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Accreditation for Chemical Laboratories

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Preface

ISO/IEC 17025 contains the requirements that testing and calibration laboratories have to meet if they wish to demonstrate that they operate to a quality system, are technically competent and are able to generate technically valid results. It replaces ISO/IEC Guide 25 and EN 45001, and is the standard which UKAS will now use in place of UKAS publication M10 to assess a laboratory's competence for the purposes of accreditation.

The publication that follows is Eurachem Guidance Document No. 1/WELAC Guidance document No. WGD 2 (Edition 1) which was produced by the joint Eurachem/WELAC Chemistry Working Group to which UKAS (as NAMAS) was an active contributor. The publication makes reference to EN 45001, EN 45002 and ISO/IEC Guide 25 throughout the text. Although these standards have been replaced by ISO/IEC 17025, the document contains continued guidance on implementation of accreditation in chemical laboratories.

The publication is also available as a free download from the website to the European cooperation for Accreditation (EA) at www.european-accreditation.org (publication reference EA-4/05).

UKAS has continued to adopt the publication, now as LAB 27, Edition 1.

To assist in using this document for further guidance, cross-referencing of ISO/IEC 17025 requirements to the appropriate sections of the Eurachem Guidance Document No. 1/WELAC Guidance document No. WGD 2 (Edition 1) are given on page A.

About the United Kingdom Accreditation Service

The United Kingdom Accreditation Service (UKAS) is recognised by the UK Government as the national body responsible for assessing and accrediting the competence of organisations in the fields of calibration, testing, inspection and certification of systems, products and personnel.

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EURACHEM Guidance Document No. 1

WELAC Guidance Document No. WGD 2

Accreditation for Chemical Laboratories

Guidance on the interpretation of the EN 45000 series of Standards and ISO/IEC Guide 25

PURPOSE

This document has been produced by a joint EURACHEM/WELAC Working Group. It supplements EN 45001 and ISO/IEC Guide 25, and provides specific guidance on the accreditation of chemical laboratories for both assessors and laboratories preparing for accreditation. It gives detailed guidance for the interpretation of EN 45001 and ISO/IEC Guide 25 for those undertaking quantitative and qualitative examination of the composition, nature and properties of materials, products and substances. The guidance is applicable to the performance of all objective measurements, whether routine, ad-hoc, or as part of research and development. EN 45001 and ISO/IEC Guide 25 remain the authoritative documents and in cases of dispute, the individual accreditation bodies, will adjudicate on unresolved matters. The guidance given in this document may also be of use to those working towards registration under GLP or certification to the ISO 9000 (EN 29000) series of Standards.

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It is intended that after a certain period of use, the content of this document will be reviewed, and the amended text republished. Users are invited to comment on the content of the existing text and suggest additional material in writing to:

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Official language

The text may be translated into other languages as required. The English language version remains the definitive version.

Copyright

The copyright of this text is held by WELAC and EURACHEM. The text may be freely copied for extended use within a laboratory but may not be copied for resale.

Note on Edition 1 reprinted September 1993

This printing incorporates corrections to typographical errors noted in Edition 1, April 1993. In addition, changes to the layout have increased the extent from the original 32 pages, but the text remains unaltered.

1 Introduction

- 1.1 The general requirements for accreditation are laid down in the European Standard *General criteria for the operation of testing laboratories* (EN 45001:1989) and *General requirements for the competence of calibration and testing laboratories* (ISO/IEC Guide 25, 3rd Edn, 1990), hereafter referred to as EN 45001 and ISO Guide 25, respectively. These requirements apply to all types of objective testing but in certain instances additional guidance is necessary to take account of the type of testing concerned and the techniques involved.
- 1.2 This document has been produced by a joint WELAC/EURACHEM Working Group. It supplements EN 45001 and ISO Guide 25, and provides specific guidance on the accreditation of chemical laboratories for both assessors and laboratories preparing for accreditation. It gives detailed guidance for the interpretation of EN 45001 and ISO Guide 25 for those undertaking quantitative and qualitative examination of the composition, nature and properties of materials, products and substances. The guidance is applicable to the performance of all objective measurements, whether routine, ad-hoc, or as part of research and development. EN 45001 and ISO Guide 25 remain the authoritative documents and in cases of dispute, the individual accreditation bodies, will adjudicate on unresolved matters. The guidance given in this document may also be of use to those working towards registration under GLP or certification to EN 29000/ISO 9000.

2 Scope

EN 45002, paras 4 & 12

- 2.1 The scope of accreditation of a laboratory is the formal statement of the range of activities for which the laboratory has been accredited; the scope is recorded on an accreditation schedule which is issued together with a laboratory's accreditation certificate. A laboratory's scope should be defined as precisely as possible so that all parties concerned know accurately and unambiguously the range of tests and/or analyses covered by that particular laboratory's accreditation. The schedule format should typically define the laboratory's accreditation in terms of:
- (i) the range of products, materials or sample types tested or analysed;
 - (ii) the tests or analyses (or types of tests or analyses) carried out;
 - (iii) the specification or method/equipment/technique used;
 - (iv) the concentration range and accuracy/precision as appropriate.
- 2.2 Accreditation bodies will only accredit laboratories for tests which have been fully documented and validated. This may include sectoral, national and international standard methods and in-house methods. The validation of standard methods should not be taken for granted — the laboratory should satisfy itself that the degree of validation of a particular method is adequate

for its purpose. Similarly the laboratory should not feel constrained to use a standard method if it has an in-house method which has superior performance, more modern technology and a degree of validation adequate for the purpose.

- 2.3 Where non-routine testing is carried out, it is recognised that a more flexible approach to scope may be necessary, but the scope must be as specific as is feasible and the quality assurance system maintained by the laboratory must ensure that the quality of the results is under control. Frequently, a single measurement technique may be used for different analytes in a wide variety of samples. This measurement stage may be covered by a single method. However, the methods used to prepare the samples for subsequent analysis may vary considerably according to the nature of the analyte and sample matrix. Thus several methods may be required to cover each different analyte matrix combination. This is illustrated by gas chromatography, a technique applicable to a wide variety of analytes. Depending on the matrix, a diverse range of methods may be used to prepare analytes for gas chromatographic analysis; however the procedures involved in the final analytical stage vary little.
- 2.4 It is accepted that sometimes it is not practicable for laboratories to use a fully documented method in the conventional sense, which specifies each sample type and determinand. However the laboratory must have a generic method or procedure for the use of the instrument in question, which includes a protocol defining the approach to be adopted when different sample types are analysed. Full details of the procedures, including instrumental parameters and ad-hoc validation, must be recorded at the time of each analysis such as to enable the procedure to be repeated in precisely the same manner at a later date. Where a particular analysis subsequently becomes routine, a full method must be written and validated. The statement in the methods column of the schedule will normally take the form of 'Documented In-house Methods' using GC-coupled mass spectrometry/NMR/FTIR etc. Where a laboratory employs analytical tools such as mass spectrometry, NMR or FTIR, it may be appropriate to use the terms qualitative and/or quantitative chemical analysis under the type of test heading in the accreditation schedule. The onus will be on the laboratory to demonstrate to the assessors that in using these techniques, it is meeting all of the criteria for accreditation. In particular, the experience, expertise and training of the staff involved will be a major factor in determining whether or not such analyses can be accredited.
- 2.5 The approach to extending or amending the scope of accreditation should be as flexible as possible. Normally the laboratory will give written notice to the accreditation body of the tests which it wishes to add to its scope, quoting Standard method references (where applicable) and providing copies of documented in-house methods or supplementary validation.
- 2.6 At this stage, the accreditation body will decide whether additional assessment is required before the extension to scope can be granted. This decision will depend on the nature and number of the tests or analyses involved. Where the extension is limited and the laboratory can demonstrate that its competence in similar or related tests has already been assessed at previous visits, the extension of scope can normally be granted by an exchange of correspondence. Where the proposed

extension involves the application of new technology or techniques, it is unlikely that it can be granted without further formal assessment.

