Quality Assurance for Research and Development and Non-routine Analysis

Co-Operation on International Traceability in Analytical Chemistry

This document has been produced primarily by a joint EURACHEM / CITAC Working Group, the membership of which is

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English Edition

Second Internet Version, November 1998

First Edition October 1998

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This document has been produced primarily by a joint EURACHEM / CITAC Working Group, the membership of which is listed in Annex A. The secretary would also like to thank all of those individuals and organisations who have contributed comments, advice and background documentation.

Production of this Guide was in part supported under contract with the UK Department of Trade and Industry as part of the National Measurement System Valid Analytical Measurement (VAM) Programme.

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English Edition 1.0, 1998
ISBN: 0 948926 11 2

Ruling language

The text may be freely translated into other languages, but where such action results in a dispute over interpretation, the guidance given in this English version is taken as being the definitive version.

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CONTENTS

1. AIMS AND OBJECTIVES

1.1 *Who this guide is for*

1.1.1 This guide is intended to be used by managers and analytical staff, both in industry and the academic world, involved in the planning, performance and management of non-routine measurements in analytical science and associated research and development. Those responsible for the evaluation of the quality of such work will also find the guide useful. It provides principles from which assessing organisations such as accreditation or certification bodies could specify assessment criteria.

1.2 *Using this guide*

1.2.1 This guide aims to state and promote quality assurance (QA) *good practice*, or at least practice that meets the professional standards of the peer group. Many of these practices have already been stated in an earlier CITAC guide (CG1)[1], which provides advice for mainly routine analysis, and an earlier EURACHEM / WELAC guide [2], which advises on the interpretation of EN 45001 and ISO Guide 25 for chemistry laboratories. Predictably there is likely to be a high degree of overlap between what is good practice in a routine situation and what is good practice in a non-routine situation. To avoid duplication those practices are only repeated below where it has been considered appropriate that further clarification is necessary for non-routine purposes. Where the guidance has **not** been restated, reference to the relevant part of the CITAC guide has been stated instead. Thus this guide should be used in conjunction with CG1.

1.3 *Emphasis of guidance*

1.3.1 There is still much discussion as to how applicable the various established quality standards/protocols, such as ISO Guide 25 [3], EN 45001 [4], ISO 9000 [5], and OECD Principles of Good Laboratory Practice (GLP) [6], are to non-routine work. GLP is study based, and the studies often involve non-routine or developmental work. R&D is compatible with the design element of ISO 9001. However it is widely argued that non-routine work does not fit easily into a highly documented and formalised quality system. For this reason the guidance is directed towards good practice rather than compliance with formal standards. The two approaches are not necessarily at odds with one another, but compliance may occasionally place requirements which are considered to be over and above what is considered to be best practice. Conversely no single quality standard necessarily covers all the elements of activity which might be considered relevant as best practice. The aim is to produce guidelines for analysts, their customers, and their managers, and not a quality manual template for an organisation. Note also that external verification, such as can be provided against a formal quality standard, is not mandatory, even though it may be desirable in some cases.

1.3.2 It is anticipated that once this guide is published it may be possible for accreditation bodies and other authoritative organisations to adapt the text for compliance purposes, for example to the published standards/protocols mentioned in §1.3.1 above.

1.4 *Customers*

1.4.1 Non-routine work regulated by this guidance may be performed for a number of different types of customer, such as:

- other departments within the same organisation which lack the specialist skills the work demands;
- external customers who commission specific tasks;
- regulatory bodies which commission the work to help enforce law, regulatory or licencing requirements;
- funding bodies which commission large work programmes, within which specific tasks lie.

2. INTRODUCTION

2.2 *What is Research and Development (R&D)?*

2.2.1 ***Research*** is a scientific investigation aimed at discovering and applying new facts, techniques and natural laws [7]. At its heart is inquiry into the unknown, addressing questions not previously asked. Research is done by a wide range of organisations: universities and colleges; government agencies; industry and contract organisations. Research projects vary widely in content and also in style, from open ended exploration of concepts to working towards specific targets.

Development in an industrial context is the work done to finalise the specification of a new project or new manufacturing process. It uses many of the methods of scientific inquiry, and may generate much new knowledge, but its aim is to create practicable economic solutions.

The combined term ***Research and Development*** can be seen as the work in an industrial or government context concentrating on finding new or improved processes, products *etc.*, and also on ways of introducing such innovations.

The use of the term ***R&D*** may not wholly encompass the activities intended to be covered by the Guidelines, but has been adopted by the authors as the most appropriate and convenient single term.

2.2.2 These guidelines are intended to cover analytical testing or measurements where for various reasons the work is non-routine or necessary procedures are not already in place, for example:

- methods already exists for the analytical problem, but have not previously been applied to the particular type of sample now encountered. The existing methods need to be evaluated and extended or adapted as necessary;
- the analytical problem is entirely new, but may be tackled by applying existing methods or techniques;
- the analytical problem is entirely new, there is no established method, and something has to be developed from the beginning.

Annex E provides some additional ideas for those carrying out R&D to develop analytical instrumentation.

2.3 *Importance of QA*

2.3.1 The importance of quality assurance is well established and accepted for routine analysis. It is less well established for R&D.

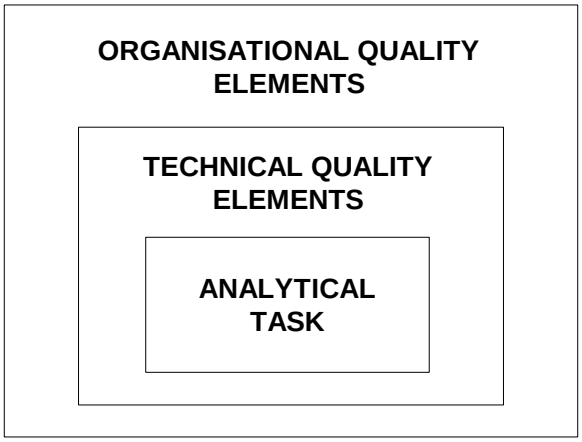

Figure 1: Nested Structure of activities

2.4 *What needs to be controlled in R&D?*

2.4.1. Figure 1 shows a hierarchical approach to quality assurance within an organisation. The outer layer represents the elements of quality assurance that apply to all levels of activity within the organisation - so-called *organisational quality elements.* These are described in chapter 5. Examples at this level include a quality management structure with a defined role within the organisation; a quality system; documented procedures for key activities; a recruitment and training policy for all staff; *etc*.. The next layer, *technical quality elements*, described in chapter 6, forms a subset and comprises specific QA elements which apply to the technical activities of the organisation, such as policy and procedures for instrument calibration and performance

checks; use of calibrants and reference materials, and; use of statistical procedures. The inner layer, *analytical task quality elements,* described in chapter 7, represents the activities carried out for particular projects or individual analytical tasks. It includes the planning, control and reporting practices recommended at the start of, during, and at completion of R&D work.

3. DEFINITIONS

3.1 ***Accreditation*** - 'Procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out specific tasks (ISO/CASCO 193 (Rev. 2), 1.11 [8] , & ISO Guide 2:1996, 12.11) [9] .

3.2 ***Certification*** - 'Procedure by which a third party gives written assurance that a product, process or service conforms to specified requirements (ISO/CASCO 193 (Rev. 2), 4.1.2 [8] , & ISO Guide 2:1996, 15.1.2) [9] .

3.3 ***Contract*** - An agreement made between two or more parties on specified terms. Typically as applied to analytical work it refers to an agreement between a laboratory (the contractor) to do work for the customer, at a specified price and within a specified timescale, with perhaps other conditions specified.

3.4 ***Customer*** - A purchaser of goods or services.

3.5 ***Project*** - 'a research or study assignment, a plan, scheme or proposal' [10]. In the analytical context a project refers to a discrete job starting with a particular problem and involving one or more tasks undertaken to solve the problem (see also study).

3.6 ***Quality Assurance (QA)*** - 'All the planned and systematic actions implemented within the quality system, and demonstrated as needed, to provide adequate confidence that an entity will fulfil requirements for quality.' (ISO 8402:1994, 3.5) [11] .

3.7 ***Quality Control (QC)*** - 'Operational techniques and activities that are used to fulfil requirements for quality' (ISO 8402:1994, 3.4) [11] .

3.8 ***Registration*** - 'Procedure by which a body indicates relevant characteristics of a product, process or service, or particulars of a body or person, in an appropriate, publicly available list (ISO/CASCO 193 (Rev. 2), 1.10 [8] , & ISO Guide 2:1996, 12.10).

3.9 In ***routine*** analysis**,** the analytical problem will have been encountered before . A suitable validated method for solving the problem will exist and may be in regular use. The degree of associated staff training, calibration and quality control used with the method will depend on sample throughput.

3.10 ***Study*** - 'an attentive or detailed examination' [10].

N.B: use of the terms 'project' and 'study' in this guide do not mean that the guide is applicable only to GLP work

3.11.1 ***System (quality)*** - 'The organisational structure, procedures, processes and resources needed to implement quality management (ISO 8402:1994, 3.6) [11] .

3.11.2 *System* has been used in this guide to refer more generally to the infrastructure within which a laboratory undertakes analytical work and in this context does not necessarily constitute a quality system. This is entirely consistent with the ISO definition.

3.12 ***Task*** - No formal definition. The use of task in this guide denotes a small discrete piece of work, several tasks making up a project or study.

3.13 ***Validation*** - 'Confirmation by examination and provision of objective evidence that the particular requirement for a specified end use are fulfilled' (ISO 8402:1994, 2.18) [11] .

3.14 ***Verification*** - 'Confirmation by examination and provision of objective evidence that specified requirements have been fulfilled' (ISO 8402:1994, 2.17) [11] .

4. PRINCIPLES FOR MAKING VALID ANALYTICAL R&D MEASUREMENTS

4.1 Six basic principles have been identified as important for laboratories making measurements to follow [12].

I. ***'Analytical measurements should be made to satisfy an agreed requirement'*** - In routine work it is usually a straightforward process to define the problem for which the analytical work is being carried out. In R&D specification of the problem is usually done as part of project definition. The customer may only have a vague idea of what the problem is and how chemical analysis can solve it, and will rely on the laboratory's technical expertise to design a suitable technical work-programme. Cost and time constraints will have to be considered as part of the

programme design. The programme will define how results will be reported and the importance of only using results in the appropriate context. Results can be badly misunderstood or misused if extrapolated outside the boundary conditions of the programme.

