Outline

- Quality standards
- Brief comparison
- ISO/IEC 17025 standard
- Management requirements
- Technical requirements

Many laboratories choose to formalise their quality systems by seeking third party accreditation and/or certification. In some cases the customer will require the laboratory to be accredited. Formal accreditation has the advantage that the laboratory gets a regular external assessment of its quality procedures.

Accredited laboratories have to set up a management system that meets the requirements of certain internationally agreed standards. Four common standards are shown on the next slide. An organisation may work to more than one standard, depending on the nature of their work.

This session will focus in ISO/IEC 17025 which is the most commonly used standard in analytical laboratories. During this session it is helpful if students have a copy of the standard available.

ISO 9001:2000, "Quality management systems - Requirements", is the quality management standard commonly used by organisations manufacturing or supplying products or services in the UK and across the world. Many analytical laboratories have ISO 9001 certification in addition to accreditation to ISO/IEC 17025 so as to include the broader aspects of their operation.

ISO/IEC 17025:2005, "General requirements for the competence of calibration and testing laboratories" is the internationally accepted document upon which national accreditation bodies (United Kingdom Accreditation Service (UKAS) in the UK) across the world base their standards for laboratory accreditation. Accreditation is given for specific tests in terms of the scope of a particular method, i.e. the analyte, the matrix and concentration range. Technical requirements feature strongly, namely, method validation, measurement uncertainty and traceability.

GLP devised by the OECD (Organisation for Economic Cooperation and Development) is different in that it is a legal requirement for particular studies. It is a set of principles intended to regulate the design, conduct, monitoring, recording and reporting of studies carried out by laboratories where these studies are to be submitted for the purpose of assessment of chemicals, foods and pharmaceuticals in support of regulatory licensing for human, animal or environmental use. The Department of Health Good Laboratory Practice Monitoring Authority (GLPMA) is responsible for administering GLP in the UK.

ISO 15189:2003 is a sector standard for medical laboratories. It may be an alternative to ISO/IEC 17025 for such laboratories. It has much in common with ISO/IEC 17025 and ISO 9001 but some of the detail relating to method validation, measurement uncertainty and traceability is less in ISO 15189 whereas aspects of sampling are more detailed.

ISO/IEC 17025 vs ISO 9001

- Management requirements of ISO/IEC 17025:2005 mirror those in ISO 9001:2000
  - to comply with ISO/IEC 17025 the laboratory must operate a quality management system that meets the principles of ISO 9001
  - ISO/IEC 17025 covers technical competence requirements not covered by ISO 9001
- ISO/IEC 17025
  - first choice for measurement laboratories

The management requirements of ISO/IEC 17025:2005 (i.e. Section 4) mirror those in ISO 9001:2000. Therefore if a laboratory is accredited to ISO/IEC 17025 it will not need to separately comply with ISO 9001 unless it wishes to cover activities other than calibration and testing measurements.

ISO/IEC 17025 was originally published in 1999. The first edition of the standard made reference to the management requirements of ISO 9001:1994. However, shortly after ISO/IEC 17025:1999 was published, ISO 9001:1994 was replaced by ISO 9001:2000.

ISO/IEC 17025 has therefore been revised to bring it in line with ISO 9001:2000. This has involved some changes to the management aspects described in Section 4 (in particular the inclusion of a section on improvement), but the technical requirements (Section 5) have not changed.

Management system

- Quality Manual
- Quality Assurance
  - organisational structure underpinning reliable results
    - internal QA gives confidence to management
    - external QA gives confidence to the customer
- Quality Control
  - planned activities designed to verify the quality of the result

Over time, organisations develop a range of procedures for the day to day operations. However, these are not always written down and may be assumed to be common knowledge within the organisation.

A management system is the organisational structure, procedures, processes and resources needed to implement the management of quality.

The starting point for an organisation setting up a management system should be to document what they do on a day to day basis.

Quality control and quality assurance are key aspects of a quality system.

Quality Control

Quality Control is the day-to-day activities which are carried out to provide a series of checks and balances on the analytical results produced by a laboratory. These activities are planned in the quality assurance system.

Quality Assurance

Quality assurance is a planned set of documented activities which are designed to ensure that the quality control programme is carried out effectively, and can demonstrate that this is so. It is the over-arching system which plans and documents the processes involved in ensuring quality.

Quality control

It costs less to prevent a problem than it does to correct it!

- Run blanks
  - check for contamination or interferences
- Analyse check (QC) samples
- Use statistical quality control
  - plot QC results on control charts
  - check the method is working consistently
- Use reference materials/substances
  - calibration
- Level of QC depends on the consequence of being wrong

Laboratories employ quality control (QC) procedures to monitor the quality of the measurements they are making. QC procedures should be carried out on a frequent basis.