- 2.7 It may be possible to fit the assessment of the additional tests for an extension to scope into a scheduled surveillance or re-assessment visit, provided that the appointed assessor has appropriate expertise, the number of tests or analyses is limited and that sufficient notice is given.

3 Staff

EN 45001, para 5.2 & ISO Guide 25, para 6

- 3.1 The laboratory management should define the minimum levels of qualification and experience necessary for the key posts within the laboratory. Chemical analysis must be carried out by, or under the supervision of a qualified and experienced analyst, qualified to degree level in chemistry or equivalent and probably holding a relevant professional qualification. Other senior laboratory staff will normally possess similar qualifications. Alternative qualifications may be accepted by the accreditation body when staff have extensive relevant experience and/or the scope of the laboratory is limited. Graduate staff should normally possess at least 2 years' relevant work experience before being considered as experienced analysts. Staff undergoing training or with no relevant qualifications may undertake analyses provided that they have demonstrably received an adequate level of training and are adequately supervised.
- 3.2 The laboratory should ensure that all staff receive training adequate to the competent performance of the tests and operation of equipment. Where appropriate this will include background training in particular techniques. Where possible, objective measures should be used to assess the attainment of competence during training. Analysts may only perform tests on samples if they are either recognised as competent to do so, or if they do so under adequate supervision. Continued competence should be monitored, for example, using quality control techniques. The need to periodically retrain staff should be considered where a method or technique is not in regular use. In each case the critical interval should be established and documented.
- 3.3 The laboratory 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 individual members of staff have been adequately trained and their competence to carry out particular accredited tests has been assessed. In some cases, it may be pertinent to state any particular limitations to competence. The records should be available for inspection by the accrediting body if required, and should also include:
- (i) academic qualifications;
 - (ii) external and internal courses attended;
 - (iii) relevant on-the-job training (and retraining as necessary).

In addition the records may include:

- (iv) participation in proficiency testing schemes, with associated data;
 - (v) technical papers published.
- 3.4 In some cases it may be more appropriate to document competence related to particular techniques rather than methods. If so, it will be necessary to define, for each method, the necessary technique-based competences required, together with any additional requirements.
- 3.5 The laboratory will also have other staff records, held centrally, listing personal details. Access to such records may be restricted by national legislation on data protection, however such information will not normally be of interest to accreditation bodies.

4 Environment

EN 45001, para 5.3.2 & ISO Guide 25, para 7

- 4.1 Samples, reagents and standards should be stored so as to ensure their integrity. The laboratory should guard against deterioration, contamination and loss of identity.
- 4.2 It may be necessary to restrict access to particular areas of a laboratory because of the nature of the work carried out there. Restrictions might be made because of security, safety, or sensitivity to contamination. Typical examples might be work involving explosives, radioactive materials, carcinogens, forensic examination, trace analysis. Where such restrictions are in force, staff should be made aware of:
- (i) the intended use of a particular area;
 - (ii) the restrictions imposed on working within such areas;
 - (iii) the reasons for imposing such restrictions.
- 4.3 Frequently, it will be necessary to segregate certain types of work which are prone to interferences from other work, or which present particular problems or hazards. Examples are trace analysis (where physical separation from high-level is necessary) and carcinogen analysis. When selecting designated areas for special 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. Once in use, access to such areas should be restricted, and the type of work undertaken there carefully controlled.
- 4.4 The laboratory shall provide appropriate environmental conditions and controls necessary for particular tests, including temperature, humidity, freedom from vibration, freedom from airborne and dustborne microbiological contamination, special lighting, radiation screening. Critical environmental conditions should be monitored.

5 Equipment

EN 45001, para 5.3.3 & ISO Guide 25, para 6

- 5.1 As part of its quality system, a laboratory is required to operate a programme for the maintenance and calibration of equipment used in the laboratory. Equipment normally found in the chemical laboratory can be categorised as:
- (i) general service equipment not used for making measurements or with minimal influence on measurements (eg hotplates, stirrers, non-volumetric glassware and glassware used for rough volume measurements such as measuring cylinders) and laboratory heating or ventilation systems;
 - (ii) volumetric equipment (eg flasks, pipettes, pyknometers, burettes etc);
 - (iii) measuring instruments (eg hydrometers, U-tube viscometers, thermometers, timers, spectrometers, chromatographs, electrochemical meters, balances etc);
 - (iv) physical standards (weights, reference thermometers);
 - (v) computers and data processors.

General service equipment

- 5.2 General service equipment will typically only be maintained by cleaning and safety checks as necessary. Calibrations or performance checks will be necessary where the setting can significantly affect the test or analytical result (eg the temperature of a muffle furnace or constant temperature bath).

Volumetric equipment

- 5.3 The correct use of volumetric equipment is critical to analytical measurements and it shall be suitably maintained and calibrated as specified in Section 8. The correct functioning of some specialist volumetric (and related) glassware is dependent on particular factors, eg the performance of pyknometers and U-tube viscometers is dependent on 'wetting' and surface tension characteristics, which may be affected by cleaning methods etc. Such apparatus may therefore require more regular calibration, depending on use. For the highest accuracy, measurements can often be made by mass rather than by volume.
- 5.4 Attention should be paid to the possibility of contamination arising from the equipment or cross-contamination from previous use. The type used (glass, PTFE, etc), cleaning, storage, and segregation of volumetric equipment is critical, particularly for trace analyses when leaching and adsorption can be significant.

Measuring instruments

- 5.5 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 (eg to check the response, stability and linearity of sources, sensors and detectors, the separating efficiency of chromatographic systems, the resolution, alignment and wavelength accuracy of spectrometers etc); see Appendix B.

- 5.6 The frequency of such performance checks 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 to drift outside acceptable limits.
- 5.7 It is often possible to build performance checks - system suitability checks - into test methods (eg based on the levels of expected detector or sensor response to calibrants, the resolution of calibrants in separating systems, the spectral characteristics of calibrants etc). These checks should be satisfactorily completed before the equipment is used.

Physical standards

- 5.8 Wherever physical parameters are critical to the correct performance of a particular test, the laboratory shall have or have access to the relevant reference standard, as a means of calibration.
- 5.9 Reference standards and accompanying certificates should be stored and used in a manner consistent with preserving the calibration status. Particular consideration should be given to any storage advice given in the documentation supplied with the standard.

Computers and data processors

- 5.10 Requirements for computers are given in section 10 and Appendix C.