II. ***'Analytical measurements should be made using methods and equipment which have been tested to ensure they are fit for purpose'.*** Whatever type of measurements are made, suitable, well maintained and calibrated equipment is vital to ensure success. It is of the utmost importance that performance characteristics of methods should be evaluated to the extent necessary to show they are suitable for the measurements for which they are being used.

III. ***'Staff making analytical measurements should be both qualified and competent to undertake the task'.*** In R&D work it may not be possible to guarantee that the staff are totally competent as the full extent of the expertise required. The needs may not be fully appreciated when the work is started. It is possible that the analyst will not have much previous experience of the problem, but should have at least a basic knowledge of the underlying concepts involved in the work.

IV. ***'There should be regular independent assessment of the technical performance of a laboratory'.*** A laboratory's internal QC may indicate consistency in the measurements made within that laboratory. Independent assessment of the measurement capability by participation in proficiency testing schemes or measurement of well-characterised reference materials gives an idea of how well the laboratory's performance would compare with that of its peers. However it is recognised that the options for such independent assessment may be limited in an R&D environment.

V. ***'Analytical measurements made in one location should be consistent with those made elsewhere'.*** Use of reference materials (where available) and assessment of measurement uncertainty of the methods in use will help ensure traceability and compatibility with others making similar measurements.

VI. ***'Organisations making analytical measurements should have well defined quality control and quality assurance procedures'.*** All of the various measures taken to ensure quality of measurements within a laboratory should be incorporated into a quality system to ensure transparent and consistent implementation. If possible some sort of external audit is desirable to verify the working of this quality system.

5. ORGANISATIONAL QUALITY ELEMENTS

5.1 ***Administrative and technical planning of the work- see also CITAC Guide CG1, section 11***[1]

5.1.1 Laboratories which carry out analytical R&D need to have staff with suitable managerial and technical abilities to plan, control, deliver and report each project. This is considered in more detail in §7.1.3.

5.1.2 Where a laboratory is carrying out a number of projects simultaneously, coordination of the project management related to use of facilities is advised. Management needs to be aware of the different projects in progress in the laboratory at a given time and the corresponding risks of one project affecting another, both from a resource point of view but also from cross contamination. Similarly where projects are spread across several departments within a laboratory or involve input from external laboratories, suitable coordination is necessary to ensure coherent delivery of the work without any adverse effect on quality.

5.2 *Quality management, corporate and local*

5.2.1 Regardless of whether the laboratory is formally recognised as compliant with a published quality management standard, it is recommended that it has a quality management system, whether formal or informal, through which its declared quality policy can be implemented. Typically this will involve staff with specific responsibilities for quality, who act as the focus and coordinators for quality matters within the laboratory. Quality also needs to be managed at various lower levels *e.g.* group, team or section. This may involve individuals having particular quality-related responsibilities as part of their duties and each member of staff should be aware of what role they have in the delivery of quality within the laboratory.

5.2.2 The management of quality in an R&D environment can be a delicate issue. A balance needs to be struck between maintaining a suitable level of control whilst at the same time not inhibiting creativity.

5.3 Record keeping and document control

5.3.1 The purpose of keeping records is so that information and data held or gathered by the laboratory can be used to compile reports, make comparisons with other data (whether contemporary or historical), repeat work, and develop new or similar processes. Record keeping and document control are sufficiently important to justify a laboratory having a centralised policy, including relevant training for staff and competence assessment. The policy might typically cover:

- use of various types of media for record keeping;
- external considerations (such as recording requirements for patent applications);
- minimum levels of information for particular operations;
- use of forms and other approved formats;

- legibility, clarity, layout of information, and ease of data retrieval;
- traceability of records to time, date, analyst, sample, equipment, project;
- use of audit trails;
- authorisation of records by the use of signatures and other methods;
- methods for ensuring a record is complete;
- cross referencing copying restrictions;
- rules for amending and authorising amendments to records;
- rules for minimum retention of data, reports and other useful information.

5.3.2 Useful information should be recorded at the time or immediately after the work is completed.

5.3.3 Document control should be extended to all formal documents used in the analytical work, that is, those documents whose use is recognised within the quality system (as defined in the quality manual) and whose format, content and use has to be reviewed and authorised. It is not unusual for a laboratory to use a hierarchical approach for its quality system documentation. This ensures a maximum of flexibility as work patterns change. The table below shows four levels of formal document.

Level	Documentation	Subject / examples
1. (Highest)	Corporate quality policy	Quality manual
2.	• Formalised internal procedures operable across the laboratory • Other (external) normative documents	Standard Operating Procedures (SOPs) Relevant laws, regulations, standards (ISO/CEN *etc.*), official methods (e.g. AOACI), Codes of Practice (COPs).
3.	Technical work instructions (specific applications)	In-house methods
4. (Lowest)	Records	Instrument logbooks, calibration records laboratory notebooks and other raw data, correspondence, reports

5.3.4 Clear responsibilities for document control should be assigned to staff. To maximise flexibility authorisation should be devolved as far down the management chain as possible, bearing in mind the need for those authorised to have sufficient expertise to make sound judgements.

5.3.5 For all controlled documents there should be a system for recalling and archiving versions of documents when they are upgraded or replaced. Suitable facilities for archiving information should be available and their use laid down within the document control policy. The use of

computer based systems is recommended to facilitate the control of documents but care is advised to ensure access to the system is only availaible to authorised staff.

5.4 ***Staff -qualifications, training and supervision of staff - see also CITAC CG1, section 10*** [1]

5.4.1 Analytical R&D must be carried out by staff having appropriate experience, knowledge and competence, consistent with the particular role they have in the work. Suitable qualifications may be academic, professional or technical, preferably with a specialisation in analytical chemistry and may also feature on-the-job training. For R&D leaders, a high level of qualifications and relevant experience is necessary. Published guidance is available [13]. The balance between academic qualifications and experience required for particular types of analytical work may vary from country to country.

Staff should receive relevant on-the-job training. The training programme should be assessed regularly and adjusted as necessary to ensure it continues to be relevant to the type of work carried out.

5.4.2 It is the responsibility of management to establish appropriate levels of supervision for each task, depending on the difficulty of the work and the capability of the analyst. It is recognised that analysts may be given unfamiliar tasks as part of their training; in such cases, management should take extra care to ensure that the level of supervision is appropriate.

5.4.3 Analysts involved with R&D will need to have or develop particular skills. For example they will have to exercise high levels of judgement about how to approach the analysis, about the selection of best methods, and about interpretation of results. They will occasionally encounter problems which are beyond their own experience and possibly also that of the laboratory, and so should have experience of literature searching and other information gathering techniques. They should maintain and develop their expertise by reading scientific literature, attending seminars and courses, participate in professional activities and be aware of colleagues who are experts in the various analytical subjects who might be able to give advice. They should also maintain an up-to-date awareness of quality assurance. Management is responsible for ensuring staff have the resources to maintain these professional skills.

5.4.4 Staff records are an important aspect of establishing the suitability of staff to undertake the analytical work. As a minimum, they should include:

- education leading to formal qualification e.g.: academic, professional, technical / vocational*;
- methodological / technical expertise;
- external and/or internal training courses attended;

- relevant on the job training;
- previous R&D experience, in terms of subject areas covered;
- list of scientific papers published, posters presented or lectures given.

** Vocational training is practical training related to a particular job, accompanied by study of the relevant theoretical knowledge. Part of the training may be provided within the laboratory, but the competence may be assessed independently and recognised via a formal qualification* [14-16] .

5.5 Equipment - see CITAC CG1, section 12. For computer controlled equipment - see CITAC CG1 section 17 and App. C [1] *and GLP guidance* [17] *.*

5.5.1 Equipment should be purchased against technical specifications derived from anticipated use and required performance capability. Where an instrument is sold on such a basis, there is an obligation on the agent or manufacturer to demonstrate to the purchaser, if required, that the instrument can meet that specification. Newly acquired items of equipment should be formally commissioned before being put into routine laboratory use, so that correct functioning and compliance with the appropriate specifications can be verified [18].

5.5.2 A list of equipment should be kept, indicating the equipment name, identification, records of commissioning, and related operating procedures, where appropriate. Records of calibration and maintenance should be kept.

5.5.3 It is not uncommon in R&D for a piece of equipment to be used by different persons, for a number of applications, perhaps in different projects, within a brief timescale. Where this is the case, special precautions for instrument cleaning and maintenance are advised, together with records detailing what the equipment has been used for, when, and by whom. This may help reduce unexpected observations which might have been caused by cross-contamination.

5.5.4 R&D may actually involve the modification of existing equipment or design of new equipment. Accepted engineering and scientific practices should be applied to design and construction. Method validation procedures and use of blanks, standards, old samples reference material can be used as part of the commissioning process.

5.6 Monitoring quality - see CITAC CG1 section 18 [1] *.*

5.6.1 Regular and systematic monitoring of quality is necessary to ensure that it is appropriate to the laboratory's needs and all aspects of it are functioning properly. Monitoring may be carried out by external bodies (different types of external assessment are described in more detail in section 8) or internally, using laboratory staff. Where there is a formal quality system internal assessment is conducted to formal procedures and known variously as audit or review [19-22] .

5.6.2 One approach to internal assessment is for a laboratory to train some of its own staff to act as internal auditors. The laboratory will benefit by involving its staff in monitoring the quality system. Assessors can be staff at any level in the organisation and should be independent of the work they are assessing, but have sufficient technical expertise and experience to be able to examine it critically.

5.6.3 All areas of the laboratory whose operations affect quality should be assessed in a systematic manner, typically at least once a year. Assessments should examine adequacy of procedures and ensure that these procedures are being followed, that suitable records are kept and appropriate actions are taken. Ideally a preplanned timetable should be followed, and over an agreed period should cover the whole quality system. It is unnecessary to examine the entire output of the laboratory - the assessment should be done on a 'sampling' basis. In the case of research it will be appropriate to select and examine entire projects or studies.

5.6.4 Even if a research laboratory's quality system is not fully documented to the requirements specified in quality standards, provided some form of work-plan is available an appropriate assessment can be made against this. For example, some of the questions which could be asked in assessment of a workplan could include:

- is the analytical task clearly described and understood?
- is there an analytical working plan or study plan, and is there evidence of adequate experimental design?
- are the task leader and other technical staff sufficiently competent?
- are the applied procedures and equipment fit for purpose?
- are calibration levels adequate and traceability suitable?
- what measures are taken to confirm the reliability of results and are the results plausible (*e.g*. duplicate analysis, use of RM/CRM, spiked samples, cross-checking by other personnel, other internal and external quality control)?
- has the work been completed and does the test report contain sufficient information (analytical results, interpretation, reference to customer requirements)?
- is the level of record keeping sufficient for its purpose?
- are scheduled milestones and deliverables being met?
- are any relevant regulatory requirements being met?