The slide lists some examples of common QC procedures:

Analysis of blanks: A blank sample is a sample which does not contain any of the analyte of interest. It should be treated in the same way as test samples. In addition, it is often useful to run a reagent blank. A reagent blank is a solution obtained by carrying out all the steps of the analytical method without any sample present. Blanks are used to look for interferences or contaminants which could affect the result of the measurement.

Analysis of standards and reference materials: These are used to calibrate equipment and ensure that the equipment and the method as a whole are working satisfactorily.

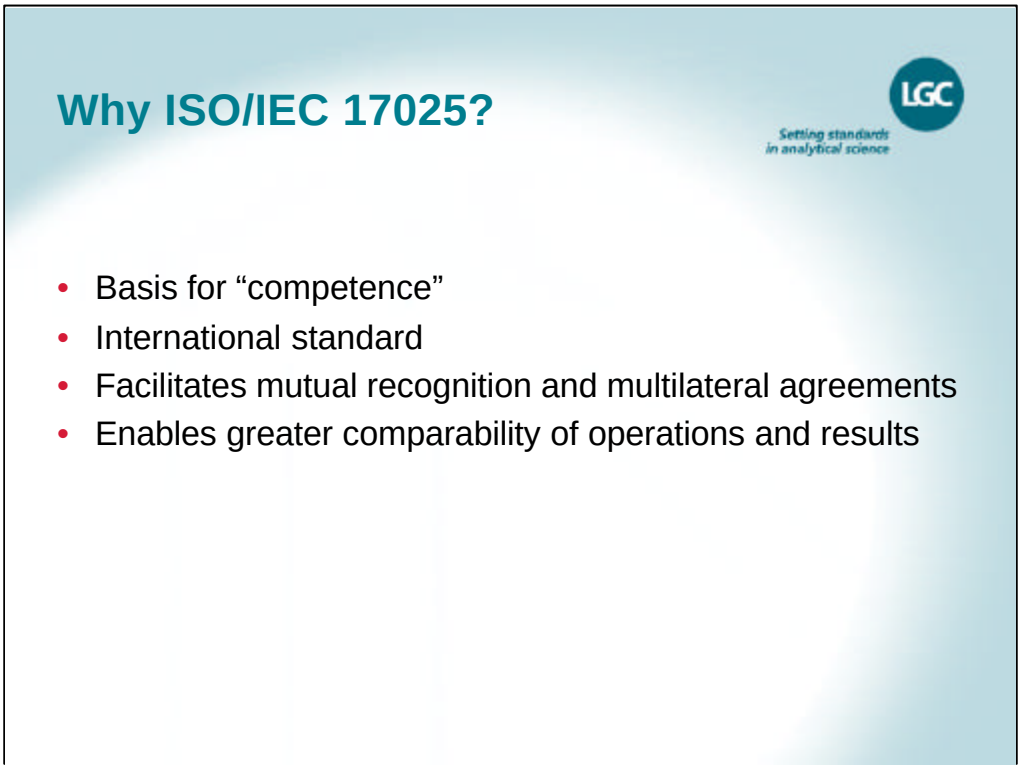
Analysis of QC samples: QC samples should be representative of test samples in terms of matrix and the level of analyte present. The QC samples are analysed regularly alongside test samples (e.g. within every batch of analyses). The results from the QC samples are used to check that the method is working consistently. The results can be plotted on a control chart (for example a Shewhart chart) to look for drift or other trends and problems.

The amount of QC that laboratories carry out (e.g. the frequency of analysis of QC samples) depends on the criticality of the measurement (i.e. what are the consequences of getting the wrong result?).