6 Reagents

ISO Guide 25, para 8.1

- 6.1 The laboratory should ensure that the quality of the reagents used is appropriate for the tests concerned. Preferably, reagents should be purchased from manufacturers who have a quality assurance system such as EN 29000/ISO 9000.
- 6.2 The grade of any reagents used (including water) should be as stated in the method together with guidance on any particular precautions which should be observed in its preparation or use. These precautions include toxicity; flammability; stability to heat, air and light; reactivity to other chemicals; reactivity to particular containers; and other hazards. Reagents prepared in the laboratory should be labelled to identify substance, strength, 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 of the reagent shall be identifiable either from the label or from records.

- 6.3 The correct disposal of reagents does not directly affect the quality of sample analysis, however it is a matter of good laboratory practice and should conform to national environmental or health and safety regulations.

7 Methods/procedures for calibrations and tests

EN 45001, para 5.4 & ISO Guide 25, para 10

- 7.1 When standard methods are used, laboratories should verify their own ability to achieve satisfactory performance against the documented performance characteristics of the method, before any samples are analysed.
- 7.2 Methods developed in-house shall be validated and authorised before use. Where they are available, certified reference materials should be used to determine any systematic bias, or where this is not possible results should be compared with other technique(s), preferably based on different principles of analysis. Determination of uncertainty must form part of this validation process and is essential for ongoing quality control.
- 7.3 All methods shall be fully documented including validation data, limitations of applicability, procedures for quality control, and calibration. A laboratory may find it convenient to adopt a common format for documenting methods - ISO 78-2:1982, *Layout for Standards - part 2: Standards for Chemical Analysis*, provides a useful model.
- 7.4 Developments in methodology and techniques will require methods to be changed from time to time. Obsolete methods should be withdrawn but must be retained for archive purposes and clearly labelled as obsolete. The revised method must be fully documented, and indicate the laboratory representative who authorised its use and from what date.
- 7.5 The difference in performance between revised and obsolete methods should be established so that it is possible to compare new and old data.
- 7.6 Where a change in method involves only minor adjustments, such as sample size, different reagents, the amended method should be validated and the changes brought to the attention of the accreditation body at its next visit. Where the proposed change in method involves a change of scope, such as a significant change in technology or methodology, the laboratory should seek the approval of the accreditation body. It shall be at the discretion of the accreditation body and its assessors to require reassessment of that technique depending on the existing scope of accredited work within that laboratory (see Section 2).

8 Calibration & measurement traceability

EN 45001, para 5.3.3 & ISO Guide 25, para 9

- 8.1 The overall programme for the calibration of measuring equipment in the chemical laboratory shall be designed to ensure that, where the concept is applicable, all measurements are traceable through certificates held by the laboratory, either to a national or international standard or to a certified

reference material. Where no such reference standard or certified reference material is available, a material with suitable properties and stability should be selected or prepared by the laboratory and used as a laboratory reference. The required properties of this material should be characterised by repeat testing, preferably by more than one laboratory and using a variety of methods, see ISO Guide 35:1989, *Certification of reference materials - General and statistical principles*.

- 8.2 Analytical tests may be sub-divided into three general classes depending on the type of calibration required:
- (i) In general, standards exist for ensuring traceability to international or national standards for equipment used for the direct measurement of fundamental properties (eg mass, length, temperature and time) or the simpler derived properties (eg area, volume, and pressure). Where these properties have a significant effect on the results of an analysis, the requirements of EN 45001, para 5.3.3 and ISO Guide 25, paras 9.1 and 9.2 shall be met.
 - (ii) 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 reference materials should be used for calibration purposes where available. New or newly acquired equipment should be checked by the laboratory before use to ensure conformity with specified design, performance and dimension requirements.
 - (iii) Instruments such as chromatographs and spectrometers, which require calibration as part of their normal operation, should be calibrated using chemicals of known and adequate purity or reference materials of known composition.
- 8.3 Frequently in chemical analysis it is not possible to calibrate individual parameters within a method. In such cases, traceable calibration of the whole method may be possible using a Certified Reference Material (CRM). The CRM is subjected to the same processes as the samples. The degree of agreement between the analysed value for the CRM and its certified value may be used to determine the accuracy of the analysed values obtained for the samples.
- 8.4 Individual calibration programmes shall be established depending on the specific requirements of the analysis. Also, it may be necessary to check instrument calibration after any shutdown, whether deliberate or otherwise, and following service or other substantial maintenance. The level and frequency of calibration should be at least that recommended by the manufacturer.
- 8.5 Procedures for performing calibrations shall be adequately documented, either as part of specific analytical methods or as a general calibration document. The documentation should indicate how to perform the calibration, how often calibration is necessary, action to be taken in the event of calibration failure. Frequency intervals for recalibration of standards should also be indicated.
- 8.6 Guidance on typical calibration intervals for various types of analytical instruments is given in Appendix B.

9 Reference materials and chemical standards

EN 45001, para 5.3.3 & ISO Guide 25, para 9.7

- 9.1 Reference materials and certified reference materials are defined in ISO/IEC Guide 30:

A **reference material** (RM) is a material or substance one or more properties of which are sufficiently established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials.

A **certified reference material** (CRM) is a reference material one or more of whose property values are certified by a technically valid procedure, accompanied by, or traceable to a certificate or other documentation which is issued by a certifying body.

Reference materials provide essential traceability in chemical measurements and are used to demonstrate the accuracy of results, calibrate equipment and methods, monitor laboratory performance and validate methods, and enable comparison of methods by use as transfer standards. Their use is encouraged wherever possible.

- 9.2 Where matrix interferences exist, ideally a method should be validated using a matched matrix reference material certified in a reliable manner. If such a material is not available it may be acceptable to use a sample spiked with a chemical standard.
- 9.3 It is important that the certified reference material has been produced and characterised in a technically valid manner. Users of CRMs should be aware that not all materials are validated to the same standard. Details of homogeneity trials, stability trials, 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 the pedigree.
- 9.4 For many types of analysis, calibration may be carried out using standards prepared within the laboratory from chemicals of known purity and composition. Some chemicals may be purchased with manufacturers certificates stating purity. Alternatively, uncertified chemical standards may be purchased from suppliers whose manufacturing processes are registered to ISO 9000/EN 29000. Whatever the source, it is the users' responsibility to verify that the quality of such standards is satisfactory. Normally a new batch of a standard should be checked against the old. Ideally, all chemical standards should be purchased from producers with demonstrated quality assurance systems such as ISO 9000/EN 29000. However a quality assurance system does not automatically guarantee the quality of the producer's products and laboratories should take all reasonable steps to confirm the quality of chemical standards.
- 9.5 The purity requirements of chemical standards may be considered in relation to the permitted tolerance of the method. For example, a tolerance of <0.1% of the target value will require a chemical standard to have a certainty of concentration significantly better than 99.9%.

- 9.6 Reference materials and chemical standards should be clearly labelled so that they are unambiguously identified and referenced against accompanying certificates or other documentation. Information should be available indicating shelf life, storage conditions, applicability, restrictions of use. Prepared standards should be treated as reagents for the purposes of labelling, see section 6.2.
- 9.7 For trace analysis the control of impurities is essential. Due regard should be paid to the manufacturers recommendations on storage and shelf life.
- 9.8 Reference materials and standards should be handled in order to safeguard against contamination or loss of determinand. Training procedures should reflect these requirements.