5.6.5 Where changes to procedures are required staff should be identified to carry out them out over an agreed timescale. Subsequent completion of the changes should be confirmed.

5.6.6 In R&D it is not unusual to make ad-hoc deviations from procedures. These may adversely influence software or hardware performance, data collection, calculations, and interpretation of results. A simple system recording deviations as they occur and confirming that consequences have been evaluated and where appropriate corrective action has been taken should ensure that there is no inadvertant loss of quality arising from the deviations.

5.7 Subcontracting

5.7.1 The laboratory should consult with the customer before placing any part of a contract with subcontractors.

5.7.2 Where one laboratory (A) subcontracts work to a second laboratory (B), B should operate to at least equivalent levels of quality as A. A should put in place whatever procedures are appropriate to assure itself of the quality of the capabilities of B and the quality of the work it is producing. This might include:

- assessing the quality of subcontractors;
- establishing a list of laboratories approved to act as subcontractors;
- reviewing data and reports of subcontractors for scientific content;
- limiting the scope for the subcontractor to work independently on the subcontract;
- checking the subcontractor's work against the initial specification, and defining corrective action if necessary.

Note that the subcontractor and the laboratory placing the subcontract could be two different laboratories within the same organisation, i.e. the arrangement could be purely internal.

6. TECHNICAL QUALITY ELEMENTS

6.1 *Unit operations*

6.1.1 R&D projects can be considered as a collection of discrete tasks or workpackages, each consisting of a number of unit processes, themselves composed of modules containing routine unit operations. The unit processes are characterised as being separated by natural dividing lines at which work can be interrupted and the test portion or extract can be stored without detriment before the next step. This is illustrated in Figure 2.

6.1.2 The benefit of this modular approach to defining R&D projects is that new R&D work is likely to contain at least some components which are familiar to the laboratory and may even be performed routinely. This approach offers benefits in terms of establishing staff competence and also in documentation of procedures.

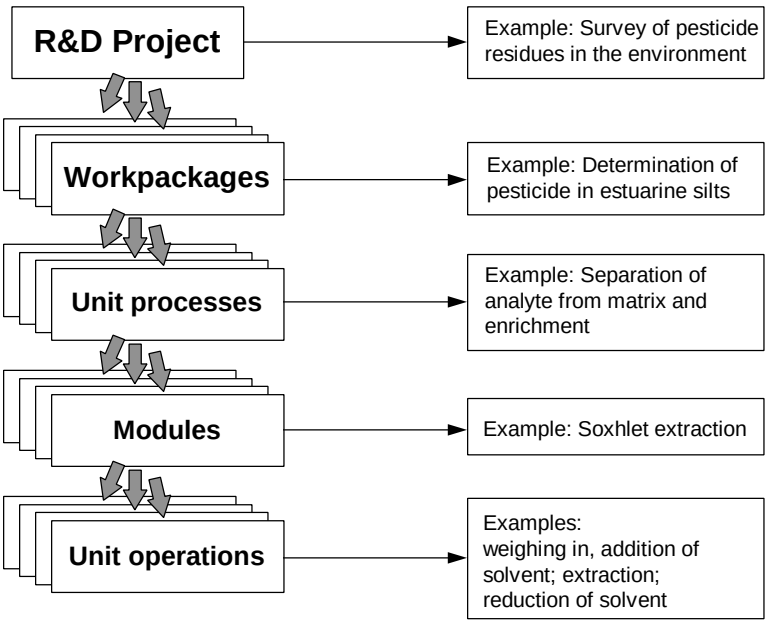

Figure 2 - Illustration of the breakdown of R&D projects into unit operations

6.2 ***Technical capability of the laboratory***

6.2.1 It is common practice to allow the general acceptance of laboratory performances by a *type of test* approach. This means, if the laboratory has demonstrated its ability to perform a particular method, it is also accepted as fit to perform similar closely related methods. This logical, but knowledge- and experience-oriented approach, enables the demonstration of valid analytical measurements to external experts without the need for elaborate validation of every single unit operation or module or process.

6.3 ***Methodology***

6.3.1 It is likely that procedures for carrying out *unit operations* and perhaps even *modules* (see Figure 2) will be sufficiently routine and/or common to other work to warrant full documentation as a written standard operation procedure (SOP). Using this principle, any new test procedure can be described by the appropriate combination of the SOPs of the relevant unit processes or modules, keeping new documentation to a minimum. Representation of new test methods by recombination of existing SOPs has a number of advantages in terms of using existing validation information and uncertainty contribution estimations. Validation of the whole workpackage or task will often be necessary but can be achieved using reference materials, *etc*.. In practice SOPs might even cover individual workpackages but care should be exercised in case this reduces the flexibility of operations.

6.3.2 SOPs provide a source of information to which analysts, carrying out a particular operation, can refer in order to ensure a consistent approach. A closely followed, well written SOP can improve the consistency of data produced for a particular process, between analysts, between laboratories, and over time intervals. Thus an SOP should contain whatever level of information is necessary to avoid ambiguity. A well written SOP also helps auditors to follow the course of the work done and so assess the validity of the data. In an R&D environment it is expected that as the science improves, so SOPs can be reviewed and changed to reflect the improvements (*e.g*. in speed, in material and money savings, in waste production, *etc*.) as long as the results are convincingly demonstrated to be comparable or better than those obtained with existing versions. Changes must be authorised, prior to use, in line with document control policy.

6.3.3 Where SOPs do not already exist or are inappropriate, contemporaneous notes should be made to describe the procedures used in the work. Sufficient detail should be recorded so that at some later time, the procedures used can be reconstructed, if necessary. Where a number of procedures were attempted before one was found that was satisfactory, records should be kept of the failures so that they can be avoided in future.

6.4 *Reagents, reference materials, and calibrants - see CITAC CG1, sections 13 & 16* [1]

6.4.1 Special attention should be given to chemical and physical properties of reagents, reference materials and calibrants (chemical and physical measurement standards). Careless preparation or poor storage may result in inadvertant degradation. This is particularly important where chemical metabolites, or chemicals about which little is known, are involved. Sometimes, the use of added preservatives or storage under inert atmospheres (*e.g*. Ar or N_2) may be appropriate.

6.4.2 Reagents, calibrants and reference materials prepared for specific R&D applications should be appropriately labelled and if appropriate, their use restricted, to prevent contamination through widespread use. Details of preparation *etc.* should be recorded in SOPs.

6.5 *Calibration & traceability - see CITAC CG1, section 15* [1]

6.5.1 Calibration establishes, for specified conditions, how the response of the measurement system relates to the parameter being measured. Calibration is usually performed using a reference material of established composition, or calibrant in which the property of interest (for example the chemical purity) is well characterised.

6.5.2 In R&D, one is more likely to encounter the situation where calibrants are absent or, if available, are poorly characterised. Where the stoichiometry of the calibrant is not known an approximate amount should be weighed and the exact amount of calibrant constituent determined with an

absolute method (coulometry, volumetry, gravimetry). Where no suitable calibrant is available the method for determining the response for the property analyte should be demonstrated.

6.5.3 Validation of the unit processes together with appropriate traceability is important to ensure that data produced is comparable with data for similar measurements made at different times, or by different analysts or laboratories, or using different methodsand different samples. Traceability can be achieved by calibration using various calibrants, reference materials or even standardised procedures. Caution is advised when using standardised procedures as frequently they contain bias which may be poorly controlled.

6.5.4 Traceability to (the) SI is often possible in chemical analysis at some level of uncertainty. Traceability can be to a standard / calibrant, whether national or international, which has been accepted as the point of reference by the analytical community concerned and which all interested parties have access to, either directly, or indirectly, through a chain of subsidiary standards. Similarly traceability can also be established to a reference method.

6.5.5 Traceability is not to be confused with the traceability from the sample via the test procedure to the final test result. This has been tentatively termed “trackability“ (from tracking back).

6.6 *Instrument performance*

6.6.1 For instrumentation, design, installation, operational, and performance qualifications are of equal importance in R&D as they are in routine work. Design and operational qualifications are briefly dealt with in §5.5.1. This section deals with operational and performance qualifications - Does the instrument/system work in the specific application and what could be the interferences? Does the instrument continue to work in the manner intended (continuing fitness for purpose)?

6.6.2 In R&D it is not sufficient to adapt existing work without demonstrating that the instrumentation works properly with the new application. Care is also needed with novel or modified instrumentation; where the performance claims of the manufacturer may no longer be true because of the modification.

6.6.3 The ultimate performance test for any calibrated analytical instrument is to analyse a certified reference material (CRM) and obtain a result within the uncertainty range stated for the CRM. If the matrix of the CRM is similar to that for the samples, and the CRM is subjected to the whole analytical process then this serves to validate the entire procedure [23-25].

6.6.4 Often in R&D, no CRM is available and it is not possible to relate a property to an existing national or international standard or calibrant. Instead, in-house reference materials can be

used. It is advisable to specify one or two materials with characterised property values appropriate to the scope of the procedure which can be used for instrument performance checks, calibration or quality control. Specific mixtures of analytes can be contrived to test certain performance parameters, for example the resolution of two compounds in a separation process.

6.6.5 In critical instances the use of a different analytical procedure and/or technique, susceptible to different interferences, is advised to check results. This check is more valuable than, for example, interlaboratory comparisons involving only a limited number of laboratories using exactly the same overall procedure and measurement technique. However, interlaboratory comparisons involving larger numbers of laboratories and different techniques are more useful still.

6.6.6. Where R&D involves testing a large number of similar samples using a particular procedure, control samples and charts can be used to monitor the continuing stability of instrument performance.

6.7 *Use of statistics*

6.7.1 Statistical techniques are an invaluable tool in the design or use of analytical methods. During the lifetime of an R&D method statistics can be used in four basic areas:

I. experimental design of the method;
II. characterisation of method performance, ruggedness and determination of uncertainty;
III. quality control of the method (once the method is in use);
IV. interpretation of populations of results.

6.7.2 In each of these areas a variety of statistical techniques may be applied or indeed are necessary, depending on the different parameters to be studied, and such chemometric approaches can also reduce time and costs. A detailed study of this area is beyond the scope of this guide; references to a number of suitable texts are provided in §9.