Setting standards in analytical science

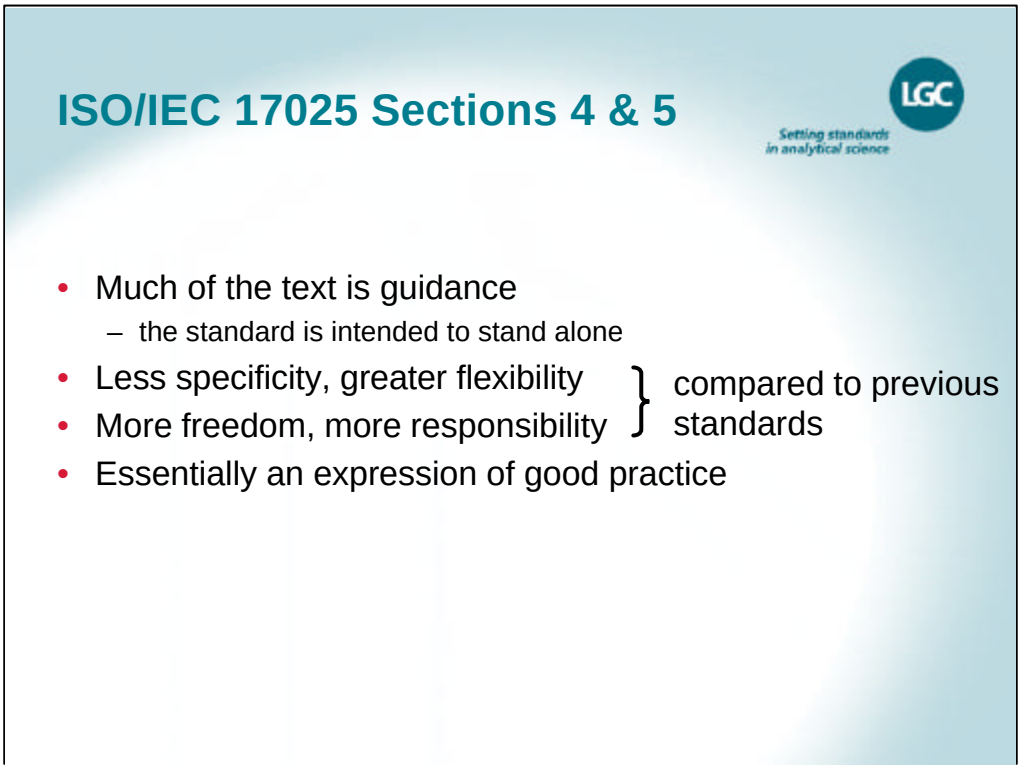
ISO/IEC 17025

Implications for Laboratories



The standard is essentially a list of criteria for best practice and competence. As it is an internationally agreed standard it should result in a level playing field for accreditation. Previously different countries had their own accreditation standards and there were no guarantees that their requirements were equivalent.

If all countries apply the ISO/IEC 17025 standard it should make it easier to compare operations and results in different countries. Ultimately this should lead to better agreement between results produced in different locations.



The requirements in ISO/IEC 17025 are consistent with what is generally considered to be good practice.

The bulk of the standard is taken up by the inclusion of guidance notes. This is because the standard is intended to stand alone. Section 4 (Management requirements) and Section 5 (Technical requirements) constitute the majority of the standard.

Compared to previous standards the laboratory is given more freedom about how to implement its management system. However, the laboratory has to take responsibility for the system they have put in place and justify what they have done.

ISO/IEC 17025 Standard

- Clause 4
  - specifies the requirements for sound management
- Clause 5
  - specifies the requirements for technical competence for the types of test the laboratory undertakes
- Appendix A
  - cross references to ISO 9001:2000
- Appendix B
  - guidelines for specific fields

The rationale behind the changes from previous standards is to bring the accreditation standard more in line with ISO 9001, this is because laboratories are often part of larger organisations which offer services other than testing or calibration. Laboratories that comply with ISO/IEC 17025 also operate in accordance with ISO 9001. The reverse is not true, certification against ISO 9001 does not itself demonstrate the competence of a laboratory to produce technically valid data.

The whole system is now assessed against a **Plan - Do - Check - Act** model, along similar lines to ISO 9001.

Clause 4 - Management (1)

- 4.1 Organization
  - legal responsibility of the laboratory
- 4.2 Management system
  - content of quality manual less rigidly defined than in previous standards
- 4.3 Document control
  - issue number, revisions marked etc
  - computer generated documentation permitted
- 4.13 Control of records

The laboratory now is required to be an entity which can be held legally responsible.

The laboratory is required to sign a contract with UKAS. This defines the conditions under which the accreditation is granted to the laboratory.

Although required to have a quality manual, the content is not rigidly defined. The starting point for writing a Quality Manual should be for the laboratory to write down what it does. It needs to include the management's commitment to compliance with the standard and a statement of the laboratory's standard of service.

Document and Record control are in two different clauses.

ISO/IEC 17025 specifically allows for the use of computers for documentation but requires procedures describing how changes are made in such documents and how they are controlled.

Clause 4 - Management (2)

- 4.4 Contract review
- 4.5 Subcontracting
- 4.6 Purchasing of services and supplies
- 4.7 Customer/laboratory relationship
- 4.8 Complaints
- 4.10 Improvement

- 4.14 & 4.15 Audit and review
  - customer feedback

There are more detailed requirements for the laboratory's relationship with the customer than was required previously for accreditation. The laboratory needs to demonstrate the customer's problem has been understood and that a course of action has been agreed.

Subcontracting to a competent laboratory either because of some unforeseen reason or because of a franchising agreement is allowed.

A key aspect of the standard relates to monitoring the performance of a laboratory. The laboratory should act on any complaints or feedback received from customers and monitor the effectiveness of any corrective actions that are put into place as the result of a complaint.