10 Use of computers

EN 45001, paras 5.3.3, 5.4 & ISO Guide 25, para 10.7

- 10.1 Guidance on the use of computers applicable to chemical testing is given below. Appendix C contains general guidance on computers which is also relevant to chemical testing.
- 10.2 In chemical testing laboratories, 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 standard materials;
 - design and performance of statistical experiments;
 - 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;
 - matching of sample and library data;
 - generation of test reports;
 - word processing;
 - communication.
- 10.3 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.

- 10.4 The chemical testing environment creates particular hazards for the operation of computers and storage of computer 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.
- 10.5 For the purposes of validation of computers used in chemical testing it is usually sufficient to assume correct operation if the computer produces expected answers when input with known parameters. It should be noted that some faults will occur only when a particular set of parameters is input. Initial validation 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 after revision of software. In chemical testing, such checks would ideally be made using a Certified Reference Material for the initial validation, with a secondary standard such as a quality control material 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 is convenient to illustrate validation using examples of typical applications:
- 10.5.1 **Word-processing packages** are widely used in laboratories to generate a wide 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 the document hard copies. More sophisticated systems read and process data to automatically produce reports in predetermined formats. Such systems will require additional checks, see 10.5.3.
- 10.5.2 **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, eg by testing reference materials, physical or chemical calibration standards or quality control samples.
- 10.5.3 **Data handling or processing systems, integration systems** Before it can be processed, the output from the analytical instrument will usually need to be converted to a digital signal using an analogue/digital converter. The digitised data is then translated into a recognisable signal (numbers, peaks, spectra according to the system) by the software algorithm. The algorithm makes various decisions (such as deciding where peaks start and finish, or whether a number should be rounded up or down) according to programmed instructions. The algorithm is a common source of strange performance and validation should test the logic behind the decisions made by the algorithm.

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 standards or reference materials. Such validation is normally acceptable.

In exceptional cases, it may be necessary to validate data processing systems in isolation, by mimicking the output from the analytical instrument using a standard electrical signal. Signal generators are commercially available, traceable to electrical standards, however these are more appropriate to the validation of analogue chart recorders and non-computing integrators, since they usually produce a voltage deflection rather than a peak. The capacity to produce synthetic peaks is necessary to be of use for computing integrators. It is possible to validate a computer based data processing system by running it in parallel to an analogue chart recorder or non-computer based integrator, calibrated against a traceable signal generator. There are several systems currently under development which consist of software capable of mimicking an analogue instrument output and thus have potential use as a validation standard. Note that since synthetic signals do not have the same noise levels as real sample signals caution should be exercised when using them for validation.

- 10.5.4 **Computer controlled automated system** This may embrace one or more of the foregoing examples, operated either simultaneously or in controlled time sequence.

System validation should be achieved by validation of individual components plus an overall check on the dialogue between individual components and the controlling computer. An 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.

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. An assessment should be made of the likely causes of system malfunction. Where possible the controlling software should be tailored to identify and highlight any such malfunctions and tag associated data. The use of quality control 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.

- 10.5.5 **Laboratory information management systems (LIMS)** LIMS systems are increasingly popular as a way of managing laboratory activities using a computer. A LIMS is a software package allowing the electronic collation, calculation and dissemination of analytical data, often received directly from other instruments and it incorporates word-processing, database, spreadsheet, and data processing capabilities. It can perform a variety of functions, typically sample registration and tracking; processing captured data; quality control; financial control; report generation. Particular validation requirements include control of access to the various functions, and audit trails to catalogue alterations and file management.

11 Laboratory audit and review

EN 45001, para 5.4.2, ISO Guide 25, para 5.3-5.5
& WELAC Guidance Document WGD 1

- 11.1 Audit and review are important aspects in the operation of a quality system. The quality audit is the periodic check that a laboratory makes on its own quality system to ensure that it is effective, implemented, and adhered to. Quality review is the periodic examination of the quality system to ensure that it meets the needs of the laboratory and the requirements of the quality standards.
- 11.2 Audit and review are dealt with in detail in WELAC Guidance Document WGD 1. A check list, detailing the aspects of a chemical laboratory which should be examined during a quality audit is listed in Appendix A of this Guide.

12 Sampling, sample handling and preparation

EN 45001, para 5.4.5 & ISO Guide 25, para 10 & 11

- 12.1 Analytical tests may be required for a variety of reasons, including 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 some sort of sample. Clearly the way samples are taken will depend on the reason for the analysis.
- 12.2 If the test portion is not representative of the original material, it will not be possible to relate the analytical result measured to that in the original material, no matter how good the analytical method is nor how carefully the analysis is performed. The final result *may* be dependent on the analytical method, it will *always* be dependent on the sampling process.
- 12.3 As analytical methodology improves and methods allow or require the use of smaller test portions the errors associated with sampling become increasingly important. Sampling errors *cannot* be controlled by the use of standards or reference materials. Sampling is always an error generating process.
- 12.4 In many areas of chemical testing the problems associated with sampling have been addressed and methods have been validated and published. A list of useful references is given in section 16. 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.
- 12.5 Selection of an appropriate sample or samples, from a larger amount of material is a very important stage in chemical analysis. 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.

- 12.6 The various terms used in sampling are dealt with in detail in recommendations published by IUPAC (see Bibliography, reference 15). For the purposes of this guidance the following definitions have been used:

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

Sample handling This refers to the manipulation to which samples are exposed during the sampling process, from the selection from the original material through to the disposal of all samples and test portions.

Sub-sample This refers 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.

Sample preparation This describes the procedures followed to select the test portion from the sample (or subsample) and includes: in-laboratory processing; mixing; reducing; coning & quartering; riffing; and milling & grinding.

Test portion This refers to the actual material weighed or measured for the analysis.

- 12.7 There are important rules to be followed when designing, adapting, or following a sampling strategy:

- (i) The analytical problem necessitating the sampling should be understood and the sampling procedure designed accordingly. The sampling strategy used will depend on the nature of the problem, eg:
 - (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.

There may be other, non-analytical factors to consider, including the nature of the area under examination.

- (ii) It is wrong to assume 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.

- (iii) The properties of the analyte(s) of interest should be taken in to account. Volatility, sensitivity to light, thermal lability, and chemical reactivity may be important considerations in designing the sampling strategy 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 errors 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 analysis where there is a danger of adsorption of the analyte into the storage vessel.
- (iv) It may be necessary to consider the use and value of the rest of the original material once a sample has been removed for analysis. Badly considered sampling, especially if destructive, may render the whole consignment valueless or inoperative.
- (v) Whatever strategy is used for the sampling, it is of vital importance that the sampler keeps a clear record of the procedures followed in order that the sampling process may be repeated exactly. Routinely used sampling procedures should be fully documented.
- (vi) 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.
- (vii) Where the laboratory has not been responsible for the sampling stage, it may be appropriate to state in the report that the samples were analysed as received. If the laboratory has conducted or directed the sampling stage, it may be appropriate to report on the procedures used and comment on any consequent limitations imposed on the results.

12.8 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 or microbiological hazard.

12.9 The enclosure of the packaging should be adequate to ensure there is no leakage of sample from the container, and that contamination cannot enter. 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 form part of the analytical report.

