of confidence that can be placed in them. A measurement result is therefore usually reported as $y \pm U$, with an indication of the coverage factor (*k*) used, the expected confidence level and a description or a reference to the procedure applied for the evaluation of the uncertainty.

16.13 The significant figures used to report the measurement result and its uncertainty should be consistent with the measurement capability. Therefore, in most analytical measurements, values for the expanded uncertainty should be reported with no more than two significant digits. The measurement result should be rounded [55] to be consistent with the stated uncertainty. For example, given a result of 215.342 mg kg^{-1} with an estimated combined standard uncertainty of 5.12 mg kg^{-1}, which corresponds to an expanded uncertainty of 10.24 mg kg^{-1}, the reported result should be: 215 mg kg^{-1} ± 10 mg kg^{-1} (k = 2, 95% confidence level).

17 Methods/procedures for calibrations and tests

17.1 It is the laboratory's responsibility to use methods which are appropriate for the required application. The laboratory may use its own judgement, it may select a method in consultation with the customer, or the method may be specified in regulation or by the customer. If methods are provided by the customer the laboratory shall ensure its capacity to carry them out and to achieve the quality requirements previously agreed with the customer.

17.2 Quality standards often favour the use of standard or collaboratively tested methods wherever possible. Whilst this may be desirable in situations where a method is to be widely used, or defined in regulation, sometimes a laboratory may have a more suitable method of its own. The most important considerations are that the method should be suitable for the purpose intended, be adequately validated and documented, and provide results that are traceable to stated references with an appropriate level of uncertainty.

17.3 The validation of standard or collaboratively tested methods should not be taken for granted. The laboratory should make sure that the method validation is adequate for the required purpose and that the laboratory personnel can achieve the stated performance criteria. Guidance on the topic of verifying the performance of a standard method is given in ISO 21748 [54].

17.4 Methods developed in-house must be adequately validated, documented, and authorised before use. Estimation of uncertainty should form part of this validation process Advice on method validation and measurement uncertainty is given in Sections 18 and 16, respectively.

17.5 Documentation of methods shall include:

- Information on the scope of applicability of the method and any limitations;
- Values for key performance characteristics such as repeatability, bias and limit of detection;
- Procedures for calibration and QC.

Information on how the result shall be reported, including the statement of its measurement uncertainty, should also be included along with instructions on how to deal with failures or out-of-specification test results. Guidance on investigating and reporting out-of-specification results is provided by IUPAC/CITAC [56]. A laboratory documenting methods may find it convenient to adopt a common format, such as ISO 78-2 [57], which provides a useful model. The documentation of methods is also discussed in the Eurachem guide on method validation [12]. In addition, advice is available from other sources such as national standardisation bodies and accreditation bodies.

17.6 Developments in methodology and techniques will require methods to be changed from time to time. Modification of methods may also be necessary as a result of investigations following poor performance in proficiency tests, or failure to meet internal quality control criteria. Method documentation must therefore be subject to adequate document control. Each copy of the method should show the issue number, date, issuing authority, and copy number. It must be possible to determine from records the most up-to-date version of each method which is authorised for use.

17.7 Obsolete methods should be withdrawn but must be retained for archive purposes and clearly labelled as obsolete. The difference in performance between revised and obsolete methods should be established so that it is possible to compare new and old data.

17.8 When methods are modified, consideration needs to be given as to whether the validation also needs to be updated. This will depend on the extent and significance of the modification. The modification may be of a minor nature, involving different sample sizes, different reagents etc. Alternatively, it may involve significant changes, such as the use of different technology or methodology. Revalidation should also be considered following changes in premises or instrumentation. The extent of revalidation will depend on the nature of the change. The laboratory, taking into account the nature of their tests, should establish rules regarding the extent of revalidation required.

17.9 Regular (though not necessarily frequent) review of the performance is required to ensure that methods are still fit-for-purpose. This may be carried out by an overall review of the outcomes of the procedures in place to assure the quality of the test results, such as results from internal quality control and PT data.

18 Method validation

18.1 Before a method is put into routine use, checks need to be carried out to ensure that the performance characteristics of a method are understood and to demonstrate that the method is scientifically sound under the conditions in which it is to be applied. These checks are collectively known as validation. Validation of a method establishes, by systematic laboratory studies, that the method is fit-for-purpose, i.e. its performance characteristics are capable of producing results in line with the needs of the customer. A method validation study starts with clear, sufficiently detailed and unambiguous descriptions of both the measurand and the method. Guidance on how to achieve this is provided by Eurachem [11, 12]. The next step is a statement of the criteria to be met, in terms of analytical performance. In some cases they may be clearly stated in regulations (see, for example, Commission Regulation (EC) 333/2007 [22]), but usually it is the task of the laboratory to translate the customer's needs into analytical requirements. The most important performance characteristics usually included in a validation study are:

- Selectivity (dealing with potential interference problems);
- Working range and linearity;
- Limit of detection/limit of quantification;
- Precision (single laboratory: repeatability, intermediate precision);
- Trueness (dealing with bias, recovery and traceability issues);
- Ruggedness;
- Measurement uncertainty.

The above characteristics are interrelated; many of them contribute to the overall measurement uncertainty. For routine applications, the data generated during an appropriately planned validation study provide the most comprehensive information for a reliable evaluation of the measurement uncertainty (see Section 16).

Good practice in method validation is described in a Eurachem Guide [12] to which the reader is referred for more detailed explanation and guidance on this topic. Note that there is no unanimous agreement on the interpretation of some of the above terms nor the conventions used in their determination. Thus, when reporting validation data, it is advisable to state any conventions followed.

18.2 The extent of validation must be clearly stated in the documented method so that the users can assess the suitability of the method for their particular needs. This may be done with an appropriate summary of the results and reference to a separate validation report.

18.3 Standard methods are normally developed and validated collaboratively by a group of experts [45-50]. This development should include consideration of all of the necessary aspects of validation and related uncertainty. However, the responsibility remains firmly with the user to ensure that the validation documented in the method is sufficiently complete to fully meet their needs. This implies that any factors likely to influence the measurement results within the stated scope of the method, but not adequately covered by the collaborative study, should be identified and evaluated in terms of their contribution to the parameters subject to validation and in particular to the estimate of measurement uncertainty. Even if the validation is complete, the user will still need to verify that the documented performance characteristics (e.g. trueness and precision) can be met in their own laboratory and that they are fit-for-purpose.

18.4 As indicated above, there are different opinions concerning the terminology and the process of method validation. For further information on the terminology see the VIM [10] and the Eurachem Guide [11]. The following explanations supplement those in other parts of this Guide and are intended to provide guidance rather than a definitive view. The following parameters are mostly related to *quantitative methods* but some additional remarks related to qualitative methods can be found in Section 18.10.