6.7.3.1 **Experimental design**. In any analytical procedure performance can be influenced by a number of different variables, such as: matrix interferences in the samples; reagent concentrations; temperature; derivatisation time; *etc*.. Experimental design is usually used to describe the stages of identifying the different factors that affect the result of an experiment, designing the experiment so that the effect of these factors is minimised, and using statistical analysis to separate the effects of the factors involved. For example, a ruggedness test will indicate firstly whether a particular method will stand up to everyday use, and will indicate which parts of the method are vulnerable to change and need to be subject to quality control. As part of the design

process regression or multiple regression analysis may be used, together with ANOVA (ANalysis Of VAriance) determinations and MANOVA (Multiple ANalysis Of Variance)[26, 27].

6.7.3.2 Statistical methods are very important in the design of sampling schemes. If used properly they can enable the desired results to be obtained with the minimum of samples and subsequent analysis. Internationally available standards have been published for the use of statistics in certain types of sampling [28]. However a broad knowledge of the history of the sample substantially helps to design a more intelligent sampling plan and reduces sampling time and costs.

6.7.3.3 SIMPLEX optimisation can be used for rapid method development where a number of factors affect method performance and to investigate all possible combinations would involve vast amounts of work [29]. Other specialised techniques which may be used in a similar way include: full factorial designs; fractions of factorial designs; Taguchi designs.

6.7.3.4 Where a large number of samples need to be processed and only a few are expected to yield "positive" results, screening techniques may be used for eliminating the large numbers of negative samples to leave the positive samples which can then be examined in more detail.

6.7.4 **Characterisation of method performance and determination of uncertainty**. This involves the evaluation of various parameters associated with the performance of the method, such as precision, trueness, *etc*., followed by a judgement as to whether these performance capabilities are sufficient to meet the needs of the method. The process is generally referred to as method validation (see §6.8.5). Determination of measurement uncertainty use similar measures to those determined during method validation and involves identification, determination and final recombination of all the sources of uncertainty arising at all stages of the analytical procedure to give an overall measure (see §6.8.6). Both method validation and measurement uncertainty make use of simple statistical measures such as means, standard deviation, variance, *etc*..

6.7.5 **Development of quality control**. The quality control procedures developed for a new method should concentrate on those parameters which have been identified as critically influencing the method. However for R&D work there may be problems in finding suitable samples for quality control purposes, and control charting techniques are less relevant in non-routine situations. Control charts can still be applied, for example to monitor instrument calibration, and the main thrust of quality control in the R&D situation is probably best directed towards ensuring instrumentation is working properly and calibrated, monitoring values from reference materials where available, and replicate analysis (consecutive and random, to monitor short and long term variation respectively).

6.7.6 **Interpretation of results**. The problems associated with validation of methods in R&D and the subsequent design of adequate quality control should be borne in mind when interpreting sets of data produced in R&D. Techniques used for the detection of outliers and measures of distribution of result populations, such as standard deviation, are particularly relevant in this case.

6.8 ***Technical requirements related to particular unit processes:***

6.8.1 In most analytical R&D situations the following unit processes (which may or may not have subsidiary modules and unit operations) may be encountered: sampling; sample preparation; separation of the analyte from the matrix and enrichment; measurement; calculation and; presentation and interpretation of the result. Guidance is generally limited to information specific or more relevant to R&D.

6.8.2 ***Sampling, - see also CITAC CG1, section 19*** [1]

6.8.2.1 Extensive guidance on sampling exists in the scientific literature [28]. There is actually little advice on sampling in R&D that is not also applicable to routine measurements.

6.8.2.2 Where R&D involves the development of new test procedures for subsequent use on real samples, method development needs to consider practical sample sizes which will typically be available for testing. During the development stages it may be useful to have large quantities of real sample available for method validation, *etc*..

6.8.2.3 R&D may involve taking types of samples which have never been encountered before, with unknown or unfamiliar analyte contents or matrix types. The samples may present unknown hazards or problems with stability, handling, and storage. The sampling strategy should try to anticipate potential problems and if possible make suitable allowances. Customers' declarations of the expected contents of samples should be treated with caution. Sampling plans should be detailed even if some of the information recorded is subsequently not needed. The analytical staff involved with the R&D should use their scientific expertise to help ensure the sampling procedure is as appropriate as possible. Where appropriate, procedures should be recorded.

6.8.2.4 Similarly, for unfamiliar samples, storage conditions should err on the side of caution. In critical cases it is strongly advised that samples are retained after analysis at least until the validity of the tests results have been confirmed by suitable review.

6.8.2.5 With samples taken for R&D purposes little may be known about their homogeneity. It is particularly important to investigate this before any subsampling is carried out to reduce the effective bulk of the sample. Any means used to homogenise the sample must not compromise its integrity. It may be appropriate to separate phases in inhomogeneous samples and treat the separate phases as different samples. Conversely it may be appropriate to homogenise the samples. The uncertainty of subsampling which is determined by the level of homogeneity may be estimated by setting up a specific study and taking more subsamples and determining the uncertainty statistically.

6.8.2.6 It may be convenient to have a single SOP describing the variety of sample treatment methods (solvation; dissolution; digestion; extraction; surface cleaning; melting; combustion; *etc*.) used by the laboratory, and containing detail on the special precautions to be taken for the different analyte groups. It should also describe how the methods are applied to blanks (spiked and unspiked), reference materials and other calibrants, and other materials used for quality contol purposes.

6.8.3 *Isolation of the analyte(s) using separation and enrichment*

6.8.3.1 Diverse techniques are available for separation and enrichment. The experience of the analyst will be an important factor in choosing the most appropriate for a particular application. For future reference, records should indicate the logic behind a particular choice.

6.8.4 *Measurements*

6.8.4.1 The measurement process consists of using a calibrated instrument to determine the net instrument signals of the test portions and various different blanks. Within run and between run changes in instrument response can be monitored using quality control samples and calibration standards.

6.8.4.2 Depending on the circumstances, this determination step may be repeated several times to allow a statistical data treatment of this single step. The determination of more than one test portion from the same sample can be used to determine (at least an estimate of) the overall repeatability of the analytical method. Where there is a suspicion that interferences are present, results obtained from test-portions using external standard calibration (using a calibration curve) can be checked by spiking test portions with known amounts of the analyte of interest.

6.8.4.3 Blank corrections for measurements should be made by calculating actual concentrations of sample and blank as indicated by the respective instrument signals and then subtracting one from the other. The practice of subtracting the blank signal from the sample signal and then calculating the result using the net signal is not recommended.

6.8.5 *Validation - see also CITAC CG1, section 22* [1]

6.8.5.1 There is a clear responsibility on the part of the test laboratory and its staff to justify the trust of the customer or data user by providing reliable data which can be used to solve the analytical problem. An implication of this is that methods developed in-house must be adequately validated, documented and authorised before use. Validation is normally quite straightforward for routine work but can be expensive and time consuming. For methods used or developed during the course of R&D, validation is equally important, but less straightforward. General guidance has been produced by EURACHEM [31].

6.8.5.2 Various options exist for characterisation of method performance. The trueness of a new method could be assessed against that of an established method, repeatability could be assessed using reference materials, and reproducibility through interlaboratory comparisons. In R&D, many of these options may not be available. Validation tools may be limited to the use of in-house reference materials, and uncertainty estimations based on error propagation principles relying on a solid understanding of the theoretical principles of the method and the practical experience of the research workers.

6.8.5.3 A suitable unit process for data treatment should include validation of the overall procedure. That means evaluation of various performance parameters of the method, and consideration of their adequacy relative to the analytical requirement. Parameters such as: limit of detection, limit of quantification, dynamic measuring range, sensitivity, repeatability (same analyst, same instrument, same laboratory, same day), reproducibility (different analyst, different instrument, different laboratory, different day), accuracy (difference from the true value) and other terms (*e.g*. robustness or ruggedness); will need to be considered.

6.8.5.4 The extent to which validation is needed, and the effort given to this task, depends on the use which will be made of the method or technique. At one limit, where new methods or techniques (or ones seldom applied) are being used, a customer requirement for durable methodology will justify extensive work on validation. In many situations, however, less than full validation is necessary or possible. Here the analysts' professional judgement will be introduced to decide those unit operations of the analysis which need to be investigated, and those whose performances can be estimated from comparable systems. The extent of validation, and the consequences in time and cost, are one of the key issues to be agreed between analyst and customer when commissioning method development.

6.8.5.5 It is generally assumed that R&D requires an increasing effort for validation since seldom applied or totally new techniques or methods are being used. The unit operation approach described above enables the possibility of recombination of the units into a large variety of testing methods. If these units can be individually validated it may be possible to estimate the overall performance capability of subsequent combinations of the modules which then require the minimum of further validation for verification. It is not necessary to define all unit operations for each possible analyte, but it might be sufficient for a group of analytes with a nearly similar matrix.

6.8.5.6 Ideally, individual recovery studies should be performed for each analyte. This can be done using a synthetic matrix similar to the sample matrix or by analyte addition (spiking) to sub-sample aliquots and determination of the increase of the measured concentration. Often the recovery factor depends strongly on the sample matrix. Guidance on acceptable recovery

ranges for similar analyte/matrix combinations may be available in the literature. Whether results should be corrected for non quantitative recoveries is the cause of much debate [32] and the client may have a preference. Reports should indicate clearly whether or not data has been changed to allow for non-quantitative recoveries.

6.8.5.7 Ideally the procedure should try to identify such a matrix effect so that any blank correction procedures can be performed properly. In analytical R&D the search for systematic errors is of greater importance since per se less is known in those fields. Wherever possible these systematic errors should be identified and if possible, eliminated.

6.8.5.8 It should be noted that methods can be validated at different levels. Analysis of CRM's with similar matrices to the test materials gives the highest confidence level for in-house validation. If the obtained results lies within the stated confidence range then the total analytical process is under control and all involved unit processes are automatically included in this validation. This means there is no need for any further method or instrument validation and no need for other more formal demands. Other mechanisms for validation are described below in order of decreasing confidence:

- taking part in inter-laboratory comparison tests;
- performing a limited number of control-analyses of the sample at a different test laboratory;
- employing several methods with different interferences possibility and obtaining only one and the same result;
- reanalysis of an in-house sample of known content.