- 12.10 The sample label is an important aspect of documentation and should unambiguously identify the sample to related plans or notes. Labelling is particularly important, further into 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 should be firmly attached to the sample packaging and where appropriate, be resistant to fading, autoclaving, sample or reagent spillage, and reasonable extremes of temperature and humidity.
- 12.11 Some samples, those involved in litigation for example, have particular requirements for labelling and other documentation. Additional labels may be required for the signatures of all people involved with the sample, including the person taking the sample and the analysts involved in the testing. This will normally be supported by documents, such as receipts, which testify that one signatory (as identified on the label) has handed the sample to the next signatory. This is to prove that the sample continuity has been maintained.
- 12.12 Samples should be stored so that there is no hazard to laboratory staff 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, nor of packaging and any related seals being damaged. Extremes of environmental conditions should be avoided, which might change the composition of the sample, for example, causing loss of analyte through degradation or adsorption. If necessary environmental monitoring should be used. An appropriate level of security should be exercised to restrict unauthorised access to the samples.
- 12.13 All staff 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. The disposal procedure should take into account the guidelines set out above.

13 Quality control

ISO Guide 25, para 5.6

- 13.1 The meaning of the terms 'quality control' and 'quality assurance' often varies according to the context. For the purpose of these guidance notes, the ISO definitions have been used, as defined below:

Quality assurance (QA) All those planned and systematic actions necessary to provide adequate confidence that a product or service will satisfy given requirements for quality (ISO 9000, 3.5).

Examples of QA: Calibration; training; instrument maintenance; audit and review.

Quality control (QC) The operational techniques and activities that are used to fulfil requirements for quality (ISO 9000, 3.4).

Examples of QC: Control charting; blank determinations; spiked samples; repeat determinations; blind samples.

- 13.2 As part of their quality systems, and to monitor day-to-day and batch-to-batch analytical performance, laboratories should operate systematic internal quality control (QC) checks and participate wherever possible in proficiency testing schemes (external QC). These measures should be clearly defined in the quality manual. The level and type of QC will depend on criticality, nature of the analysis, frequency of analysis, batch size, degree of automation, and test difficulty and reliability.
- 13.3 Quality control samples are typical samples which are sufficiently stable and available in sufficient quantities as to be available for analysis over an extended period of time. Over this period the variation in method performance can be monitored by monitoring the analysed value of the QC sample, usually by plotting it on a chart.

Internal QC

- 13.4 The level adopted should be demonstrably sufficient to ensure the validity of the results. As a guide, for routine analysis the level of internal QC typically should be not less than 5% of the sample throughput, ie, 1 in every 20 samples analysed should be a QC sample. For more complex procedures, 20% is not unusual and on occasions even 50% may be required. For analyses performed infrequently, a full system validation should be performed on each occasion. This may typically involve the use of a reference material 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.
- 13.5 Further information on quality control and in particular the use of control charts may be found in the Bibliography, see Section 16.

Proficiency testing (external QC)

- 13.6 One of the best ways for an analytical laboratory to monitor its performance against both its own requirements and the norm of other laboratories is to participate regularly in proficiency testing schemes. Proficiency testing helps to highlight not only repeatability and reproducibility performance between laboratories but also systematic errors, ie bias. Accreditation bodies recognise the benefit of these schemes and strongly encourage laboratories to participate in proficiency testing as an integral part of their quality assurance protocols. It is important to monitor proficiency testing results as a means of checking quality assurance and take action as necessary. In certain instances, accreditation bodies may specify participation in a particular proficiency testing scheme as a requirement of accreditation.

14 Measurement uncertainty

EN 45001, para 5.4.3, ISO Guide 25, para 13.2
& WECC Document 19-1990

- 14.1 **Measurement uncertainty** is an estimate attached to a measurement which characterises the range of values within which the true value is asserted to lie (ISO/DIS 3534-1). Every measurement has an uncertainty associated with it, resulting from errors arising in the various stages of sampling and analysis and from imperfect knowledge of factors affecting the result. For measurements to be of practical value it is necessary to have some knowledge of their reliability or uncertainty. A statement of the uncertainty associated with a result conveys to the customer the quality of the result.
- 14.2 A statement of uncertainty is a quantitative estimate of the limits within which the true value of a measurand (such as an analyte concentration) is supposed to lie. Uncertainty is expressed as a standard deviation or a calculated multiple of the standard deviation. In obtaining or estimating the uncertainty relating to a particular method and analyte, it is essential to ensure that the estimate explicitly considers all the possible sources of uncertainty. Repeatability or reproducibility, for example, are not generally acceptable as estimates of the overall uncertainty, since neither takes into account any systematic effects inherent in a method. (In general it is assumed that corrections are made for known systematic errors.)
- 14.3 Any analytical measurement result is liable to deviate from the true value for a variety of reasons. For example, temperature effects on volumetric equipment, reflection and stray light in spectroscopic instruments, variations in electrical supply voltages, individual analysts' interpretation of specified methods and incomplete extraction recoveries are all potential sources of error. As far as reasonably possible, such errors should be minimised by external control or explicitly corrected for, for example by applying a suitable correction factor. The exact deviation of a single measurement result from the (unknown) true value is, however, impossible to obtain, so the likely range of deviation must be estimated.
- 14.4 It is common practice to identify Random effects and, so called, Systematic effects on a measurement process. In estimating overall uncertainty, it is most important to realise that both types of effect contribute to the overall uncertainty associated with a result.
- 14.5 Random effects cause errors which vary from measurement to measurement, giving rise to components of uncertainty in the estimate of the true value. Such a component of uncertainty may be referred to as a 'Random Uncertainty'. The value of the uncertainty component associated with random effects may be estimated by measuring the dispersion in results over a suitable number of determinations under a representative range of conditions. In an investigation of random uncertainty, the number of measurements should not normally be less than ten.
- 14.6 Systematic effects result in errors which are constant within repeatability time scales. Where the possibility of a particular systematic effect is recognised, but

its effect on the result is not known exactly, a second type of uncertainty contribution arises. This second type of uncertainty contribution, hereafter referred to as 'type 2' uncertainty, is often more difficult to determine. The size can be estimated on the basis of a mathematical model, experience, international laboratory inter-comparisons, etc. Also this type 2 uncertainty contribution has to be expressed as a standard deviation. Even where a systematic effect, such as a method bias, is recognised and a correction can be made, the exact correction required is, like the true value, unknown. The difference between the exact correction and the estimate used also gives rise to an uncertainty in the estimate of the true value.

- 14.7 It is important to note that type 2 components of uncertainty arise even when the correction for systematic deviation arising from a particular cause is expected to be zero. For example, calibration of an AA instrument using an appropriate reference solution implies that the correction for systematic error should be zero. However, the match of reference solution and sample is unlikely to be perfect, and the difference in instrument response will produce an unknown, systematic error in analytical results for that type of sample. Further, the reference solution itself will, in general, deviate by a small, unknown amount from its nominal analyte content. Both of these cases give rise to type 2 uncertainty components.
- 14.8 The primary task in assigning a value to the uncertainty of a measurement is the identification of the relevant sources of uncertainty and the assignment of a value to each contribution. The separate contributions must then be combined by the method given in 14.16 in order to give an overall value. A record should be kept of the individual sources of uncertainty identified, the value of each contribution, the source of the value (for example, exploratory work, literature reference, certified calibration limits etc.).
- 14.9 In identifying relevant sources of uncertainty, consideration must be given to the complete sequence of events necessary to achieve the purpose of the analysis. Typically this sequence includes sampling and sub-sampling, sample preparation, extraction, clean-up, concentration or dilution, instrument calibration (including reference material preparation), instrumental analysis, raw data processing and transcription of the output result.
- 14.10 Each of these generic stages, or others identified in the particular case, will have associated sources of error. Where these can practically be identified clearly and the respective contribution to overall uncertainty determined or estimated, this should be done. Where particular stages in a determination produce an interim result, it is useful to estimate the uncertainty associated with each interim result.
- 14.11 Where individual sources of error for each stage (such as temperature effects, weighing error etc.) can not be practically measured, it may be possible to consider grouped effects. For example, the repeatability of a measurement may serve as an estimate of the total random uncertainty for those stages over which the process is strictly repeatable. Similarly, an estimate of a part of the type 2 uncertainty may be derived from known inter-laboratory variation for a method, derived from inter-laboratory studies.