18.5 ***Selectivity*** of a method refers to the extent to which the method can be used to determine particular analytes in mixtures or matrices without interferences from other components with similar characteristics. The applicability of the method should be studied using various samples, ranging from pure measurement standards to mixtures with complex matrices. In each case the recovery of the analyte(s) of interest should be determined and the influences of suspected interferences duly stated. Any restrictions on the applicability of the method should be recorded in the method documentation.

18.6 ***Working range and linearity:*** For quantitative analysis, the working range for a method is determined by examining laboratory samples with different analyte concentrations and determining the concentration range for which acceptable uncertainty can be achieved. A prerequisite for carrying out quantification is to establish a calibration function for the final measuring instrument. For that reason, it may be relevant to consider separately the method working range and the instrument working range. In both cases the working range is generally more extensive than the linear range, which is determined by the analysis of a number of samples of varying analyte concentrations and calculating the regression statistics from the results, usually using the method of least squares. For the instrument working range the relationship of analyte response to concentration does not have to be perfectly linear for a method to be effective. Where linearity is unattainable for a particular procedure, a suitable algorithm for calibration should be determined. Working range needs to be established for each matrix covered in the method scope.

18.7 The ***limit of detection (LOD)*** is the lowest amount of the analyte that can be detected by the method at a specified level of confidence. Its value is likely to be different for different types of sample. LOD is a complex parameter which is particularly important in trace level analysis. For more detailed explanation and guidance refer to the Eurachem Guide [12].

18.8 The ***limit of quantification (LOQ)*** is the lowest concentration of analyte that can be determined with an acceptable level of uncertainty and can, therefore, be set arbitrarily as the required lower end of the method working range. For more detailed explanation and guidance refer to the Eurachem Guide [12].

18.9 ***Precision*** is a measure of the closeness of agreement between mutually independent measurement results obtained under specified conditions. It is usually expressed by statistical parameters which describe the spread of results, typically a standard deviation. Precision is generally dependent on analyte concentration, and this dependence should be determined and documented. Deciding on the 'specified conditions' is an important aspect of evaluating measurement precision. *Repeatability* is a type of precision expected to represent the smallest variation in results. It is a measure of variability in results when measurements are performed on the same material by a single analyst using the same method and equipment over a short timescale. *Intermediate precision* gives an estimate of the variation in results when measurements on the same material are made in a single laboratory using the same method over an extended timescale, and therefore under conditions that are more variable than repeatability conditions. Other parameters can be varied during the period of the study (e.g. analyst, reagents, equipment) and it is important for these to be documented. Reproducibility, expected to represent the largest variation in results, is a measure of the variability in results when measurements are made in different laboratories. Precision is a component of measurement uncertainty (see Section 16). Note that there are some special considerations regarding precision in relation to qualitative measurements (see Section 18.10).

18.10 The statements of precision described in Section 18.9 relate to quantitative analysis. Qualitative analysis can be treated in a slightly different way. Qualitative analysis effectively is a measurement that provides a yes/no answer at a given threshold analyte value. For qualitative methods, the precision cannot be expressed as a standard deviation or relative standard deviation, but may be expressed as true and false positive (and negative) rates. These rates should be determined at a number of concentrations; below, at and above the threshold level. Data from a confirmatory method should be used if an appropriate method is available. If such a method is not available, spiked and unspiked blank samples may be analysed. Further information on establishing the performance of qualitative methods can be found in the Eurachem Guide [12].

18.11 Confirmation (of identity) requires the measurement to be performed by more than one technique, where the techniques are based on different physico-chemical principles. Confirmation increases confidence in the result obtained. In some applications, for example the analysis of unknown organic compounds by gas chromatography, the use of confirmatory techniques is essential.

18.12 ***Trueness*** of a method is generally estimated as bias, i.e. the systematic error. Three approaches are commonly used during validation for the determination of bias: a) analysis of RMs, b) recovery experiments using spiked samples, and c) comparison with results obtained using another method. The issues associated with the estimation of bias and recovery are discussed in Section 15.4.

18.13 ***Ruggedness*** (sometimes also called ***robustness***) provides an indication of a method's

reliability during normal use. A ruggedness study evaluates a method's capacity to remain unaffected by small variations in method parameters. It involves deliberately introducing small changes to the method and examining the consequences. A large number of factors may need to be considered, but because most of these will have a negligible effect, it will normally be possible to vary several at once, particularly if experimental design tools are used. A commonly applied approach is described by AOAC [58] and a practical example of its application in the area of testing for drug residues in food of animal origin is given in Commission Decision 657/2002/EC [59]. Ruggedness should be established for methods developed in-house. However, it is not generally necessary for an individual laboratory to carry out ruggedness testing when implementing a standard method being used within in its scope, as ruggedness should have been established prior to publication of the method.

19 Calibration

19.1 Calibration is defined as an 'operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication' [10]. A discussion of the concept of calibration can be found in the Eurachem Guide [11]. The usual way to perform a calibration is to subject known amounts of the quantity (e.g. using a measurement standard) to the measurement process and monitor the measurement response over the expected working range. More detailed information on RMs is given in Section 20. Guidance on linear calibration using RMs is given in ISO 11095 [60].

19.2 The overall programme for calibration in the chemical laboratory shall be designed to ensure that all measurements that have a significant effect on test or calibration results are traceable to a measurement standard, preferably a national or international measurement standard such as a CRM (see Section 15). Where appropriate and where feasible, CRMs should be used. Where formally designated measurement standards are not available, a material with suitable properties, homogeneity and stability should be selected or prepared by the laboratory and used as a laboratory measurement standard. The required properties of this material should be characterised by repeat testing, preferably by more than one laboratory and using a variety of validated methods (see ISO Guide 35 [61]).

19.3 Analytical tests may be sub-divided into general classes depending on the type of calibration required.

19.3.1 Some analytical tests depend critically on the measurement of physical properties, such as weight measurement in gravimetry and volume measurement in titrimetry. Since these measurements have a significant effect on the results of the test, a suitable calibration programme for these quantities is essential. The requirements and methods for the calibration and control of balances are described in a Euramet Guide [62], while procedures for the calibration of volumetric devices, such as piston pipettes and burettes, are described in ISO 8655 [63-69]. In addition, the calibration of measuring devices used to establish the purity or concentration of all the chemical standards used needs to be considered.

19.3.2 Where a test is used to measure an empirical property of a sample, such as flashpoint, equipment is often defined in a national or international standard method and traceable RMs should, where available, be used for calibration purposes. New or newly acquired equipment must be checked by the laboratory before use to ensure conformity with the specified design, dimensions and performance requirements.

19.3.3 Instruments which require calibration as part of their normal operation, such as spectrometers or those used for chromatography, should be calibrated using RMs of known composition (usually solutions of pure chemicals).