A new requirement in the 2005 version of the standard is the need for the laboratory to continually improve the effectiveness of its management system.

Clause 4 - Management (3)

- 4.9, 4.11, 4.12 Formal procedure for nonconforming testing
  - cause analysis
  - corrective action
  - monitor and evaluate effectiveness
  - continuous improvement
  - preventive action

ISO/IEC 17025 takes a systematic approach to stating the requirements for ensuring the quality of data.

As well as a specific section, “assuring the quality of test and calibration results”, it links formal procedures for taking corrective action and for evaluating its effectiveness, finding out what caused the problem and taking preventive action to reduce the risk of recurrence, into the audit and review process.

The approach fosters a learning process within the laboratory so that as a particular problem is detected, a solution is implemented and tested to ensure that the remedial action is effective. The specific lesson learnt is then propagated throughout the quality system leading to gradual improvements and elimination of weak spots. (Plan, Do, Check, Act)

Clause 5 - Technical requirements

- 5.2 Personnel
- 5.3 Accommodation and environmental conditions
- 5.4 Method selection and validation
  - measurement uncertainty
- 5.5 Equipment
  - equipment qualification
- 5.6 Measurement traceability
- 5.7 Sampling
- 5.8 Handling of test and calibration items
- 5.9 Assuring the quality of test and calibration results
- 5.10 Reporting the result
  - opinions and interpretations

The laboratory is required to ensure the competence of staff who operate specific equipment and/or carry out tests. Staff are deemed qualified on the basis of appropriate education, training and experience and must have demonstrated their competence.

If tests are sensitive to environmental conditions these have to be controlled and monitored. The environmental conditions should not jeopardise the results of tests - keep areas separate where this might occur.

Requirements for method validation and measurement uncertainty are clear and well defined. All methods prior to accreditation have to show that enough validation data has been produced and an appropriate uncertainty estimate has been produced and documented.

A difference occurs in the case of opinions and interpretations. This section effectively extends the applicability of the standard. Practical implementation of this section is becoming clearer and implementation has begun in a number of countries. Note that it is the *person giving the opinion or interpretation* that is accredited, *not* the opinion or interpretation.

Validation (ISO/IEC 17025)

"*Confirmation* by examination and the provision of *objective evidence* that the particular requirements for a *specific intended use* are fulfilled"

- specific intended use = analytical requirement (c.f. contract review)
- objective evidence = experimental data → method performance parameters
- confirmation (from comparison of requirement with evidence)

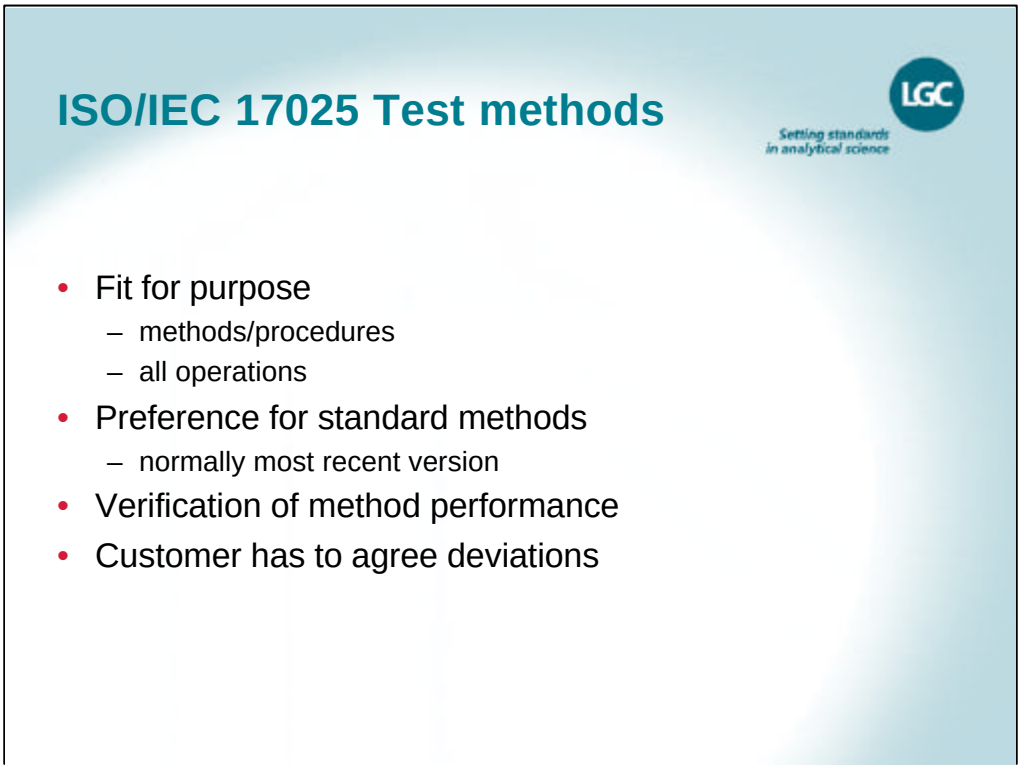
Method validation is a key aspect of ensuring the quality of analytical results. Before any method is used to analyse test samples it should have been evaluated to demonstrate that it is capable of producing results that are fit for purpose.