- 14.12 It is essential to consider type 2 uncertainties arising outside the scope of such studies. For example, nominal values for reference materials are typically quoted as a range, and where several laboratories use the same reference material in a collaborative trial, the uncertainty in the reference material value is not included in the inter-laboratory variation. Where a certified reference material other than that used for calibration is available, this may be used to provide an independent estimate of the value of the type 2 contributions to uncertainty, but the effects of changes in matrix between sample and reference material should be taken into account.
- 14.13 Typically, uncertainty contributions for analytical results might fall into four main groups:
- (i) Contributions from random effects, typically estimated from repeatability experiments.
 - (ii) Type 2 contributions such as operator, calibration uncertainty, scale graduation errors, equipment and laboratory effects, estimated from inter-laboratory reproducibility trials.
 - (iii) Type 2 contributions outside the scope of inter-laboratory trials, such as reference material uncertainty.
 - (iv) Other sources of uncertainty, such as sampling variability and matrix effects.

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 measure and record individual uncertainty component values where available as a check on the group contribution.

- 14.14 It is often commercially impractical to measure uncertainties for every test and sample type. Where a particular test is carried out frequently, it may be sufficient to investigate the uncertainty once only or at discrete intervals. Alternatively, adequate investigation of a similar test or system may suffice, the value being treated as an estimate of standard deviation.
- 14.15 Uncertainty contributions for each source must all be expressed in the same way and in the same units, as standard deviations. In some cases, this will entail some conversion. For example, reference material limits, and some other type 2 contributions, are often presumed to have absolute limits. A convenient approximation is to treat a rectangular distribution of width W as a normal distribution of standard deviation $W/(2.3)$ for the purposes of summation. Confidence intervals may be converted to standard deviations by dividing by the appropriate value of Student's t for large samples (1.96 for 95% confidence limits).
- 14.16 Once a catalogue of uncertainties is available, the straightforward combination of the standard deviations is appropriate, applying the general law of error propagation. This is achieved by taking the square root of the sum of the squared contributing uncertainty components, all expressed as standard deviations.

Where interim results are combined by multiplication or division, the combined *relative* standard deviation (RSD) is calculated by taking the square root of the sum of the squared RSDs for each interim result, and the combined standard deviation calculated from the combined RSD.

- 14.17 The overall uncertainty is expressed in the overall standard deviation or as a multiple of it. In some cases it is preferable to convert the overall uncertainty to a confidence interval. In this case two times the overall standard deviation is estimated to approach a 95% confidence interval.

15 Validation

- 15.1 As well as the assessment of uncertainty for a particular method, other checks need to be considered to ensure that the performance characteristics of the method are understood and 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 performance characteristics of the method meet the specifications related to the intended use of the analytical results. The performance characteristics determined include:

- Selectivity & specificity
- Range
- Linearity
- Sensitivity
- Limit of detection
- Limit of quantitation
- Ruggedness
- Accuracy
- Precision

These parameters should be clearly stated in the documented method so that the user can assess the suitability of the method for their particular needs.

Standard methods will have been developed collaboratively by a group of experts. In theory this development should include consideration of all of the necessary aspects of validation. However, the responsibility remains firmly with the user to ensure that the validation documented in the method is sufficiently complete to fully meet his or her needs. Even if the validation is complete, the user will still need to verify that the documented performance can be met.

Inevitably there are differing opinions to the theory behind the calculation of these parameters. The following explanations are intended as a guide rather than a definitive view.

- 15.2 **Selectivity** of a method refers to the extent to which it can determine particular analyte(s) in a complex mixture without interference from the other components in the mixture. A method which is perfectly selective for an analyte or group of analytes is said to be **specific**. The applicability of the method should be studied using various samples, ranging from pure 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 in the applicability of the technique should be documented in the method.

- 15.3 **Range** For quantitative analysis the working range for a method is determined by examining samples with different analyte concentrations and determining the concentration range for which acceptable accuracy and precision can be achieved. 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 from the results, usually using the method of least squares. The relationship of analyte response to concentration does not have to be perfectly linear for a method to be effective. For methods showing good linearity 5 different standards (plus a blank) are usually sufficient for producing calibration curves. More standards will be required where linearity is poor. In qualitative analysis, it is commonplace to examine replicate samples and standards over a range of concentrations to establish at what concentration a reliable cut-off point can be drawn between detection and non-detection.
- 15.4 **Linearity** is determined by the analysis of samples with analyte concentrations spanning the claimed range of the method. The results are used to calculate a regression line against analyte calculation using the least squares method. It is convenient if a method is linear over a particular range but it is not an absolute requirement. Where linearity is unattainable for a particular procedure, a suitable algorithm for calculations should be determined.
- 15.5 **Sensitivity** is the difference in analyte concentration corresponding to the smallest difference in the response of the method that can be detected. It is represented by the slope of the calibration curve and can be determined by a least squares procedure, or experimentally, using samples containing various concentrations of the analyte.
- 15.6 The **limit of detection** of an analyte is determined by repeat analysis of a blank test portion and is the analyte concentration whose response is equivalent to the mean blank response plus 3 standard deviations. Its value is likely to be different for different types of sample.
- 15.7 The **limit of quantitation** is the lowest concentration of analyte that can be determined with an acceptable level of accuracy and precision. It should be established using an appropriate standard or sample, ie it is usually the lowest point on the calibration curve (excluding the blank). It should not be determined by extrapolation.
- 15.8 **Ruggedness** Sometimes also called **robustness**. Where different laboratories use the same method they inevitably introduce small variations in the procedure, which may or may not have a significant influence on the performance of the method. The ruggedness of a method is tested by 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. The technique is covered in detail by the AOAC (8). Ruggedness is normally evaluated by the originating laboratory, before other laboratories collaborate.

- 15.9 The **accuracy** of a method is the closeness of the obtained analyte value to the true value. It can be established by analysing a suitable reference material. Where a suitable reference material is not available, an estimation of accuracy can be obtained by spiking test portions with chemical standards. The value of spiking is limited, it can only be used to determine the accuracy of those stages of the method following the spiking. Accuracy can also be established by comparison with results obtained by a definitive method or other alternative procedures and via intercomparison studies.
- 15.10 The **precision** of a method is a statement of the closeness of agreement between mutually independent test results and is usually stated in terms of standard deviation. It is generally dependent on analyte concentration, and this dependence should be determined and documented. It may be stated in different ways depending on the conditions in which it is calculated. Repeatability is a type of precision relating to measurements made under repeatable conditions, ie: same method; same material; same operator; same laboratory; narrow time period. Reproducibility is a concept of precision relating to measurements made under reproducibility conditions, ie: same method; different operator; different laboratories; different equipment; long time period.