19.3.4 In some cases, calibration of the whole analytical process can be carried out by comparing the measurement output from a sample with the output produced by a suitable RM that has been subjected to the same full analytical process as the sample. The RM may be either a synthetic mixture prepared in the laboratory from materials of known (and preferably certified) purity, or a purchased certified matrix RM. However, in such cases, a close match between the test sample and the matrix RM, in terms of the nature of the matrix and the concentration of the analyte, has to be assured. ISO Guide 33 provides guidance on the use of RMs [70].

19.4 In many cases, calibration is only performed on the final measurement stage. For example, calibration of a gas chromatograph may be carried out using a series of measurement standards which are synthetic solutions of the analyte of interest at various concentrations. Such calibration does not take into account factors such as contamination or losses that occur during the sample preparation, or extraction and derivatisation stages. It is therefore essential during the method validation process to explore the potential problems of contamination and losses by taking matrix RMs or spiked samples through the whole measurement process, and design the day-to-day calibration procedure and QC checks accordingly (also see Section 15.4).

19.5 Individual calibration programmes shall be established depending on the specific requirements

of the analytical method. It may be necessary to check instrument calibration after any shutdown and following service or other substantial maintenance. The level and frequency of calibration should be based on previous experience and should be at least that recommended by the manufacturer. Guidance on calibration is given in Appendix B which includes typical calibration intervals for various types of simple instruments and indicates the parameters which may require calibration in more complex analytical instruments. The frequency of calibration required will depend on the stability of the measurement system, the level of uncertainty required and the criticality of the work. Instruments such as chromatographs and mass spectrometers that are affected by drift may require the use of frequent drift checks and recalibration during the course of a single measurement session. Additional guidance on how to establish suitable calibration intervals is given by OIML [71].

19.6 Procedures for performing calibrations shall be adequately documented, either as part of a specific analytical method or as a general calibration document. The documentation should include how to perform the calibration and intermediate checks of calibration status, how to determine the uncertainty of the calibration, how frequently calibration and checks are required, and action to be taken in the event of calibration failure. A description of how to estimate the uncertainties associated with a linear least squares calibration curve is given in the Eurachem/CITAC Guide [13]). Frequency intervals for the calibration of physical measurement standards should also be indicated and, where feasible, procedures and plans for intermediate checks of their calibration status should be in place.

19.7 The calibration of volumetric glassware is primarily performed indirectly by mass determination of a specific volume of water of known density at a given temperature [72]. If the glassware is subsequently used with liquids having properties that are very different from water (wetting characteristics, surface tension etc.) the uncertainty in the measured volume would be expected to increase. This is particularly pertinent for volumetric glassware calibrated to deliver a certain volume. For methods to obtain a result having a low overall uncertainty, the determination of volume indirectly through mass and density of the particular liquid(s) is recommended.

20 Reference materials

20.1 A series of ISO documents relating to RMs is available [61, 70, 73-76].

20.2 Reference materials and certified reference materials are defined in Section 3. They are used for calibration, method validation, evaluating measurement uncertainty, quality control and for training purposes. However, a specific RM can only be used for one purpose in a measurement, e.g. for calibration or for QA purposes. Figure 1 shows a typical analytical process and illustrates the role of RMs in relation to calibration, method validation and QC.

20.3 RMs may take a variety of forms, including pure substance RMs, matrix RMs and solutions or mixtures. The following are all examples of RMs:

- 99% pure sodium chloride;
- An aqueous solution with mass concentrations of copper (II) sulfate equal to 10 g/l and magnesium chloride equal to 20 g/l;
- A powdered polymer with a particular molecular weight distribution range;
- A crystalline solid melting in the range 150-151 °C;
- A dried milk powder containing a known amount of vitamin C.

20.4 For many types of analysis, calibration may be carried out using materials prepared within the laboratory from chemicals of known purity and composition (for example solutions of known concentration). Some chemicals may be purchased with a manufacturer's certificate stating purity. Alternatively, chemicals of a stated but uncertified purity may be purchased from reputable suppliers. Whatever the source, it is the user's responsibility to establish that the quality of such materials is fit-for-purpose. Sometimes additional tests will need to be carried out by the laboratory. Normally a new batch of a chemical should be checked against the previous batch. Ideally, all chemicals to be used as RMs should be purchased from producers with demonstrated quality management systems. However, a QMS does not automatically guarantee the quality of the producer's products and laboratories should take all reasonable steps to confirm the quality of critical materials. The control of impurities is important, especially for trace level analysis, where they may cause interferences. Due regard should be paid to the manufacturer's recommendations on storage and shelf life. In addition, caution is needed, as suppliers do not always provide information about all impurities.

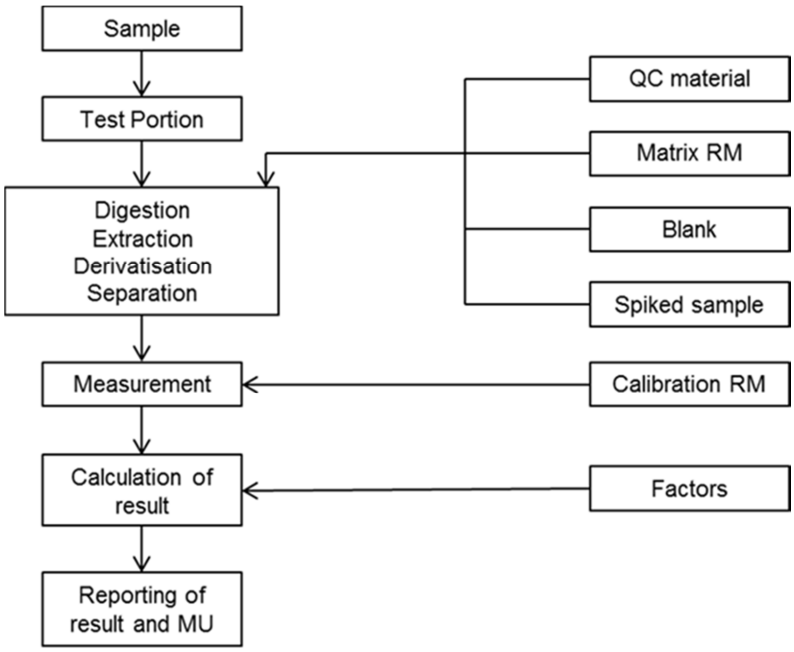

Figure 1 – Example of a typical analytical process, showing the role of RMs

20.5 The use of appropriate RMs enables analysts to demonstrate the traceability of results by calibrating equipment, to validate methods and to monitor the method's performance. They may also be used as transfer (measurement) standards for comparison of methods. Their use is strongly encouraged wherever appropriate.