6.8.6 ***Measurement uncertainty - see also CITAC CG1, section 21*** [1]

6.8.6.1 Uncertainty should be estimated and quoted in a way that is widely accepted, internally consistent and easy to interpret. More detailed guidance has been published by EURACHEM [32]. Where appropriate, uncertainty should be quoted with the analytical result, so that the user can be assured of the degree of confidence that can be placed on the result.

6.8.6.2 The most significant contributions to the overall uncertainty of a measurement are usually due to the sampling processes and the accuracy of the determination of recovery factors. Contributions due to instrument performance are generally less significant.

7. ANALYTICAL TASK QUALITY ELEMENTS

7.1 ***Preparation and planning before starting work:***

7.1.1 ***Definition of task and project design***

7.1.1.1 Planning and preparation is a critical part of analytical R&D, especially where new analytical methods are generated or extensive validation of generic methods is required. The effort put into planning depends on the complexity and requirements of the work, previous experience, the extent to which the work is unfamiliar or novel in its character, the number of persons or organizations involved, expenditure for new equipment, consequences of wrong results, the duration of the work, deadlines *etc*.. A flowchart such as the one shown shown in annex B may assist planning. As a rule of thumb, proportionally more planning is needed for high risk work. When costing project work it is important to correctly estimate the resources needed in the planning or subsequent management stages. The structure of the project should be flexible enough to allow creative problem solving. The project management team is responsible for planning activities within the project and allocating resources to cover these activities. The sort of activities involved include:

- scoping;
- milestone planning;
- objective/goal setting;
- resource allocation and costing;
- contract control;
- financial control;
- change management;
- liaison with customers.

7.1.1.2 Task definition is the first stage of planning and should provide sufficient information to allow more detailed planning or indicate viability of proceeding. Go/no-go decision criteria should be incorporated in the project structure at the earliest opportunity. It is vital to establish a good link with the client to ensure work is defined adequately and thus maximise the chances of a productive outcome to the project. The sort of areas covered in task definition may include:

- nature of the problem that the work is intended to address, seeking clarifying from the client as necessary;
- objective, goals and expected information, purpose of results/data, intended use of information;
- type of material/product/matrix to be analysed/amount available/safety considerations;
- sampling procedures/sampling plans, statistical methods;
- element/species/determinand/property to be analysed/determined;
- methodology, generic methods to be used, destructive/non-destructive methods;
- required accuracy (or precision, bias, *etc*. as appropriate) and related equipment performance requirements;
- validation procedures and use of reference materials, standards, reference methods;
- required date of completion;

- available resources (personnel, equipment);
- expected use of subcontraction;
- success/failure criteria where appropriate;
- expected/permissible costs and expenditures;
- reference to exploratory work and review of literature required for definition and execution of the task;
- degree of confidentiality necessary;
- requirements and arrangements for archiving;
- ownership of intellectual property;
- possible strategy for dissemination and exploitation.

7.1.1.3 A questionnaire can be used to help define work. The example shown in annex C is adapted from one used for routine work. Note it is not exhaustive but illustrates some of the issues which should be addressed.

7.1.1.4 Where limited amounts of sample are available it is particularly critical to have a clear strategy in place before beginning work. Use of non destructive methods should be considered.

7.1.2 *Project design and research plan*

7.1.2.1 Once task definition is complete the research plan(s) can be drawn up. The laboratory management should involve the client, and the laboratory staff from the very beginning in order to ensure that the finalised project as far as possible meets the client's requirements, is technically possible and suitable resources are available within the specified timescale. The project should be structured by a logical sequence of tasks or workpackages, points of decision where the work can change direction if necessary, and points of achievement. (milestones, target dates) which enable progress to be monitored. All contractual or technical issues should be resolved before the analytical work is begun. Particularly where operations may be complex, use of flowchart, such as that shown in annex B, a decision tree or other diagrams, may help to clarify the procedure.

7.1.2.2 The **research plan** defines:

- Goals: Set clear final (and if appropriate, intermediate) goals (measurable objectives including go/no-go decision points/acceptance criteria. Establish what questions need to be answered at each stage and the corresponding results/data required to answer them.
- Tactics: Outline the strategy to be used at each stage. If necessary subdivide tasks into manageable, defined workpackages (unit operations) with discrete goals.

- Resources: Define the resources (personnel, equipment, facilities, consumables) needed at each stage.
- Time schedule: Define start and end of project, dead lines for intermediate goals, and minimum critical path for completing work.

7.1.2.3 Research plans should contain as much detail as is necessary to define the tasks involved. For isolated tasks the plan may simply be an entry in a notebook or a form. A more detailed plan will be necessary for larger, more complex tasks or when time and cost constraints are to be closely controlled, or when high risk or significant investments depend on the outcome of the work. If there is significant doubt as to whether the work can be completed successfully by a single route, then alternative plans should be defined.

7.1.2.4 A workpackage typically consists of a discrete piece of work with: defined starting and finishing times/dates; necessary starting conditions (particularly if the workpackage is one in a sequence); a goal (achievement of which indicates successful completion of the workpackage); a budget indicating financial, time and other resource restrictions; a note of any particular resource requirements; a statement of the roles and responsibilities of the various staff involved with delivery at all levels from management to technician; a specification for reporting progress and the final goal.

7.1.2.5 Milestones are points of appraisal (usually)at the end of a workpackage. Their timing is normally fixed within the overall project timetable. They are points at which decisions can be made either to proceed with the project, to stop, or to select a particular path in the workplan for further action. Where appropriate the client should be involved in any important decisions.

7.1.2.6 A number of tools are available to assist project design and control [33]. They include:

- bar charts (Gantt chart);
- PERT chart (program evaluation and review technique);
- CPM (critical path method).

7.1.3 *Resource management of task*

7.1.3.1 Large or multitask projects may involve scientists from several departments of the laboratory and perhaps outside specialist subcontractors. The role of project management is particularly important in order to ensure the project team functions smoothly, with all members co-operating and aware of their roles and responsibilities. Particular attention should be given to:

- definition of the project management hierarchy, with leaders in particular areas, and defined authority and responsibility for all team members;

- involvement of all personnel pertinent to the project (including the client) in defining the task and assignments, and in planning the project;
- setting clear tasks and goals which are challenging but achievable;
- early consultation with the management of specialists in other departments or organisations, involved in the project. Unresolved questions concerning priorities and workload, and budget contributions often disrupt good team work;
- communication. Hold meetings at appropriate intervals for exchange of information, problem solving, consultation, reporting, coordination and decision making.

For small, simple projects the same principles can and should be applied in a cut-down form.

7.1.3.2 Resource management at the planning stage may include:

- evaluation of the skills and facilities required for the project, comparing those against what is available, and plans to cover any shortfall. This includes special considerations such as environmental controls, special equipment and reagents, protective clothing, decontamination procedures;
- costing the planned deployment of personnel and facilities and set budgets for the various parts of the work (time and finance budget);
- establishment of a timetable for the work consistent with client requirements and the availability of personnel and facilities at each stage;
- availability and allocation of resources to defined tasks and/or appointed dates/ decision points (e.g. milestones) and including resource distribution in the project plans;
- definition of a system for monitoring time and resource expenditure in the project;
- identification of potential problems with disposal of samples, reagents and contaminated equipment, arising as a result of the work.

7.2 While the work is in progress:

7.2.1 Progress review/monitoring analysis

7.2.1.1 Progress of work and status of expenditure should be controlled by comparing achievements and use of resources against the planned budgets at convenient points within the work, typically at regular intervals or completion of milestones. Informal reviewing should be carried out individually by the laboratory staff as work progresses. Unexpected difficulties or results, or major deviations from goals may call for extraordinary reviews and interim reports with replanning of the work and reallocation of resources as necessary.

7.2.1.2 Progress should be reported to laboratory management or the client, in the format and at the time intervals agreed at the planning stage. Typically reports might cover: a review of the project plans; information on whether the work is running to schedule and will achieve its objectives - on-time/late/at all, an account of technical progress with achievements and failures/setbacks; and information on resources.

7.2.1.3 Effective project management requires records of laboratory data, observations, and reported progress against milestones or goals to be clear and comprehensive so that decisions made during the project and the underlying reasons are easily understood and laboratory work and results can be repeated if required. Records should include laboratory note books, computer print-outs, instrument charts indicating all activities, working conditions and instrument setting, observations during experimental work, as well as justification for tactics and/or changing plans.

7.2.1.4 Ultimately, the level of data recorded should comply with customer requirements, or those laid down for scientific papers, published standard methods, or other requirements such as patents or licences. It should be sufficient to enable other scientists to repeat the experiments and obtain data compatible with the original work. Thus:

- all experimental details, observations, and data necessary for possible replication of the work must be recorded;
- records should be made 'at the time' and kept as up-to-date as possible;
- records should be traceable to particular samples, tasks or projects, people, time;
- details of unsuccessful work should be recorded - In R&D it is worthwhile reporting failures as well as successes.

7.2.2 *Data verification*

7.2.2.1 Data verification should show that a new or adapted method gives consistent results with a particular sample. If results are not consistent with established data, the analytical procedure may need to be improved until the required consistency is achieved. Management should be aware that data and method validation costs form a significant part of the total costs of R&D.

7.2.2.2 The unit operations, as listed in §6.8.1, may influence one another, but contribute individually to variations in results. A step-by-step verification may often be impractical although it may be feasible and useful to study particular performance characteristics of particular stages of the sequence of operations. In R&D plausibility of data may be checked either using literature data, theoretical considerations, or using specially prepared reference materials and model substances.

7.2.3 *Changing direction*

7.2.3.1 Where a review of progress shows that a particular line of investigation is likely to be unsuccessful, goals or/and chosen tactics and tasks may have to be changed. Such a change may already have been anticipated during planning. Changes should be made in consultation with the client where appropriate and justified in reports.

7.3 *When the work is complete:*

7.3.1 *Achievement review*

7.3.1.1 The completed work should be reviewed by management to evaluate achievements. Experiences gained at all stages of the project may provide lessons for planning and carrying out similar work in the future. The review might typically cover:

- aspects of technical achievement such as differences between goals and results, problems encountered and how they were solved, usefulness of the results;
- compliance with budgeted costs and timescales, with explanations for any deviations, correlation of expenditures and technical results;
- quality of work of individual contributors;
- consequences of project and results to the laboratory (organisation, personnel, equipment, methods and procedures, possibility of dissemination or exploitation);
- satisfaction of client.

7.3.1.2 The achievement review may be supplemented by an external peer review, *e.g*. when data is published in scientific journals, or third party review (audit).