Validation has three important parts. When applied to method validation, these translate as:

1 the specific intended use or application, is the analytical requirement which derives from the problem that the analysis is intended to solve;

2 the objective evidence is usually in the form of data from planned experiments, from which the appropriate method performance parameters are calculated;

3 the confirmation is taken as a satisfactory comparison of the performance data with what is required, i.e. the method is fit for purpose.



Clauses 5.4.1 and 5.4.2 in ISO/IEC 17025 describe general information for selecting methods in response to customer requirements. The essential condition is that the method is fit for purpose. This applies to all procedures from those used for the initial sampling through handling, transport, preparation, analysis to reporting. The laboratory must inform the customer if the customer proposes a method that is inappropriate or out of date.

The standard sets out a definite hierarchy of methods with international standards at the top, followed by published methods and then laboratory-developed methods. Generally a laboratory is required to use the most recent validated version of a method.

In all cases staff are required to demonstrate that they can use the method to its declared performance potential, in other words verify the performance. This is an important requirement which is hidden in this general clause and would benefit from being more explicit in the validation clause.

Where it is necessary to deviate from an agreed method the customer's agreement must be obtained.

Fitness for purpose

- Define the purpose - the problem/enquiry
  - qualitative, semi- quantitative, quantitative
  - constraints: time, cost, quality
  - criticality
- Define the performance criteria
- Experimental plan

The practical process that determines the suitability of a method for providing useful analytical data

In general terms, analytical methods are used to analyse customers' samples and the data generated from the analysis are used to solve the customer's problem. This holds true provided that the correct measurement is made on the right sample. Thus the process of understanding the problem and making the right choice of method is fundamental to the success of analysis. This links in directly to the contract review requirements of ISO/IEC 17025, clause 4.4.

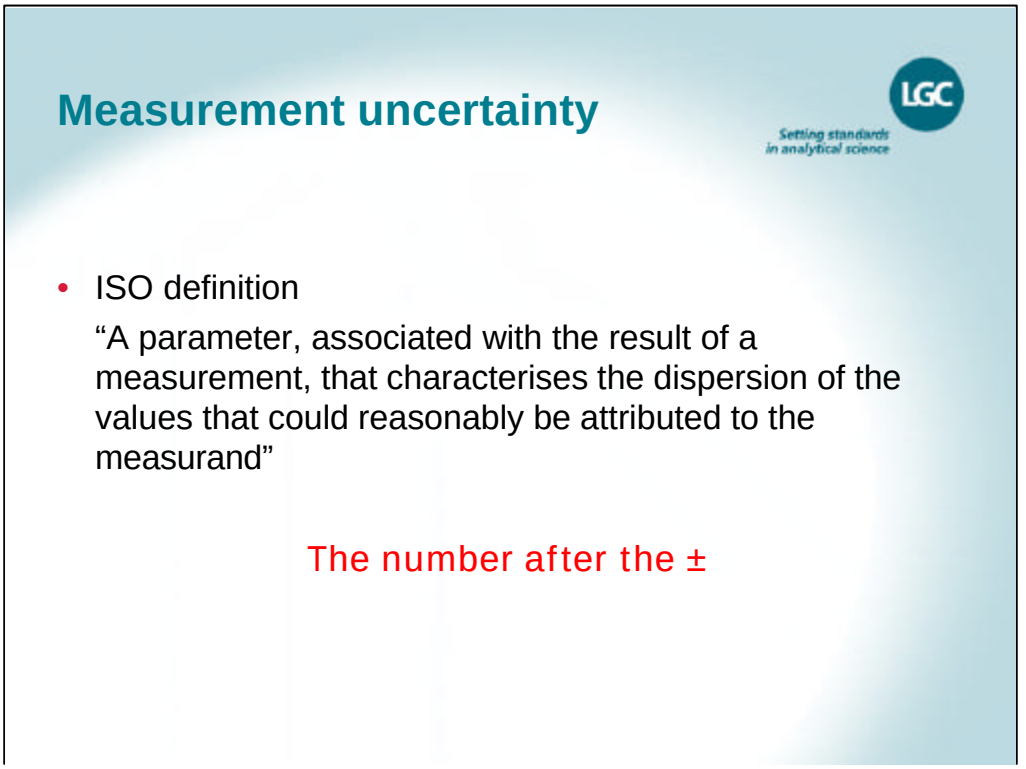
So, starting with the customer's problem it is possible to determine what is to be expected of the method. This is known as, 'scoping the method'.