20.6 The uncertainty associated with the stated purity of a pure substance CRM needs to be considered in relation to the uncertainty associated with other aspects of the method. Ideally, the uncertainty associated with the property value of a RM, used for calibration purposes, should not contribute more than one third of the overall measurement uncertainty.

20.7 An important factor in selecting RMs is their commutability. This is the property of an RM whereby it is demonstrated to behave similarly to test samples under the same measuring conditions. The concept is defined in VIM [10] and discussed further in the Eurachem Guide [11]. Specific guidelines for RMs used in laboratory medicine are published by CLSI [77]. In general, the composition of the RM should be as close as possible to that of the samples. Where matrix interferences potentially exist, ideally a method should be validated using a matched matrix RM certified in a reliable manner. If such a material is not available it may be acceptable to use a sample spiked with a RM.

20.8 It is important that any CRM used has been produced and characterised in a technically valid manner. Users of CRMs should be aware that not all materials are produced with the same degree of rigour. Details of homogeneity and stability studies, the methods used in certification, and the uncertainties and variations in the stated analyte values, are usually available from the producer and should be used to judge their reliability. The material must be accompanied by a certificate, which includes an estimate of the uncertainty associated with the certified value. ISO 17034 [75] specifies criteria for the competence of RM producers.

20.9 RMs and CRMs should be clearly labelled so that they can be unambiguously identified and referenced against accompanying certificates or other documentation. Information should be available indicating shelf life, storage conditions, applicability, and restrictions of use. RMs prepared within the laboratory, e.g. as solutions, should be treated as reagents for the purposes of labelling (see Section 14.6).

20.10 The handling of measurement standards should safeguard against them becoming contaminated or degraded. Procedures for training personnel should reflect these requirements.

21 Quality control and proficiency testing

21.1 The meaning of the terms 'quality control' (QC) and 'quality assurance' (QA) often vary according to the context. According to ISO 9000 [9], QA addresses the activities the laboratory undertakes to provide confidence that quality requirements will be fulfilled, whereas QC describes the individual measures which are used to actually fulfil the requirements (see Sections 3.6 and 3.7).

21.2 Once method performance criteria have been set and method validation completed successfully, as part of a laboratory's QMS, specific controls need to be applied to the method to verify that it remains in control during routine use, i.e. its performance continues to be fit-for-purpose. During the validation stage the method is largely applied to samples of known content. Once the method is in routine use it is used for samples of unknown content. Therefore, suitable QC should be planned and implemented to allow ongoing monitoring of day-to-day and batch-to-batch analytical performance. The level and type of QC will depend on the nature, criticality and frequency of the analysis, batch size, degree of automation and test difficulty, and also on the lessons learnt during development and validation processes. QC can take a variety of forms, both inside the laboratory (internal) and between the laboratory and other laboratories (external).

21.3 ***Internal QC*** refers to procedures undertaken by laboratory personnel for the continuous monitoring of operations and measurement results in order to decide whether results are reliable enough to be released [78-80]. This includes replicate analysis of stable test samples, blanks, standard solutions or materials similar to those used for the calibration, spiked samples, blind samples and QC samples. The use of control charts is recommended, particularly for monitoring the results obtained from the analysis of QC samples [81-85].

21.3.1 The level of QC adopted must be demonstrably sufficient to ensure the validity of the results. Different types of QC may be used to monitor different types of variation within the process. QC samples, analysed at intervals in the sample batch will indicate drift in the system; use of various types of blank will indicate any contribution to the instrument signal from sources other than the analyte; duplicate analyses of routine test samples will give a check of repeatability.

21.3.2 QC samples are typical samples which are sufficiently stable and homogeneous, and available in sufficient quantity, to allow repeat analysis over time. As long as the QC sample result is acceptable it is likely that results from samples in the same batch as the QC sample can be taken as reliable. To quickly assess if the result from a QC sample is acceptable the results are usually plotted on a control chart. A frequently used control chart (known as an x-chart or Shewhart chart) consists of a central line representing the mean value for the QC sample and two other lines described as warning limits and action limits. These limits are set at $\pm 2s$ and $\pm 3s$ about the mean value respectively (where s is an experimentally obtained estimate of the standard deviation or a target standard deviation based on a requirement). Detailed criteria for assessing QC results against the limits are required to enable the laboratory to make best use of the QC results and take appropriate action when necessary [79, 80, 82]. In order to set realistic limits on the control chart, the initial measurements made on the QC sample to estimate the standard deviation must reflect the way the method is actually intended to be used on a day to-day basis. If this is not done, then the experimentally obtained standard deviation will be unrealistically small, resulting in limits being set on the chart which cannot possibly be complied with in normal use. Since the initial estimate of s is often based on a relatively small dataset, it is generally advisable to reassess the limits after one year or when sufficient results have been collected [80]. Over this period, the standard deviation obtained from the QC sample results provides a reliable estimate of the intermediate precision of the method.

21.3.3 The use of various types of blanks enables the analyst to ensure that results obtained for test samples can be suitably corrected to remove any contributions to the response which are not attributable to the analyte.

21.3.4 Replicate analysis of routine test samples provides a means of checking for changes in precision in an analytical process, which could adversely affect the result [86]. Replicates can be adjacent in a batch to check repeatability. Analysis of blind samples is effectively a form

of repeat analysis and provides a means of checking precision. It consists of replicated test portions placed in the analytical batch, possibly by the laboratory supervisor, and is so-called because the analyst is not normally aware of the identity of the test portions or that they are replicates. Thus the analyst has no preconceived ideas that the particular results should be related. Standards or materials similar to those used for calibration, placed at intervals in an analytical batch, enable checks to be made that the response of the analytical process to the analyte is stable.

21.3.5 It is the responsibility of the laboratory management to set and justify an appropriate level of QC, based on risk assessment, taking into account the reliability of the method, the criticality of the work, and the feasibility of repeating the analysis if the QC sample result is unacceptable. It is widely accepted that for routine analysis, a level of internal QC of 5% is sufficient, i.e. 1 in every 20 samples analysed should be a QC sample. However, for robust routine methods with high sample throughput, a lower level of QC may be reasonable. For more complex procedures, a level of 20% is not unusual and on occasions even 50% may be required. In some sectors, for example water analysis, guidance is available on the level of QC required [87]. For analyses performed infrequently, a full system validation should be performed on each occasion. This may typically involve the use of a RM containing a certified or known concentration of analyte, followed by replicate analyses of the sample and spiked sample (a sample to which a known amount of the analyte has been deliberately added). Those analyses undertaken more frequently should be subject to systematic QC procedures incorporating the use of control charts and check samples.

21.4 ***Proficiency testing (External Quality Assessment):*** Regular participation in PT, also known as external quality assessment (EQA), is a recognised way for a laboratory to monitor its performance against both its own requirements and the norm of peer laboratories. PT helps to highlight variation between laboratories (reproducibility) and, in some circumstances, systematic errors (bias). PT schemes and other types of interlaboratory comparison are accepted as being an important means of monitoring the degree of equivalence of measurement results at national and international levels.