7.3.2 ***Reporting, technology transfer and publication:***

7.3.2.1 R&D may be reported in various ways. Primarily a report should be made to the client in the format previously agreed and be written in a language that the client can readily understand. The report should provide sufficient information to enable the client, any subsequent user, or assessor of the report to be able to follow any arguments, and if required, repeat any or all stages of the experimental work and obtain compatible results. In particular:

- the meaning of the test results should not be distorted by the reporting process;
- appropriate use should be made of conventions for rounding of numbers and expression of decimal places and significant figures;
- where appropriate, results should include an estimate of the associated uncertainty with its corresponding confidence level.

7.3.2.2 Compared to scientific publications, project reports typically contain project oriented information (technical, financial statements *etc*.), conclusions and recommendations, and usually present the findings in a less technical way.

7.3.2.3 If the work has yielded data, observations, new methods, techniques or new knowledge, of interest to the wider community, then dissemination or exploitation of the work is an important issue. Dissemination or exploitation can take a number of forms: lectures, publications in journals; patents; licences; standards; training material. Permission for dissemination or exploitation must be sought from the laboratory, the client or whoever else owns the intellectual property. Where it is hoped that new methods can be adopted more widely, further performance evaluation may be required, perhaps using collaborative study. Methodology must be described unambiguously, and in sufficient detail to allow others to be able to follow the arguments and replicate the work, otherwise its credibility may be adversely affected.

7.3.3 ***Archiving***

7.3.3.1 Archiving primarily involves the secure storage of samples, analytical records, results, methods and other information for later retrieval and use. The method of archiving and the time for which material is kept depends on what is archived and why. It may be done for a number of reasons:

- legal or regulatory requirement;
- requirement of customer or some other external agency (e.g. accreditation body);
- verification of previous work and procedure at later stages of the project;
- validation of methods and results after completion of laboratory work and reporting/ publication;
- proficiency testing or collaborative studies with samples;
- post-report questioning by client or peer review;
- problems associated with duplication of work/results; technology transfer;
- keeping the information benefits the laboratory.

7.3.3.2 Samples should normally be stored until the likelihood of their requiring retest has been ruled out or they have deteriorated to an extent where retest would be meaningless (unless study of their deterioration is part of the work).

7.3.3.3 An important feature of an effective archive system is knowing what it contains and being able to find things quickly. Use of a searchable data-base is recommended and offers some protection against illness, death, or transfer of expert staff and also helps to save time and money by providing a means of preventing the inadvertant duplication of earlier work.

7.3.3.4 Where space is important text based material can usually be archived in electronic or photographic form. Back-up copies should be kept in remote, flameproof storage. The use of different media may be preferred in different sectors, and use of others prohibited.

7.3.3.5 Retention of data, reports and other useful information should be consistent with regulatory and customer requirements.

8. EXTERNAL VERIFICATION

8.1 Whilst the laboratory may monitor the quality of its work by internal assessment, independent external assessment may be useful, in order to:

- demonstrate its quality to customers, regulatory bodies, funding bodies, or other external parties;
- compare its level of quality with others in order to make improvements.

8.1.2 Whilst it is a straightforward process for a laboratory carrying out routine work to apply a structured quality assurance system and use it to regulate laboratory performance, the ever changing nature of work in an R&D laboratory demands a more flexible and less bureaucratic approach. It is a widely held opinion that the rigidity of conventional formal quality assurance systems and their associated means of external assessment restrict the creativity of thought and practice required in an R&D environment. A number of options are available for externally assessing R&D:

- formal assessment against conventional quality assurance standards (ISO Guide 25, ISO 9000, and Good Laboratory Practice);
- benchmarking;
- visiting groups and peer review of publications;
- ranking of laboratories;
- external quality assessment.

8.2 *Formal Assessment against published quality assurance standards*

8.2.1 *ISO Guide 25* [3]

8.2.1.1 Traditionally the preferred route for routine laboratory environments, formal accreditation against standards derived from ISO Guide 25 provides an independent assessment against objective criteria that a laboratory is competent to perform specific calibration or testing measurements. The assessment is carried out by peers, that is specific measurement methods are assessed by colleagues from other organisations with expertise in those measurements, who can judge whether the procedures in use are technically valid. Accreditation is granted on the basis of the laboratory's ability to perform tests and does not cover peripheral issues, such as administrative procedures not related to the measurements, and perhaps more important, expert but subjective interpretation of the measurement data. Accreditation cannot guarantee the reliability of a measurement result. However it does provide recognition that the conditions under which the measurement was made maximises the probability of the measurement being verifiable. Even where there is no formal verification of compliance against ISO Guide 25, it remains a very useful technical quality assurance model for laboratories to refer to in order to regulate the quality of R&D.

8.2.1.2 Because accreditation is granted against a specified schedule of measurements, it is currently difficult and expensive to apply it to R&D. The 1998 revision of ISO Guide 25, now incorporates much of ISO 9001 [34]. However the definition of R&D used in ISO Guide 25 may not

necessarily correlate with its use in this document. In theory, R&D consisting of objective non-routine measurements, which could be fully documented and validated, could be accredited, provided the laboratory considered it to be cost-effective to do so.

8.2.1.3 It is sometimes possible for accreditation to be formally granted for groups of tests rather than specific tests, particularly where the laboratory in question has a proven quality system and has a high degree of established expertise in the technique relevant to the group of tests. It should be possible to extend this accreditation to whole types of test (see annex D). Whether or not accreditation could be granted for the unit operations described in §6 above is a matter for conjecture. Although a logical development of the principle of granting accreditation for test types, accreditation bodies currently only accredit the whole test. Some ideas of how accreditation of R&D might be achieved by type of test is given in annex D.

8.2.2 ***ISO 9001*** [5]

8.2.2.1 ISO 9000 is unspecific about how technical work should be performed. The certification assessment is primarily aimed at the management of procedures and assessors are not normally from a relevant technical background. ISO 9000 requires no specific assessment of the validity of work and enables the laboratory to set its own level of quality. Certification thus has merits for assessment of how the overall work is managed but on its own does not assure its validity.

8.2.2.2 The main merit of applying ISO 9001 to an R&D environment lies in its use for controlling the organisation and project management aspects of work. There should be no reason why a laboratory cannot have certification to ISO 9001 to organise, manage and perform R&D work, using the more technically exacting requirements of ISO Guide 25 as a basis for the technical side of its work.

8.2.3 ***Good Laboratory Practice (GLP)*** [6]

8.2.3.1 A laboratory operating to GLP (OECD Principles of Good Laboratory Practice) will have demonstrated that it has a management system and laboratory procedures which would enable a third party to reconstruct any GLP compliant study. GLP is concerned with traceability of the materials used, especially samples, and good descriptions of analytical methods. It is not, per se concerned with technical quality elements such as accuracy or precision, though many of the laboratory system elements required by GLP considerably assist in the delivery of technical quality. GLP traces its origins to testing in support of toxicological assessments carried out in support of product registration but in theory there is no reason why it cannot be applied to all areas of measurement. Elegibility of work for formal registration of compliance depends on the policy of the national bodies which administer GLP principles in each country.

8.3 *Benchmarking*

8.3.1 Benchmarking is a continuous, systematic process in which a laboratory/organisation compares its practices and procedures with comparable activities in other organisations in order to make improvements. It can be carried out at various levels with various partners (who need not be laboratories): internal; external; competitive; non-competitive; and *best-practice* (the acknowledged leaders of the process being benchmarked). When benchmarking with other organisations, an agreed Code of Conduct is vital to ensure an effective, efficient and ethical process, whilst protecting both parties. A typical benchmarking process is shown in Figure 3.

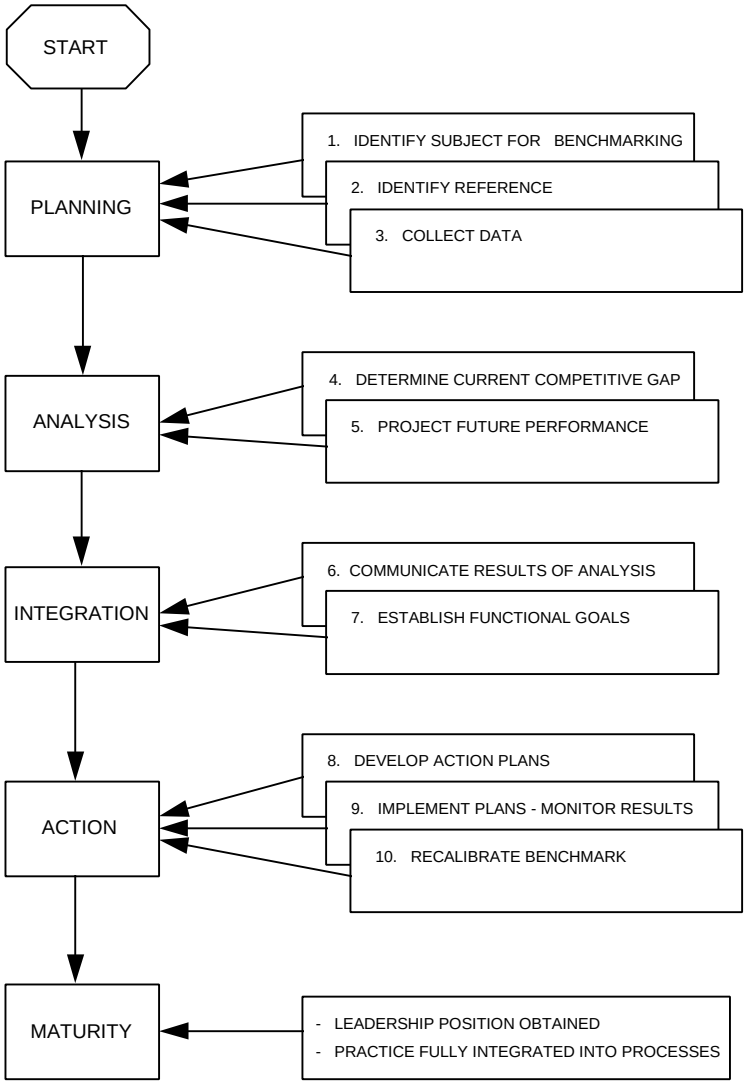

Figure 3: The Benchmarking Process

8.3.2 *Examples:*

1. External: A laboratory can assess its purchasing procedures by benchmarking with another organisation known to have very good purchasing procedures.
2. Internal: Group A in a laboratory wins only 10% of possible contracts whilst group B in the same laboratory wins 50%. By benchmarking its bidding procedures against those of group B, group A ought to be able to improve its success rate at winning contracts.