It is also necessary to consider constraints such as time, available laboratory resources, size of samples. In extreme cases it may be that a customer's problem cannot be solved using the technology available within the time and resource constraints that they have imposed.

Once the method is scoped and other constraints have been considered, the laboratory is in a position to select a suitable method which has the required performance criteria. It may be able to select a standard or published method with suitable performance capabilities. If such a method is not available and the laboratory has to develop its own, this new method needs to be evaluated against the set target values. In all cases the data must establish that the method used is fit for purpose.

Consultation with the customer during method development is required. This ensures work remains focused on the customer's needs. The customer's agreement is required should it be necessary to deviate from an agreed plan.

Method validation is the practical process that allows the analyst to evaluate whether a particular method is capable of producing useful analytical data.



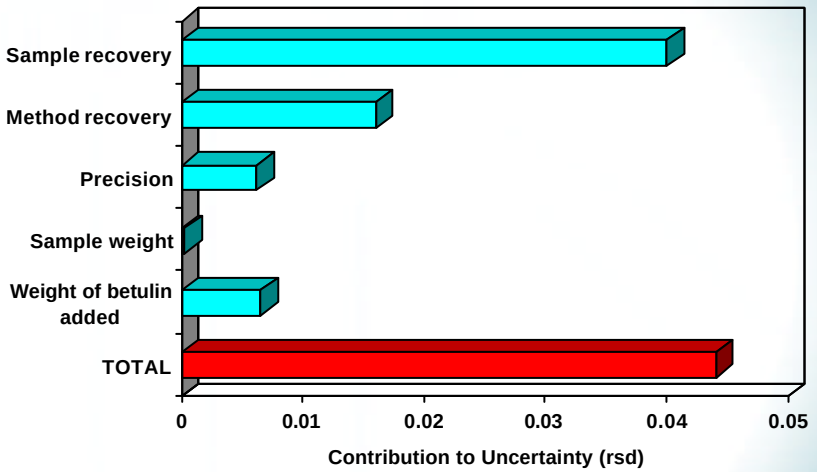
The ISO Guide to the Expression of Uncertainty in Measurement (ISO 1993, 2nd ed 1995) is the primary document applicable to uncertainty estimation.

The definition is lengthy, but one factor is crucial; the uncertainty value quoted combines all uncertainties, whether arising from random variation or systematic effects. In other words, the uncertainty estimate should have considered everything that may cause the result to vary.

Broadly speaking, measurement uncertainty is the extent to which the quoted result might reasonably differ from the "true value".

When evaluated properly, measurement uncertainty gives us an indication of the quality of that result. It helps the analyst to decide whether a particular method is likely to produce results that are fit for purpose (i.e. will the uncertainty be small enough?).

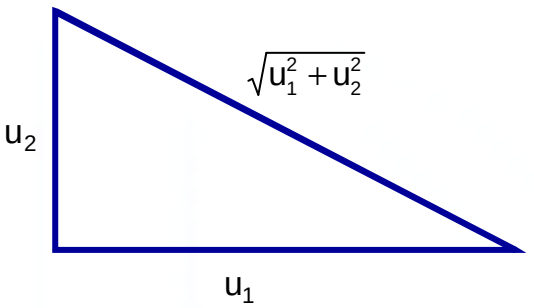
Uncertainty components
Determination of cholesterol



There will be a number of factors that contribute to the uncertainty in the final result. The slide shows the uncertainty budget for the determination of cholesterol in fats and oils.

The chart shows that the individual uncertainty components are not simply added - the TOTAL bar at the bottom of the chart is not long enough for this to be the case.

Combining uncertainties



Uncertainty contributions are combined by taking the square root of the sum of their squares, just like calculating the long edge of a triangle. For this to work, each 'contribution' must be expressed as an uncertainty (in the form of a standard deviation) in the final result of the measurement.

For example, uncertainty in a solution concentration (solute mass divided by solution volume) may arise from temperature effects; the solution temperature can only be controlled within a range, not perfectly. The temperature control range is the uncertainty in the temperature. The resulting uncertainty in the concentration would involve a calculation using the temperature coefficient of expansion of the liquid.

One useful effect of this method of combination is that small contributions have very little effect on the overall uncertainty. For example, a contribution less than a fifth of the largest contribution changes the combined uncertainty by less than 2%.