16 Bibliography

Below is a selection of references for further information:

1. Murdoch, J., 'Control Charts', Macmillan 1979.
2. Garfield, F. M., 'Quality Assurance Principles for Analytical Laboratories', Association of Official Analytical Chemists, Arlington VA, 1984.
3. Association of Public Analysts, 'A Protocol for Analytical Quality Assurance in Public Analysts' Laboratories', APA, London, 1986.
4. Dux, J. P., 'Handbook of Quality Assurance for the Analytical Chemistry Laboratory', Van Nostrand Reinhold, New York, 1986.
5. Taylor, J. K., 'Quality Assurance of Chemical Measurements', Lewis Publishers, Michigan, 1987.
6. British Standard BS 5700:1984, + AMD 5480:1987, 'Guide to process control using quality control chart methods and cusum techniques' (complements BS 5701:1980 and BS 5703:1980).
7. Miller, J. C., and Miller, J. N., 'Statistics for Analytical Chemistry', Ellis Horwood, Chichester, 1988.
8. Youden, W. J., and Steiner, E. H., 'Statistical Manual of the AOAC', Association of Official Analytical Chemists, 1975.
9. Smith, R., and James, G. V., 'The Sampling of Bulk Materials', The Royal Society of Chemistry (Analytical Sciences Monographs No 8).
10. Garfield, F. A., 'Sampling in the Analytical Scheme', *J. -Assoc. Off. Anal. Chem.* **1989**, 72(3), 405-411.

11. Kratochvil, B., and Taylor, J. K., 'Sampling for Chemical Analysis', *Anal. Chem.* **1981**, 53(8), 924A-938A.
12. Kratochvil, B., Wallace, D., and Taylor, J. K., 'Sampling for Chemical Analysis', *Anal. Chem.* **1984**, 56(5), 113R-129R.
13. Horwitz, W., 'Problems of Samplings and Analytical Methods', *J. -Assoc. Off. Anal. Chem.* **1976**, 59(6), 1197-1203.
14. Enell, J. W., "Which Sampling Plan Should I Choose?", *Journal of Quality Technology* **1984**, 16(3), 168-171.
15. Feder, P. I., 'Sampling From Batches', *Journal of Quality Technology* **1975**, 7(2), 53-58.
16. Horwitz, W., 'Nomenclature for sampling in Analytical Chemistry - (Recommendations 1990)', IUPAC, *Pure Appl. Chem.* **1990**, 62(6), 1193-1208.
17. 'Sampling, Standards, and Homogeneity, ASTM Special Technical Publication 540', presented at a symposium at the 75th Annual Meeting, ASTM, Los Angeles, CA, June 25-30, 1972. Available from American Society For Testing and Materials, 1916 Race St, PA 19103.
18. 'Handbook for Sampling and Sample Preservation of Water and Waste Water', EPA-600/4-82-029, September 1982, and 'Addendum', EPA-600/4-83-039, August 1983. Copies of both available from the Office of Research and Development, Publications, Center for Environmental Research Information, US EPA, Cincinnati, OH 45268.
19. International Standards for sampling: ISO 707:1985; ISO 2859-Part 1:1989; ISO 2859-Part 2:1989; ISO 3951:1989; ISO 7002:1986; ISO 8213:1986; ISO 6206:1979.

Appendix A

Quality audit - areas of particular importance to a chemistry laboratory

A1 Staff

- (i) Staff are properly trained and up-to-date training records are being maintained.
- (ii) Tests are only carried out by authorised analysts.
- (iii) The performance of staff carrying out analyses is observed.

A2 Equipment

- (i) The equipment in use is suited to its purpose.
- (ii) Major instruments are correctly maintained and records of this maintenance are kept.
- (iii) Traceable equipment, eg balances, thermometers, glassware, timepieces, pipettes etc are calibrated, and the appropriate calibration certificates demonstrating traceability to national standards are available.
- (iv) Calibrated equipment is appropriately labelled or otherwise identified.
- (v) Instrument calibration procedures are documented and records of calibration are satisfactorily maintained.
- (vi) Appropriate instructions for use of equipment are available.
- (vii) Instrument performance checks show that performance is within specification.

A3 Methods and procedures

- (i) In-house methods are fully documented and appropriately validated.
- (ii) Alterations to methods are appropriately authorised.
- (iii) The most up-to-date version of the method is available to the analyst.
- (iv) Analyses are following the methods specified.

A4 Standards, calibrants and certified reference materials

- (i) The standards actually required for the tests are held.
- (ii) The standards are certified or are the 'best' available.

- (iii) The preparation of working standards is documented.
- (iv) Standards and reference materials are properly labelled and correctly stored.
- (v) New batches of standards are compared against old before use.
- (vi) The correct grade of materials is being used in the tests.
- (vii) Where reference materials are certified, copies of the certificate are available for inspection.

A5 Quality Control

- (i) There is an appropriate degree of calibration for each test.
- (ii) Where control charts are used, performance has been maintained within acceptable criteria.
- (iii) QC checksamples 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.
- (iv) Results from the random re-analysis of samples show an acceptable measure of agreement with the original analyses.
- (v) Where appropriate, performance in proficiency testing schemes and/or inter-laboratory comparisons is satisfactory and has not highlighted any problems or potential problems. Where performance has been unsatisfactory, corrective action has been taken.

A6 Sample management

- (i) There is an effective documented system for receiving samples, identifying samples against requests for analysis and showing progress of analysis and fate of sample.
- (ii) Samples are properly labelled and stored.

A7 Records

- (i) Notebooks/worksheets include the date of test, analyst, analyte, sample details, test observations, all rough calculations, any relevant instrument traces, and relevant calibration data.
- (ii) Notebooks/worksheets are completed in ink, mistakes are crossed out and not erased, and the records are signed by the analysts.
- (iii) Where a mistake is corrected the alteration is signed by the person making the correction.
- (iv) The laboratory's procedures for checking data transfers and calculations are being complied with.

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

A8 Test reports

- (i) The report meets the requirements of EN 45001 and/or ISO Guide 25, and the method.

A9 Miscellaneous

- (i) There are documented procedures in operation for handling queries and complaints and system failures.
- (ii) The Laboratory Quality Manual is up-to-date and is accessible to all relevant staff.
- (iii) There are documented procedures for sub-contracting work.

Appendix B

Calibration intervals and performance checks

B1 Guidance is given in Table App B-1 on the calibration of equipment in common use in analytical laboratories and on which the calibration of other instruments may be dependent. More comprehensive advice is available in the literature (2) and also in equipment manuals.

Table App B-1

	Type of Instrument	Frequency of check	Parameters to be checked
(a)	Balances	Depends on use	Linearity, Zero point Accuracy (using standard weights *)
(b)	Volumetric glassware	Depends on use	Accuracy Precision (pipettes/burettes)
(c)	Hydrometers (working)	Annually	One point calibration versus reference hydrometer
(d)	Hydrometers (reference)	5 years	One point calibration using standard of known specific gravity
(e)	Barometers *	5 years	One point
(f)	Timers (see note)	2 years or less depending on use	Accuracy
(g)	Thermometers (reference *)	5 years Annually	Critical points on scale Fixed points eg ice point
(h)	Thermometers (working)	Annually depending on use	Check specific points against reference thermometer

Note: Those instruments marked * will normally be calibrated in an accredited calibration laboratory.