8.4 ***Visiting groups and peer review.***

8.4.1 These types of review involve the use of groups of senior level experts, probably from a wide range of sources, to evaluate a laboratory. The evaluation can be directed either at the laboratory itself or at the laboratory's scientific output.

8.4.2 In the former case the evaluation is likely to be against the laboratory's stated objectives, with a strong emphasis on the excellence of the science, staff, and facilities. Such groups typically act on behalf of R&D funding bodies and are a popular form of assessment in the academic world. The terms of reference of such groups may vary from group to group and there are no universally recognised criteria against which assessments are carried out. The sort of areas covered might include:

- whether staff have appropriate training and qualifications, and are fully conversant with the aims and objectives of their work;
- awareness of staff to published work in their subject areas;
- quality and availability of scientific support services;
- adequacy of resources;
- degree of scientific collaboration;
- effectiveness of technology transfer;
- management of the R&D programme;
- whether the organisation of projects effectively meets customer needs.

8.4.3 The strength of the visiting groups approach is that it concentrates on the quality of the science. However the way it is used at present makes it is weak in several other respects:

- it lacks harmonised and transparent criteria;
- it tends to look at work retrospectively;
- it is subjective and susceptible to bias.

8.4.4 Assessment visits for accreditation/certification/registration purposes (see above) and visits by customers are a special subset of visiting groups / peer review. In the case of customers, those visiting may lack technical expertise in the areas concerned.

8.4.5 Peer review of publications, also known as citation analysis, involves:

- assessment of the number and quality of publications the laboratory under examination has published in the scientific press;
- assessment of how much those publications are being cited by colleagues within the same research field.

Citation analysis traces its origins to law but is now a widely used, significant research tool, adopted from the field of information science to a range of subject areas. The Science Citation Index (SCI) was first published in 1961. Four particular applications have been reported [35, 36]:

1. to assess the impact of individuals, institutions and journals;
2. to investigate hypotheses about the history and sociology of science;
3. to study performance characteristics of information search and retrieval;
4. evaluation tool

Increasingly it is used in the analysis of departmental output or as a measure of the value of the work of a department [37, 38].

8.4.6 Some journals will only accept papers for publication that have been the subject of satisfactory peer-review (this is the most common type of peer-review mechanism in use today). As a consequence it is more difficult to publish in these journals. From a citation analysis point-of-view, publication in a respected journal will score better than one in a less respected journal - the so called impact factor. Criteria, ranking journals in order of merit, are published annually by the Institute for Scientific Information. This system has some merit, as published work often reflects the competence and expertise of the publishing laboratory. A laboratory can deliberately raise the profile of its work by publishing as often as possible in the most highly regarded journals. However publication is not always an option and laboratories which do not publish are not necessarily producing poor quality work. One should also be aware that the status of journals sometimes change with time. Citation analysis has a number of other limitations, making it a dangerous technique to use in isolation:

- method papers are cited more often than empirical or theoretical papers, and tend to be referenced due to utility rather than innovation or novelty;
- work ahead of its time is not cited because there are no other scientists interested in the same field of work;
- citations are proned to discrepancies *e.g.* misspellings;
- citatations are rarely complete or comprehensive. Citation counts need to be seen mainly as indicators, and comparisons can only be made if identical citable and citing pools are used;
- negative or contradictory citations tend to indicate a lack of value to the work.

8.4.7 Patents and licences are other forms of dissemination and exploitation that can be used as a measure of a laboratory's output.

8.5 ***Ranking of organisations***

8.5.1 This involves comparing laboratories against a set of common criteria and ranking them on the basis of the comparison.

8.6 *External Quality Assessment procedures (also known as Proficiency Testing)*

8.6.1 Participation in external quality assessment schemes provides an external measure of performance. In non-routine work or R&D, relevant schemes may be difficult to identify or may give an unrealistic impression of performance. Other types of interlaboratory comparison are perhaps more relevant to R&D, such as co-operative studies, but these do not give the same measure of laboratory performance. It should also be recognised that the proficiency testing schemes which give the most reliable measure of performance are those in which the participating laboratories receive the test samples blind.

8.7 *Conclusions*

8.7.1 No single method of assessment stands out as being the most suitable for monitoring the quality of non-routine and R&D work. It is recommended that where some kind of external assessment is required a combination of approaches should be taken and formal assessment should be confined wherever possible to those parts of the quality system that remain stable from project to project, *e.g*. the management levels and technical infrastructure. Typically this could be established for the 3-tier quality system approach as follows:

Quality	**Verification**	
Elements	**Formal**	**Informal**
Organisational	• Certification to ISO 9000	• Follow ISO Guide 25 • Benchmarking • Self assessment
Technical	• Accreditation to ISO Guide 25 / EN 45001	• Follow ISO Guide 25 • Visiting groups • Benchmarking • Peer review
Analytical task	• Registration to GLP • Proficiency testing	• Follow GLP principles

8.7.2 The informal verification principles outlined above could be made more formal if required and the declared compliance with particular standards, guides or protocol could be independently assessed by a suitable outside body, *e.g*. a visiting group, or consultant, examining inputs,such as:

- existence of project plans where no elaborated methods are available;

- maintenance and calibration schedules;
- record keeping.

and outputs, such as:

- reports and publications;
- satisfactory participation in relevant proficiency testing, external quality assessment or other intercomparisons.

8.7.3 A well functioning quality system need not stifle creativity in R&D, and is vital for ensuring the smooth transfer of technology from research to diagnostic or commercial environments. Research workers must have an appreciation of the quality requirements of clients and quality must be designed into every process.

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Annex A Composition of EURACHEM / CITAC R&D / Non Routine Analysis Working Group

Name	Affiliation	Country	Background	Liaison Links
Prof C Adams	Unilever	UK	Industry/ Academic	DIRAG, EURACHEM UK
Prof K Cammann	ICBFhM	Germany	Academic	EURACHEM, EUROLAB, ISO/IUPAC/AOAC
ir HA Deckers	RvA	Netherlands	Industry	WOBAC, EUROLAB EAL
Prof Z Dobkowski	Ind. Chem. Res. Inst.	Poland	Government	Polish Chem. Soc., AOAC, EURACHEM
Mr D Holcombe	LGC	UK	Government	ISO/IUPAC/AOAC
Dr PD LaFleur	Kodak	USA	Industry	CITAC
Dr P Radvila	EMPA	Switzerland	Government	SAPUZ, EUROLAB-CH, EURACHEM
Dr C Rohrer	Lenzing AG	Austria	Industry	
Dr W Steck	BASF AG	Germany	Industry	CITAC, EURACHEM
ir P Vermaercke	S.C.K.	Belgium	Industry	BELTEST

Other inputs to the guide were made by :

(a) CITAC Working Group with members from: Australia; Austria; Belgium; China; Germany; Hong Kong; Japan; Korea; Mexico; The Netherlands; Russia; Switzerland; United Kingdom; United States.

(b) EURACHEM full, associate and observer members from: Austria; Belgium; Commission of the EC; Cyprus; Czech Rep.; Denmark; Finland; France; Germany; Greece; Hungary; Iceland; Ireland; Italy; Luxembourg; Malta; The Netherlands; Norway; Poland; Portugal; Russia; Slovakia; Slovenia; Spain; Sweden; Switzerland; Turkey; United Kingdom; United States; AOACI; FECS.

(c) Miscellaneous inputs have been made by colleagues from Australia, Austria, Belgium, Canada, Cyprus, Czech Rep., Denmark, European Commission SMT Programme, Finland, Germany, Hungary, Iceland, Ireland, Israel, Italy, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom, United States.

2.1 ***About CITAC and EURACHEM***

2.1.1 ***CITAC*** - *Co-operation on International Traceability in Analytical Chemistry* arose from an international workshop held in association with the Pittsburgh Conference in Atlanta, March

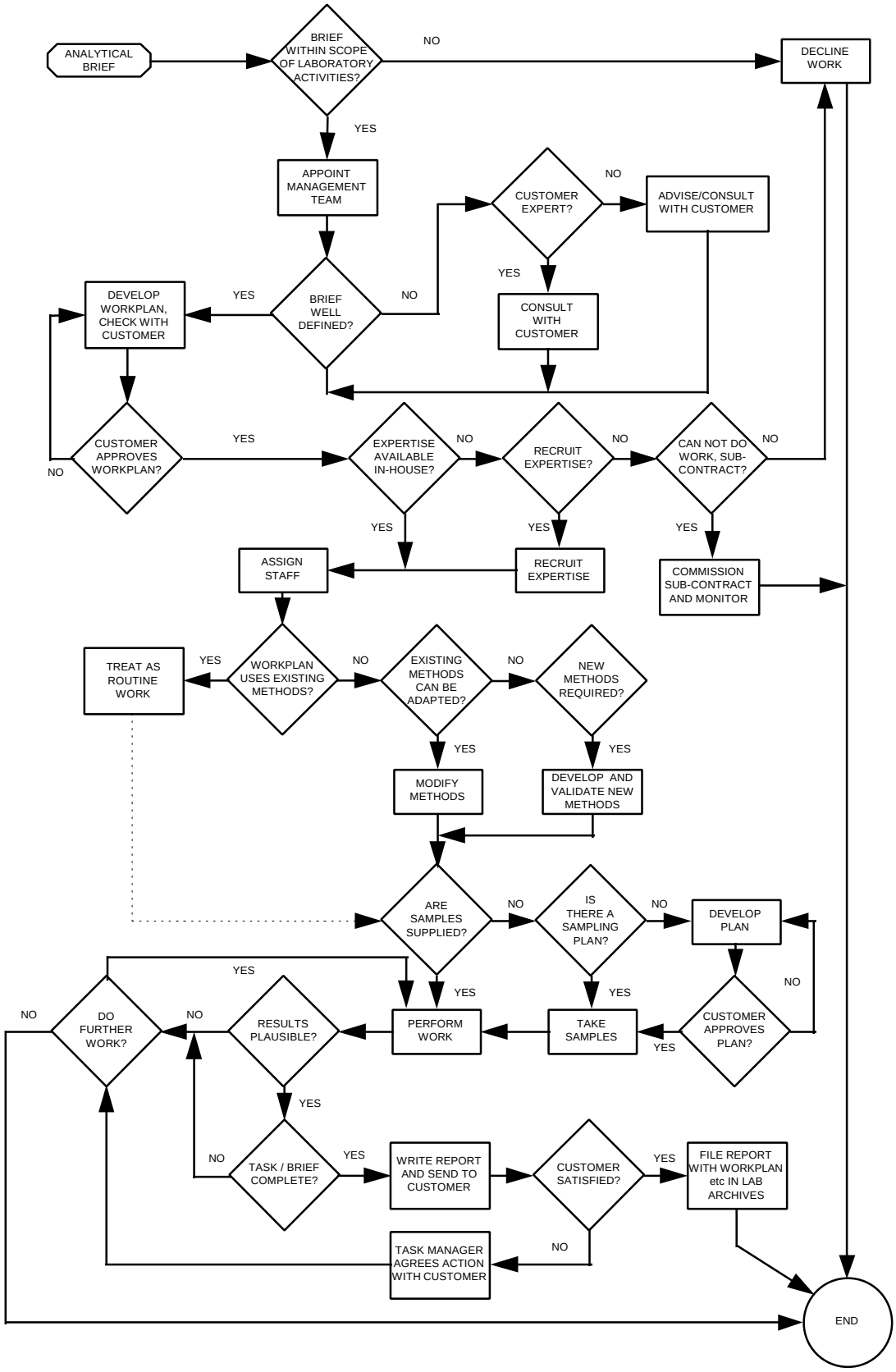
1993. CITAC aims to foster collaboration between existing organisations to improve the international comparability of chemical measurement. A working group co-ordinates activities which include: production of a directory of reference materials under development; preparation of quality system guidelines for the production of reference materials; preparation of a directory of chemical metrology activities; definition of criteria for establishing traceability to the mole; and preparation of an international guide to quality in analytical chemistry [1].