21.5 Accreditation bodies recognise the benefit of these schemes and strongly encourage laboratories to participate in PT/EQA as an integral part of their quality management. It is important to monitor PT results and take action as necessary. In certain instances, accreditation bodies may specify participation in a particular PT scheme as a requirement for accreditation. The value of PT is of course only as good as the schemes themselves. Requirements for the competence of PT providers are described in the standard ISO/IEC 17043 [88]. The statistical aspects of PT schemes are described in ISO 13528 [89]. Practical information on how to select, use and interpret PT schemes is presented in a Eurachem Guide [90]. Information about a large number of schemes can be found in the EPTIS database (www.eptis.bam.de). However, for emerging fields of analysis or rare applications in particular, there may be no scheme available that is fully appropriate. These, and other limitations, are considered in an EA guidance document on the level and frequency of participation in PT [91] and guidance form IUPAC/CITAC on the selection and use of proficiency testing schemes for a limited number of participants [92].

21.6 ISO/IEC 17025 [2] states that quality control data shall be analysed and, where they are found to be outside pre-defined criteria, planned action shall be taken to correct the problem and to prevent incorrect results from being reported. Therefore, the data obtained from QC activities and participation in PT should be checked and interpreted against predetermined limits immediately. Moreover, it is recommended to plot results and review trends in the data obtained from QC/PT. The laboratory's QMS should include procedure(s) for identifying nonconforming work in relation to QC and PT results, and policies for identifying and implementing appropriate corrective actions.

22 Computers and computer controlled systems

22.1 In the laboratory, computers have a wide variety of uses, including:

- Control of critical environmental conditions;
- Monitoring and control of inventories;
- Calibration and maintenance schedules;
- Stock control of reagents and measurement standards;
- Experimental design;
- Statistical analysis of data;
- Scheduling of samples and monitoring of work throughput;
- Control chart generation;
- Monitoring of test procedures;
- Control of automated instrumentation;
- Capture, storage, retrieval, processing of data, manually or automatically;
- Data transfer;
- On-board instrumental data processing;
- Matching of sample and library data (e.g. comparing mass spectra);
- Sample tracking;
- Generation of test reports;
- Word processing;
- Communication;
- Laboratory information management systems (LIMS).

Guidance on the management of computers and software in laboratories in the context of ISO/IEC 17025 [2] accreditation has been produced by Eurolab [93].

22.2 Interfaces and cables provide physical connections between different parts of the computer or between different computers. It is important that interfaces and cables are chosen to suit the particular application since they can seriously affect speed and quality of data transfer.

22.3 The chemical testing environment creates particular hazards for the operation of computers and storage of electronic media. Advice can usually be found in the operating manuals, however particular care should be taken to avoid damage due to chemical, microbiological or dust contamination, heat, damp, and magnetic fields.

22.4 Initial checking should verify as many aspects of a computer's operation as possible. Similar checks should be carried out if the computer's use is changed, or after maintenance, or revision of software. Where a computer is used to gather and process data associated with chemical testing, for validation of that function, it is usually sufficient to assume correct operation if the computer produces expected answers when input with known parameters. Computer programs performing calculations can be validated by comparison with manually generated results. It should be noted that some faults will occur only when a particular set of parameters is input. For this reason, it is necessary to ensure that the dataset to be used for validation provides all the variables that may occur during the expected use. At least three sets of data are necessary for the validation. If commercial software is used, the validation can be replaced by the certification provided by the manufacturer. In all cases the software must be verified before use. In chemical testing, suitable checks on the data gathering and handling functions could be made using a CRM for the initial validation, with a secondary measurement standard such as a QC sample used for regular repeat checks. Any recommendations made by the manufacturer should be taken into consideration. The validation procedure used for a particular system and any data recorded during validation should be documented. It may be difficult to validate these systems in isolation from the analytical instrument producing the original signal. Usually the whole system is validated in one go, by using chemical measurement standards. Such validation is normally acceptable. The validation required in particular cases is discussed in Sections 22.4.1-22.4.6.

22.4.1 ***Word processing packages*** are widely used in laboratories to generate a variety of documentation. The laboratory should ensure that the use of word processing packages is controlled sufficiently to prevent the production of unauthorised reports or other documents. In the most simple cases, where the computer acts as little more than an electronic typewriter, validation is achieved by manually checking and approving hard or soft copies. More sophisticated systems read and process data to automatically produce reports in predetermined

formats. Such systems will require additional checks.

22.4.2 ***Spreadsheet packages*** are commonly used in laboratories to store, collate, summarise and present data, to calculate measurement results from instrument outputs, to plot charts and to carry out statistical analysis. For certain applications (particularly statistical analysis) in-built functions may be used rather than entering the relevant equations manually. In either case, spreadsheets should be validated to confirm that any equations/in-built functions used return the correct value. It is particularly important to establish that the correct input data are being referenced. Spreadsheets can be validated by using a test dataset and comparing the results with manual calculations. Procedures should be put in place to minimise the risk of incorrect data entry/transfer and to ensure that any calculations cannot be edited (either intentionally or accidentally) after the spreadsheet has been validated.

22.4.3 ***Microprocessor controlled instruments*** will normally have a self-checking routine which is activated when the instrument is switched on, and will include the recognition and checking of all peripheral equipment. Often the software is not accessible. Under most circumstances validation can be performed by testing the various aspects of instrument function using known parameters, e.g. by testing RMs, physical or chemical measurement standards or QC samples.

22.4.4 ***Data handling or processing systems, integration systems.*** The output from measuring instruments will usually need to be converted to a digital signal using an analogue/digital converter, before it can be processed. The digitised data are then translated into a recognisable signal (numbers, peaks, spectra according to the system) by the software algorithm. Programmed instructions are provided by the algorithm for a number of factors, e.g. deciding where peaks start and finish, whether a number should be rounded up or down. The algorithm is a common source of unexpected performance and validation should test the logic behind the decisions made by the algorithm.

22.4.5 ***Computer controlled automated system.*** This may embrace one or more of the foregoing examples, operated either simultaneously or in a controlled time sequence. Such systems will normally be validated by checking for satisfactory operation (including performance under extreme circumstances) and establishing the reliability of the system before it is allowed to run unattended. The validation should consist of a validation of individual components, plus an overall check on the dialogue between individual components and the controlling computer. An assessment should be made of the likely causes of system malfunction. One important consideration is that the computer, interfaces and connecting cabling have sufficient capacity for the required tasks. If any part of the system is overloaded, its operation will slow down and possibly data may be lost. This could have serious consequences where the operations include time sequenced routines. Where possible the controlling software should be tailored to identify and highlight any such malfunctions and tag associated data. The use of QC samples and standards run at intervals in the sample batches should then be sufficient to monitor correct performance on a day-to-day basis. Calculation routines can be checked by testing with known parameter values. Electronic transfer of data should be checked to ensure that no corruption has occurred during transmission. This can be achieved on the computer by the use of 'verification files' but, wherever practical, the transmission should be backed-up by a hard copy of the data.