Measurement uncertainty in ISO/IEC 17025

- Calibration laboratories* “shall have and shall apply a procedure…”
- Testing laboratories “shall have and shall apply procedures….”
  - “at least attempt to identify all components and make a reasonable estimation”
  - “…. based on knowledge of performance and … validation data”

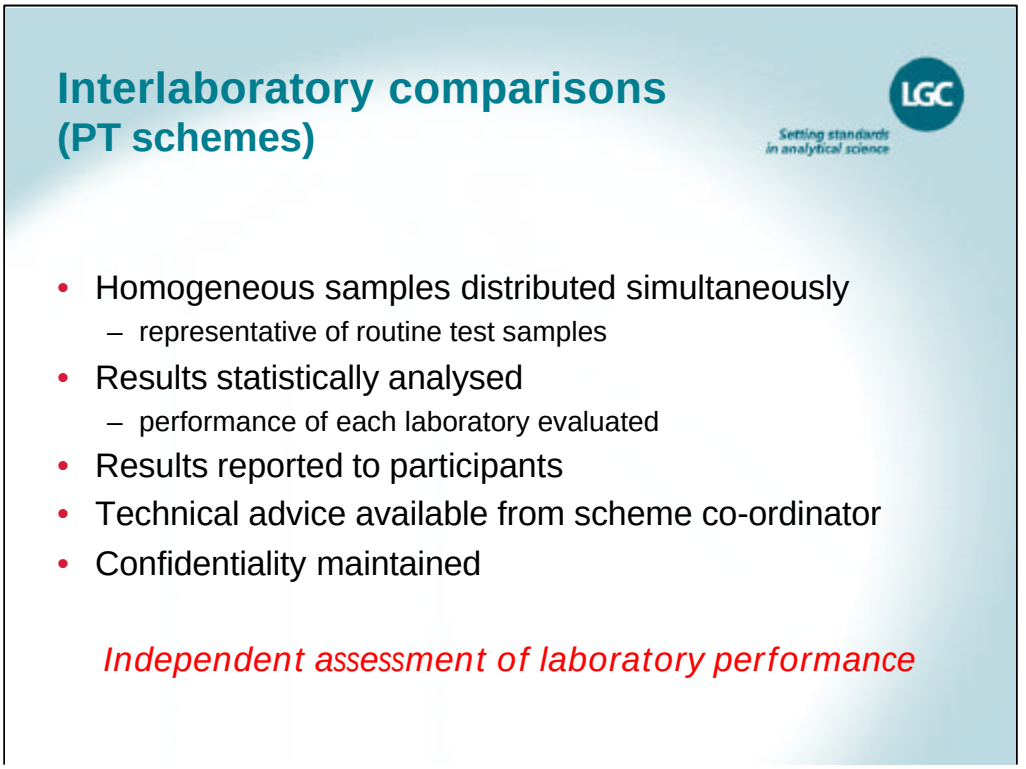
**Or test laboratories doing own calibrations*

Traceability

- "Property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards through an unbroken chain of comparisons all having stated uncertainties" (VIM 1993)
- 'Stated references'
  - calibration standards
  - traceable reference materials for independent checks

Traceability defines the scale of measurement. The next section of the course deals in detail with traceability.

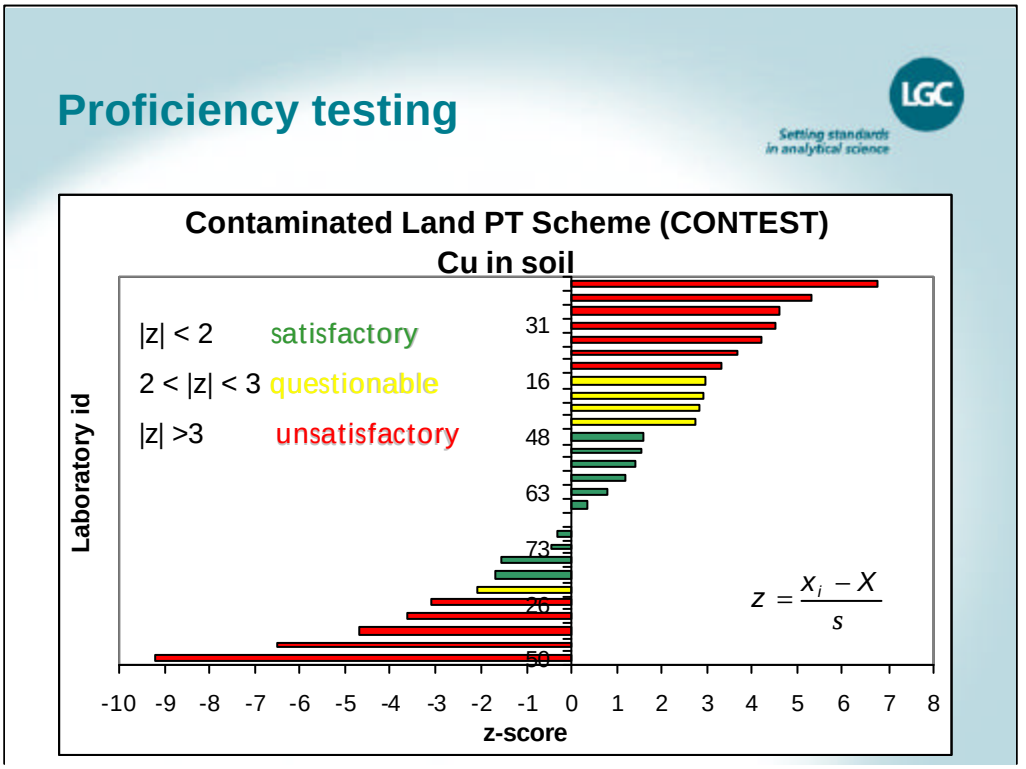
Reference: International Vocabulary of Basic and General Terms in Metrology (VIM), ISO, 1993.