National radio-time signals, such as the Greenwich time signal in the UK, or telephone time signals, provide a suitable traceable reference standard for calibration of both absolute time and time difference. Timers with quartz/electronic movements are inherently more accurate and stable than conventional mechanical timers and will need to be calibrated less often.

General comments on laboratory equipment by type

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

B2.1 Chromatographs (general):

- (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/thermostating (accuracy, precision, stability, ramping characteristics);
 - (v) Autosampler (accuracy and precision of time routines).
- B2.2 Liquid and ion chromatography:**
- (i) Composition of mobile phase;
 - (ii) Mobile phase delivery system (precision, accuracy, 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 standard solutions.
- B2.4 Heating/cooling apparatus, including freeze driers, 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 standard thermometer or pyroprobe;
 - (ii) Thermal stability, reproducibility;
 - (iii) Heating/cooling rates and cycles;
 - (iv) 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 accuracy, precision, stability;
 - (ii) Source stability;
 - (iii) Detector performance (resolution, selectivity, stability, linearity, accuracy, precision);
 - (iv) Signal to noise ratio;
 - (v) Detector calibration (mass, ppm, wavelength, frequency, absorbance, transmittance, bandwidth, intensity etc);
 - (vi) Internal temperature controllers and indicators where applicable.
- B2.6 Microscopes:**
- (i) Resolving power;
 - (ii) Graticule calibration (for length measurement).
- B2.7 Autosamplers:**
- (i) Accuracy and precision of timing systems;
 - (ii) Accuracy and precision of sample delivery systems.

Appendix C

Use of computers - general guidance

C1 Definitions

- C1.1 ISO 2382-1:1984 lists fundamental terms used in computing; definitions are ISO derived wherever possible:
- C1.2 **Computer** A device consisting of one or more associated processing units and peripheral units that is controlled by internally stored programmes which can perform arithmetic calculations and other logical operations without outside intervention.
- C1.3 **Data** (ISO 2382-1:1984) A representation of facts, concepts, or instructions in a formalised manner suitable for communication, interpretation or processing by humans or by automatic means.
- C1.4 **Data-processing** The capture, storage, and processing of data to transform it into information more suitable for decision making.
- C1.5 **File - Computer** (ISO 2382-1:1984) A set of related records treated as a unit.
- C1.6 **Hardware** (ISO 2382-1:1984) Physical equipment in contrast to software.
- C1.7 **Interface** (ISO 2382-1:1984) A shared boundary between two functional units defined by functional characteristics, common physical interconnection characteristics, signal characteristics, as appropriate. The concept involves the specification of the connection of two devices having different functions.
- C1.8 **Program** A set of instructions for the computer to follow.
- C1.9 **Record** (ISO 2382-1:1984) A group of related data elements treated as a unit.
- C1.10 **Software** Programs, procedures, rules and any associated documentation pertaining to the operation of a computer system.
- C1.11 **Validation (Computer)** The checking of data for correctness, or compliance with applicable (of data processing) standards, rules and conventions. In the context of equipment rather than data, validation involves checking for correct performance etc.

C2 Operating procedures

- C2.1 Where software can be physically separated from a computer and has separate operating manuals and supplementary procedures these shall be available to operators.
- C2.2 Any deviations from established procedures shall be documented to an extent appropriate to repeating the procedures at a later date.

C2.3 The laboratory should document any special procedures relating to security, power failure, file management (including archiving, file repair, file back-ups), validation and training.

C3 Data protection

C3.1 The laboratory should take appropriate measures to safeguard the integrity of computers, software and any associated data. Arrangements should satisfy any sectoral, national or international regulations governing data protection.

C3.2 The laboratory should prevent unauthorised access to computers. Suitable measures will include secure areas, keyboard locks and password routines, voiceprints and fingerprints, but may include additional safeguards when the equipment is theoretically accessible from outside the immediate laboratory, eg via a modem or through a network.

C3.3 For each computer system, or specific application, the laboratory should assess the degree of risk of deliberate or accidental access and set a level of security appropriate to the importance and vulnerability of the data.

C3.4 All software, and subsequent updates should be authorised before use, having been first screened for viruses and validated. The laboratory should prohibit the use of unauthorised software on computers. Ideally software should only be obtained from reputable sources or written in-house. Authorisation for use of the obsolete versions of software should be rescinded, to prevent further use.

C3.5 Where the software or data is accessible it may be vulnerable to deliberate or accidental change. As a general rule data should not be stored on a computer, but wherever possible, it should be downloaded and stored so as to protect its integrity.

C3.6 Where software and data files have been downloaded for archiving they should be stored so as to reduce the likelihood of accidental loss or corruption. Suitable secure storage will be fireproof, flood resistant and shielded from strong magnetic and electric fields. Specialist safes are available. Where archived files are duplicated the copies should be segregated from one another.

C3.7 Where access to software or data is possible, the laboratory should incorporate suitable safeguards so that any changes, either deliberate or accidental, are highlighted and retained. Wherever possible software audit trails should be used. In commercial data handling systems, any processing of raw data usually results in the creation of a new 'results' file leaving the original raw data file unchanged.

C3.8 Where software is inaccessible, instrument performance is only likely to be affected by mechanical or electrical failure and it is unlikely that in such circumstances the instrument will appear to function correctly whilst giving the wrong results. Such breakdown is likely to be evident as total system failure.

C3.9 Where software is written in such a way that the content of a file is intended to be easily accessible for changing, there is normally a mechanism as part of the file management system that indicates the date of the last change to a particular file and in some cases indicates the complete history for each file. Such file management mechanisms should be used wherever possible.

C4 Maintenance

C4.1 Software is often imperfect. It must be fully documented. Wherever possible a record of known faults ('bugs') should be obtained from the supplier and any effect that these may have on the day-to-day running of the software established. In use a record should be kept of any errors noted in the operation of the software. For software written in-house, bugs should be noted as they occur. If it is not possible to correct the bugs the implications on operation should be assessed.

C4.2 When outside contractors are brought in to perform system maintenance, safeguards should be taken to ensure that the integrity of any sensitive data is preserved. If necessary, these safeguards should include a written undertaking by the contractor not to divulge any information to which they are exposed.

C5 Validation

C5.1 Computers, whatever their type, suffer from the 'black-box' syndrome: an input is made at one end, an answer is produced at the other. Because what happens inside cannot be seen, it must be assumed that the box is functioning correctly. For the purposes of validation it is usually acceptable to assume correct operation if the computer produces expected answers when input with well-characterised parameters.

C5.2 The degree of validation necessary depends on the exact use of the computer. For each computer, the proposed use should be defined so that the degree of validation necessary may be established.

C6 Record keeping/archiving

C6.1 Where software has been updated, a record should be kept of the revision history.

C6.2 Where sample results are archived it is necessary to store all of the information required to reproduce the original answers. In addition to the raw data files this will include any associated data-processing files and if appropriate, the relevant version of the operating software. In extreme cases it may be necessary to retain obsolete hardware in order to run the archived software. In such cases, it may be more practical to archive the data as a hard copy.