22.4.6 ***Laboratory Information Management Systems*** are widely used as a way of managing laboratory activities. A LIMS is a computer based system with software which allows the electronic collation, calculation and dissemination of data, often received directly from analytical instruments. It incorporates word-processing, database, spreadsheet, and data processing capabilities and can perform a variety of functions, including: sample registration and tracking; test assignment and allocation; worksheet generation; processing captured data; QC; financial control; and report generation. The operation of the LIMS may be confined to the laboratory itself or it may form part of a company-wide computer system. Information may be input manually or downloaded directly from analytical instrumentation or other electronic devices such as bar-code readers. Information can be output either electronically or as hard-copies. Electronic outputs could consist of raw or processed data written to other computers either within the organisation, or remote. Similarly the information could be downloaded to an external storage device. Where

data cross from one system to another there may be a risk of data corruption through system incompatibility or the need to reformat the information. A well designed system enables high levels of QA to be achieved, right from the point of sample entry to the production of the final report. Particular validation requirements include management of access to the various functions, and audit trails to catalogue alterations and file management. Where data are transmitted electronically it will be necessary to build in safety checks to guard against data corruption and unauthorised access.

22.5 ISO/IEC 17025 [2] has specific requirements in relation to the control of documents and records. Any electronic system used for the generation and management of documents/records must therefore meet these requirements. In many respects, electronic systems can simplify document management and control. However, a number of key aspects still need to be considered. These include:

- Accessibility;
- Security, in particular controls to prevent unauthorised modification;
- Retrieval – will the documents/records still be accessible after future hardware/software upgrades?

23 Laboratory audit and review

23.1 See Sections 3.8 and 3.9 for terminology.

23.2 An important aspect of quality management is the periodic re-examination of the QMS by the laboratory management. In general, all aspects of the QMS should be examined at least once a year. The system should be examined in two ways.

1) It should be examined to ensure that it is sufficiently well documented to enable adequate and consistent implementation, and that personnel are following the procedures described. This examination is commonly known as an internal audit (as opposed to the external assessment carried out by accreditation bodies).

2) The QMS should be examined to see whether it meets the requirements of the laboratory, its customers and, if appropriate, the quality management standard. Over a period of time the needs of the laboratory and its customers will change and the QMS should evolve to continue to fulfil its purpose.

This second type of examination is commonly known as management review and should be carried out at least annually. It is carried out by the laboratory management and draws on information from a number of sources. These include results from internal audits, external assessments, performance in PT schemes, internal QC studies, revision of procedures, market trends, customer complaints and compliments, etc. ISO 19011 [94] provides guidance on the auditing of management systems.

23.3 The programme of internal audits and management review is normally delegated by the management of the laboratory to the laboratory quality manager, who is responsible for ensuring that auditors have the correct technical knowledge, training, guidance and authority necessary for their work. A timetable of the internal audit of specific areas of the laboratory must be drawn up each year, including the audit criteria and the personnel involved. The results are reported at the management review. Internal audits are normally carried out by the quality manager or other laboratory personnel who work outside of the area they are examining. This may not always be possible where the number of personnel is small. Sometimes it is necessary to ask an external person (to undertake an audit or management review), or another qualified person to carry out the audit alone or assisted by a qualified person working in the area.

23.4 Audits may be carried out in two basic ways:

1) In a horizontal internal audit, the auditor will examine in detail single aspects of the QMS, for example calibration, training procedures and records, or reports.

2) In a vertical internal audit the auditor will select a sample and follow its progress from sampling (or receipt of the sample) through to reporting of result(s) and sample disposal, examining all aspects of the QMS relating to its testing (calibration, results from participation in PT, quality controls, control of instruments, etc.).

ISO/IEC 17025 [2] states that the cycle for internal audits should normally be completed within one year.

23.5 A check list, with examples, of aspects of a chemical laboratory which could be relevant for examination during an internal audit is shown in Appendix A of this Guide. It is a requirement that all points of the relevant ISO standard are covered and controlled over the internal audit period. Afterwards, a report is required documenting the noncompliances and shortcomings, and the timescale of the required implementation of corrections and improvements to the QMS. It is necessary that these points are followed up and can be closed in a specific period of time. The laboratory should also monitor and demonstrate the effectiveness of the actions taken.

23.6 The management review should be carried out at regular intervals. Once a year is normally sufficient although, for laboratories with extensive scopes of accreditation, it may be necessary to split the management review into discrete modules that can be examined during the course of the year. The laboratory should establish a procedure for planning, performing and reporting of management reviews and follow up – including a fixed agenda, comprising the issues mentioned in Section 23.2.

Appendix A – Quality audit: Areas of particular importance to a chemistry laboratory

A.1 Personnel

i) Personnel who operate specific equipment, perform tests and/or calibrations, evaluate results, sign test reports and calibration certificates, and/or provide opinions and interpretation are qualified on the basis of appropriate education, training, experience and/or demonstrated skills.

ii) On-the-job training is carried out against established criteria, which are relevant to the present and anticipated tasks of the laboratory. The effectiveness of the training is evaluated. Up-to-date records of the training are maintained.

iii) Tests and calibrations are carried out only by authorised analysts. Personnel undergoing training have appropriate supervision.

iv) The performance of personnel carrying out analyses is observed by the auditor.

v) The performance of authorised personnel is continuously monitored.

A.2 Accommodation and environmental conditions

i) The laboratory environment is suitable for the work carried out.

ii) The laboratory services and facilities are adequate for the work carried out.

iii) There is adequate separation of potentially conflicting work.

iv) The laboratory areas are sufficiently clean and tidy to ensure the quality of the work carried out is not compromised.

v) There is adequate separation of sample reception, preparation, clean-up, and measurement areas, to ensure the quality of the work carried out is not compromised. In the case of small laboratories where management of space is not feasible, management of time (i.e. effective scheduling of different aspects of the work) is required.

vi) Adherence to health and safety regulations is consistent with the requirements of the QMS.

vii) Environmental conditions are monitored and recorded when specified in methods or procedures, or where they influence the quality of the results. Tests and calibrations are stopped when the environmental conditions jeopardise the results of the tests and/or calibrations.

viii) Access to, and use of, areas affecting the quality of the tests and/or calibrations is maintained under appropriate control.

ix) Measures are taken to ensure good housekeeping in the laboratory. Special procedures are implemented where necessary, for example where particular cleaning protocols are required to ensure the quality of results.