Section 5.9 of ISO/IEC 17025 (Assuring the quality of test and calibration results) requires laboratories to participate in interlaboratory comparison or proficiency testing (PT) programmes.

There are a number of actions within the operation of a PT scheme which are common to the vast majority of schemes. These involve obtaining and preparing sufficient test samples, testing for homogeneity and stability, characterising samples (including assigning true or reference values). These samples can then be distributed to participants - usually simultaneously - ensuring the integrity of the samples is preserved, along with any specific instructions, information (such as the time period to submit the results), reporting proformas, etc. Results are then received by the scheme organiser, and these are entered into their data processing system and checked, before the data are processed and the results evaluated. The final report is then prepared, checked and distributed to participants.

In the majority of schemes participants receive a performance score, based on statistical analysis of the data from the PT round by the scheme organiser. One of the common scoring systems used in proficiency testing schemes (the z-score) is described on the following slide.



Each participant in a PT exercise receives a statistical score which they can use to judge how well they have done. One of the most common scoring systems used is the z-score.

Performance assessment in PT generally involves calculating the difference between a laboratory's result and a target value (also known as the assigned value), and comparing this difference with a target range.

In the equation for 'z' shown on the slide, x_i is the laboratory result, X is the target value and s is the target range. There are a number of different approaches that PT scheme organisers can use to establish the target value and target range. One of the most common approaches is to obtain the values from the data submitted by the participants. The data are usually treated to minimise the effects of any extreme values returned by the laboratories. This can be done by carrying out outlier tests to identify extreme values which are then removed before calculation of the target value or range. An alternative approach is the use of robust statistics which reduce the effect of extreme values on the calculated mean and spread.

Laboratories use the z-score to judge their performance. An absolute z-score of less than 2 is considered satisfactory. An absolutes score between 2 and 3 is considered questionable. A score greater than 3 indicates an unsatisfactory result. The scores are based on the properties of the Normal distribution of data. For normally distributed data one expects 95% of values to be within 2 standard deviations of the mean. There is a 5% chance that a result may be greater than 2 standard deviations away from the mean but still be a valid result. This is why a score of between 2 and 3 is used to indicate a questionable result. It is not that likely that a valid result would be that far away from the mean, but once in a while, purely by chance, a laboratory will produce a result that is more than 2 standard deviations from the mean. There is only a very small chance (around 0.3%) that a valid result would be more than 3 standard deviations away from the mean. A z-score of 3 therefore indicates an unsatisfactory result.

Summary

- Accreditation provides an independent assessment of a laboratory's quality procedures
- ISO/IEC 17025 is the most commonly used standard in analytical laboratories
- Consistent with good practice and VAM principles
- Main emphasis is
  - increased customer dialogue
  - continuous improvement
- User has freedom but extra responsibility (QA & QC)

Workshop 2
Choosing an analytical laboratory

- Apple grower wants some apples analysed to determine the levels of pesticide residues present
- Analysis is required to ensure residue levels do not exceed the current maximum residue levels defined in legislation
- Apple grower: What questions would you ask the laboratory to establish whether they are capable of carrying out the work?
- Laboratory: What questions would you ask the apple growers before agreeing to take on the work?

Divide the group into two teams. One team will take the role of the apple grower whilst the the other will act as the laboratory. Each group should draw up a list of questions they want to ask the other team, bearing in mind the requirements of ISO/IEC 17025. The session concludes with a question and answer session where the two groups discuss the problem. It is useful for each group to have a copy of ISO/IEC 17025.

Further information on the scenario is given in the document 'Workshop 2'.

A list of key issues is given in the document 'Workshop 2 Answers'.

Acknowledgement

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- For further information on the VAM programme visit www.vam.org.uk