2.1.2 ***EURACHEM*** was established in 1989 to provide a focus for analytical chemistry and quality related issues in Europe. It is a network of European national laboratories which have an interest or responsibility for chemical analysis. It provides a framework which facilitates collaboration between analysts throughout Europe to improve the quality of analytical measurements and provides a forum for the discussion of common problems and for developing an informed and considered approach to both technical and policy issues.

Up-to-date information on EURACHEM activities is available from its twice yearly newsletter, or from its website http://www.vtt.fi/ket/eurachem.html.

Both CITAC and EURACHEM secretariats can be contacted via the drafting secretary at the address shown at the front of the guide.

Annex B: Flowchart showing typical lifecycle of R&D project



Annex C Questionnaire for Analytical Work

A. Client

Contact person:
Tel:/Fax:
Address:

B. Objective /goals/required information

Requested analysis:

☐ qualitative/semi-quantitative, limit of detection:
☐ quantitative, range of concentration:
Previous analysis/results:

C. Costs

- Expected costs:
- Cost limits:

D. Date of completion/schedule

Date of intermediate results/reports:
Deadline for final results/report:

E Sampling ☐ client ☐ laboratory ☐ other

Date of sampling:
Source/producer:
Responsible person:
Number of samples:

F. Description of sample(s)

Identification:
Approx. composition:
Main component: Minor constituent:
Intended use:
Packaging/stability:
Special care for storage/ transport/ stabilisation:
Pretreatment/ preconditioning:
Reference materials/ reference sample

G. Methodology

Description of methods used for sampling, sample preparation, measurement
Standard method:
Generic method:
New/adapted method: R&D for new method:

Validation for adopted method:

Annex D Proposals for the accreditation of R&D tests by type.

D1 Purpose

The accreditation of types of tests serves to provide a flexible description for the scope of accreditation. This annex sets out proposals for possible conditions under which accreditation might be granted for tests by type. Note the responsibility for defining such conditions strictly lies with accreditation bodies.

D2 Area of application

These proposals should be applicable to all testing laboratories aiming for flexibility in their scope of acccreditation, especially with regard to R&D work.

D3 Definitions

D3.1 ***Type of test:***

"Sector (of a testing field) with similar technical-methodological features, with comparable calibration, validation and training principles." Types of test may be defined on a technology or application related basis. For example:

- gas chromatography (or perhaps more broadly "separation techniques");
- atomic spectroscopy;
- thermoanalysis;
- primary fire characteristics.

D3.2 ***Testing field***

"Testing fields are sizable sectors distinguished by common fundamentals of a technical, methodological and training related nature." For example:

- chemical and physio-chemical analysis;
- biological investigations;
- medical laboratory diagnostics.

D3.3 ***Flexibilisation***

Flexibilisation of the scope of accreditation is understood to comprise all measures to be taken for accreditation not directed exclusively at the accreditation of individual test methods.

D4 **General**

The accreditation of types of tests means that the testing laboratories are given the opportunity to introduce new test methods within the approved type of test or of modifying existing methods without having to obtain approval from the accreditation authority in each individual case in advance. It also allows confirmation of the competence of R&D analytical activities on the basis of general work.

Accreditation of a type of test is granted under certain conditions and within the limits governed by the experience which has already been demonstrated by the laboratory for that type of test. Making the scope of accreditation flexible with respect to the methods used does not necessarily imply making it flexible with respect to the sample types under test.

D5 **Recommended conditions for the accreditation of types of tests**

For every type of test for which the laboratory requires accreditation it should submit to the accrediting body:

- a sufficient number of different test methods, SOPs or test reports;
- procedures for validation or verification as part of the type of test;
- corresponding records of validation and verification.

The methods submitted must reflect adequate operator competence (*e.g*. technical range) within the type of test applied for. For new or modified test methods, complete documentation and validation is required. For R&D, appropriate test reports and/or generic SOPs may be submitted instead of the test methods.

The laboratory should have available at all times a list of the methods currently covered by its accreditation. The list can be submitted to the accreditor as part of the monitoring procedure, with new or modified methods identified.

D6 **Assessment of the scope of accreditation**

In the accreditation of types of tests, the assessment is directed in particular towards:

- the organisational prerequisites the testing laboratory has to meet for it to validate or verify new or modified test methods;
- the qualifications and experience of staff and management and the policies on further training;
- the level of technical equipment;
- the procedures for testing;
- the quality management system;

- the records of validation and verification carried out.

The assessor has the responsibility for selecting and inspecting key test methods and equipment. The following criteria are amongst those that might be used as a basis for such selections:

- the technical complexity of the tests;
- the possible consequences of errors in performing the tests;
- the frequency of use of the test methods;
- the ratio of routine and non-routine tests.

The extent of the checks should be sufficient to allow the accrediting body to be confident of the capability of the laboratory to introduce new methods or to modify existing methods or to carry out R&D. At the same time the checks must not impose unreasonable costs on the laboratory. The assessor's report should indicate to which test items the respective types of test relate.

D7 **Scope of accreditation of types of tests**

The scope of accreditation may be specified in terms of:

1. testing field(s);
2. type(s) of test(s);
3. test method(s);
4. item(s) under test.

Annex E R&D to develop analytical instrumentation

E1 The following specific interpretation is recommended for R&D to develop analytical instrumentation.

E2 ***Introduction***

Instrumental R&D involves the improvement of existing analytical systems or development of entirely new systems. The basis for the R&D usually arises from the need for novel systems which are: faster; more sensistive; more accurate; more precise; more discriminating; simpler (and easier to use); more economic; more environmentally friendly; or applicable to different particular analyte(s)/sample matrix combinations. Occasionally it may be carried out on a purely speculative basis, *i.e.* with no particular end application in mind, for example, to investigate the practical potential of a particular measurement principle.

Instrumental R&D projects generally involve building and evaluating prototype instrumentation, making and evaluating changes until the prototype evolves either to a state where performance objectives have been met or further development is not viable. The prototype might be a whole new instrument or an accessory (such as a detector or a chromatography column) for an established instrument.

E3 ***Planning***

Instrumental R&D project planning involves objective setting as with conventional analytical R&D. The research plan effectively involves setting out the strategy for the project and defining the criteria against which the performance of the prototype can be assessed.

E4 ***Experimental design***

The project should include experiments to evaluate and validate instrument performance and to help define the behaviour of the instrument under calibration. Long term stability / acceptable performance should be monitored before the equipment is put into routine use. A means of controlling calibration should be established, either through external adjustment or fixed internally. Suitable standards, blanks, reference materials or check samples of known content can be used in these experiments.

The criteria which cause deterioration of instrument performance should be identified, and wherever possible routines established for controlling these criteria. Where instrument performance is particularly sensitive to operator skill, optimum operating procedures should be established. Checking procedures, using standards, check samples, test mixtures *etc.*, should be established as part of the monitoring process.

Where the instrument under development involves the processing of raw data or signal through some form of algorithm, access to the raw data/signal is advised so that the basic instrumental performance and signal processing can be checked independently.

A number of ways to evaluate and validate the novel instrumentation are possible. Where other techniques/ procedures/ instrumentation exist for the particular measurement application these could be used for the parallel evaluation and validation of the novel instrumentation. Collaborative trial could be used, either involving several laboratories each evaluating the novel instrumentation, or the developing laboratory comparing results generated by its own use of the novel instrumentation against other laboratories using other techniques.

E5 ***Data recording***

Data from instrument evaluation should include a record of conditions under which the instrument is, and is not, working satisfactorily. Typically this will include information on analyte and matrix condition, presence of particular chemical, spectral and physical interferents, temperature, humidity, electrical, magnetic settings. Sufficient data should be recorded over extended time periods and differing conditions to establish the reliability of the technology.

E6 ***Reports***

Where new instrumentation is successfully developed, the reports from the prototype evaluation and validation stages will form the basis for use of the instrumentation in more widespread use, *i.e*. the report is effectively the operating manual. It should include user-friendly instructions for operation of the instrument, applicability, information on storage, calibration and maintenance, and performance checks. Where appropriate, there should be an explanation of how the raw signal is processed by the algorithm for zeroing purposes, so that in routine use incorrect assumptions are not made in the subtraction of blanks. New instrumentation should be subject to equipment qualification procedures before being put into use.

E7 ***Evaluation***

Where the novel instrumentation performance overlaps with existing instrumentation, the success of the R&D can be evaluated by comparison of the two instruments against agreed performance criteria. Unless something is being developed for a particular end use, it is probably easier to test the instrumentation initially against simple problems and then more demanding problems as familiarity with the technique and the behaviour of the instrument improves. In general if the instrument appears to function correctly with one analyte in a single matrix this is not satisfactory evidence for the soundness of the technique per se. However it

may be acceptable where the that particular analyte/matrix pair are the main reason for the R&D work.