A.3 Equipment

i) The laboratory has available all equipment required for the correct performance of the tests and/or calibrations. The equipment in use (and any associated software) is suitable for its intended purpose.

ii) Appropriate instructions for use and maintenance of equipment (including manuals) are available.

iii) Equipment is used by authorised personnel.

iv) Major instruments are correctly maintained and records of this maintenance are kept.

v) Equipment is calibrated or checked before use.

vi) Programmes for the metrological control of instruments are established.

vii) Critical equipment (e.g. balances, thermometers, glassware, timepieces, pipettes) is uniquely identified, appropriately calibrated (with suitable traceability), and the corresponding certificates or other records demonstrating traceability to national measurement standards are available.

viii) Calibrated equipment is appropriately labelled or otherwise identified to ensure that it is not confused with uncalibrated equipment and to ensure that its calibration status (including the date when last calibrated and the date or expiration criteria when recalibration is due) is clear to the user.

ix) Instrument calibration procedures and performance checks are documented and available to users. These procedures should include acceptance criteria, even when the metrological control is outsourced.

x) Instrument performance checks and calibration procedures are carried out at appropriate intervals and show that calibration is maintained and day-to-day performance is acceptable. Appropriate corrective action is taken where necessary.

xi) Intermediate checks needed to maintain confidence in the calibration status of the equipment are carried out according to defined procedures.

xii) Test and calibration equipment, including both hardware and software, is safeguarded from adjustments which would invalidate the test and/or calibration results.

xiii) Where calibrations give rise to a set of correction factors, the laboratory has procedures to ensure that copies (e.g. in instrument software/spreadsheets) are correctly updated.

xiv) Records of calibration, performance checks and corrective actions are maintained.

A.4 Test methods and method validation

i) Laboratory developed methods are appropriate for the intended use, fully documented, appropriately validated and authorised for use.

ii) The introduction of test and calibration methods developed by the laboratory is a planned activity and is assigned to qualified personnel.

iii) The laboratory demonstrates that standard (published/official) methods are fit-for-purpose, and that published performance levels can be achieved.

iv) Alterations to methods are documented, technically justified, authorised, and accepted by the customer.

v) Authorised copies of published and official methods are available.

vi) The most up-to-date version of the method is available to the analyst.

vii) Analysts are (observed to be) following the methods specified.

viii) Laboratory developed methods contain at least the following information:

a) appropriate identification;

b) scope;

c) description of the type of item to be tested or calibrated;

d) parameters or quantities and ranges to be determined;

e) apparatus and equipment, including technical performance requirements;

f) chemicals, measurement standards (including RMs) required, with specifications for purity;

g) environmental conditions required and any stabilisation/equilibration period needed;

h) description of the procedure, including:

- affixing of identification marks, handling, transporting, storing and preparation of items,
- checks to be made before the work is started,
- checks that the equipment is working properly and, where required, calibration and adjustment of the equipment before each use,
- the method of recording the observations and results,
- any safety measures to be observed.

i) criteria and/or requirements for approval/rejection;

j) data to be recorded and method of analysis and presentation;

k) the uncertainty or the procedure for estimating uncertainty.

ix) Methods include a specified timescale for review.

A.5 Reagents and measurement standards (including reference materials)

i) The laboratory has a programme and procedure for the calibration of its measurement standards. The procedures should include acceptance criteria.

ii) Measurement standards are calibrated by a body that can provide traceability.

iii) A measurement standard is used for only one purpose (e.g. calibration or performance checks).

iv) Measurement standards are calibrated before and after any adjustment.

v) Checks needed to maintain confidence in the calibration status of reference, primary, transfer or working standards and RMs are carried out according to defined procedures and schedules.

vi) The measurement standards required for the tests are readily available.

vii) The measurement standards are certified or are the 'best' available.

viii) The preparation of working measurement standards and reagents is documented.

ix) Property values of RMs are traceable to SI units of measurement where possible, or to property values of appropriate CRMs. RMs prepared in-house are checked as far as is technically and economically practicable.

x) Measurement standards, RMs and reagents are properly labelled and correctly stored. Where appropriate 'opening' and 'use-by' dates are shown on the label.

xi) New batches of measurement standards and reagents critical to the performance of the method are compared against old batches before use.

xii) The correct grade of each material is being used in the tests.

xiii) Where measurement standards are certified, copies of the certificate are available for inspection.

A.6 Quality control

i) There is an appropriate level of QC for each method.

ii) QC check samples are being tested by the defined procedures, at the required frequency and there is an up-to-date record of the results and actions taken where results have exceeded action limits.

iii) Where control charts are used, performance has been maintained within acceptable criteria.

iv) Results from the random re-analysis of samples show an acceptable measure of agreement with the original analyses.

v) QC data are analysed and, where they are found to be outside pre-defined criteria, planned action is taken to correct the problem and to prevent incorrect results from being reported.

vi) Where appropriate, performance in PT schemes and/or interlaboratory comparisons is satisfactory and has not highlighted any problems or potential problems.

vii) There is an effective system for linking PT performance into day-to-day QC.

A.7 Handling of test items

i) There is an effective documented system for receiving test items, identifying test items against requests for analysis, showing progress of analysis, issuing reports, and tracking the fate of test items.

ii) Test items are properly labelled and stored.

iii) Upon receipt records are kept of abnormalities, or departures from normal or specified conditions, as described in the test method.

iv) The laboratory has procedures and appropriate facilities for avoiding deterioration, loss or damage to the test item during storage, handling and preparation.

v) Storage conditions of test items are monitored and recorded.

A.8 Records

i) Notebooks/worksheets or other records show the date of test, analyst, analyte(s), sample details, test observations, QC, all rough calculations, any relevant instrument output (e.g. chromatograms), raw data, and relevant calibration data.

ii) Notebooks/worksheets are indelible, mistakes are crossed out rather than erased or obliterated, and the records are signed by the analysts.

iii) Where a mistake is corrected the alteration is traceable to the person making the correction.

iv) The laboratory has procedures for checking data transfers and calculations and is using them.

v) Observations, data and calculations are recorded at the time they are made.

vi) In the case of records stored electronically, the laboratory adopts adequate measures to avoid loss of or change to the original data.

A.9 Test reports

i) The test report provides information about the measurement result(s) in a clear, accurate, concise and unambiguous manner.

ii) The information given in reports is consistent with the requirements of the standard and the customer, and reflects any provisions made in the documented method.

iii) The test report includes the following information:

a) title;

b) the name and address of the laboratory;

c) unique identification of the test report and on each page an identification and a clear identification of the end of the test report or calibration certificate;

d) the name and address of the customer;

e) identification of the method used and, where appropriate, reference to an International Standard;

f) a description of the condition of, and unambiguous identification of, the item(s) tested or calibrated;

g) the date of receipt of the test item and the date of performance of the test;

h) reference to the sampling plan or sample taking procedure clarifying whether sampling was carried out by the laboratory or other body;

i) the test results with the correct number of significant figures and, where appropriate, the units of measurement;

j) the name, function and signature or equivalent identification of person authorising the test report or calibration certificate;

k) where relevant, a statement to the effect that the results relate only to the items tested or calibrated.

iv) Where applicable, the test report also contains a statement of the estimated uncertainty of the results as well as opinions and interpretations, and other additional information which may be required by specific methods, customers or groups of customers.

v) When the test report contains results of tests performed by subcontractors, these results are clearly identified.

vi) When the test report contains results from accredited methods the appropriate accreditation mark is included. Where the test report contains results from both accredited and non-accredited methods this is clearly indicated.

A.10 Miscellaneous

i) Documented procedures are in operation to handle queries, complaints and system failures.

ii) There is adequate evidence of corrective action (in the case of system failures) and preventive action. Effectiveness is evaluated in both cases.

iii) The Laboratory Quality Manual is up-to-date and is accessible to all relevant personnel.

iv) There are documented procedures for subcontracting work, including verification of the suitability of subcontractors.

v) Vertical audits on random samples (i.e. checks made on a sample, examining all procedures associated with its testing from receipt through to the issue of a report, and sample retention and disposal) have not highlighted any problems.

Appendix B – Instrument calibration and performance checks

B1. The purpose of periodic calibration is to:

i) Improve the estimate of the deviation between a reference value and a value obtained by using a measuring instrument (correction);

ii) Improve the uncertainty in this deviation, at the time the instrument is used;

iii) Confirm that there has been no alteration of the measuring instrument which could introduce doubt about the results obtained during the period.

B.1.1. Before the establishment of calibration periods the laboratory must know:

i) The maximum permissible error (mpe) with which the instrument can perform the measurements;

ii) Factors related to the type of instrument, possible deterioration and drift, and the manufacturer's recommendation;

iii) The extent to which the measuring instrument is used, the severity of the environmental conditions (humidity, temperature) and level of expertise of the personnel using the measuring instrument;

iv) The trend of the data obtained from previous calibration records;

v) Cost-benefit ratio.

B.1.2 Guidance is given in Table B1 on the calibration of equipment in common use in analytical laboratories and on which the calibration of other instruments may be dependent. Table B2 gives guidance on equipment validation and verification of performance. More comprehensive advice is available in the literature [71] and also in equipment manuals.

Table B1 – Guidance on calibration and calibration checks of laboratory equipment

This information is provided for guidance purposes and the frequency will be based on the need, type and previous performance of the equipment.

Type of equipment	**Requirement**	**Suggested frequency**
Balances	Full traceable calibration	Annually in the first 3 years, followed by less frequently, based on satisfactory performance
Calibration weights	Full traceable calibration	Every 5 years
Check weight(s)	Check against calibrated weight or check on balance immediately following traceable calibration	Every 2 years
Volumetric glassware	Gravimetric calibration to required tolerance	Annually
Pipettors/pipettes	Full traceable calibration	Annually
Hydrometers (working)	One point calibration versus reference hydrometer	Annually
Hydrometers (reference)	One point calibration using measurement standard of known specific gravity	5 years
Barometers	5 years	One point
Reference thermometers (liquid-in-glass)	Full traceable re-calibration Single point (e.g. ice-point check)	Every 5 years Annually
Reference thermocouples	Full traceable re-calibration Check against reference thermometer	Every 3 years Annually
Working thermometers and thermocouples	Check against reference thermometer at ice-point and/or working temperature range	Annually

Note: Some instruments will normally be calibrated in an accredited calibration laboratory, and should at least provide results traceable to national measurement standards.

Table B2 – Guidance on equipment validation and verification of performance

This information is provided for guidance purposes and the frequency will be based on the need, type and previous performance of the equipment.

Type of equipment	**Requirement**	**Suggested frequency**
Balances	Check zero, and reading against check weight	Daily/each use
Pipettors/pipettes	Check accuracy and precision of volume dispensed by gravimetric method	Regularly (to be defined by taking account of the frequency and nature of use)
Temperature controlled equipment	(a) Establish stability and uniformity of temperature (b) Monitor temperature	(a) Initially, periodically, at documented frequency, and after repair/modification (b) Daily/each use
Timers	Check against national time signal	Annually
pH meters	Adjust using at least two buffers of suitable quality	Daily/each use

B2. The following aspects of the instruments listed below, may need to be checked, depending on the method:

B2.1 *Chromatographic equipment:*

i) Overall system checks, precision of repeat sample injections, carry-over;

ii) Column performance (capacity, resolution, retention);

iii) Detector performance (output, response, noise, drift, selectivity, linearity);

iv) System heating/thermostatting (trueness, precision, stability, ramping characteristics);

v) Autosampler (trueness and precision of time routines).

B2.2 *Liquid and ion chromatographs:*

i) Composition of mobile phase;

ii) Mobile phase delivery system (pressure, precision, trueness, pulse-free).

B2.3 *Electrode/meter systems, including conductivity, pH and ion-selective:*

i) Electrode drift or reduced response;

ii) Fixed point and slope checks using chemical measurement standards.

B2.4 *Heating/cooling apparatus, including freeze dryers, freezers, furnaces, hot air sterilisers, incubators, melting and boiling point apparatus, oil baths, ovens, steam sterilisers and water baths:*

i) Periodic calibration of temperature sensing system using the appropriate calibrated thermometer or pyroprobe;

ii) Thermal stability;

iii) Heating/cooling rates and cycles;

iv) Temperature gradients in ovens and furnaces;

v) Ability to achieve and sustain pressure or vacuum.

B2.5 *Spectrometers and spectrophotometers, including atomic absorption, fluorimetric, inductively coupled plasma-optical emission, infra-red, luminescence, mass, nuclear magnetic resonance, ultra-violet/visible and X-ray fluorescence:*

i) Selected wavelength trueness, precision, stability;

ii) Source stability;

iii) Detector performance (resolution, selectivity, stability, linearity, trueness, precision);

iv) Signal to noise ratio;

v) Detector calibration (mass, wavelength, frequency, absorbance, transmittance, bandwidth, intensity etc.);

vi) Internal temperature controllers and indicators where applicable.

B2.6 *Microscopes:*

i) Resolving power;

ii) Performance under various lighting conditions (fluorescence, polarisation, etc.);

iii) Graticule calibration (for length measurement).

B2.7 *Autosamplers:*

i) Trueness and precision of timing systems;

ii) Reliability of sequencing programmes;

iii) Trueness and precision of sample delivery systems.

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