PART 1

GENERAL PROVISIONS

SECTION 1.1.

INTRODUCTORY CHAPTERS

CHAPTER 1.1.1.

QUALITY MANAGEMENT IN VETERINARY TESTING LABORATORIES

SUMMARY

Valid laboratory results are essential for diagnosis, surveillance and trade. Such results are achieved by the use of good management practices, valid test and calibration methods, proper technique, quality control and quality assurance, all working together within a quality management system. Laboratory quality management includes technical, managerial and operational elements of testing and the interpretation of test results. A quality management system enables the laboratory to demonstrate both competency and an ability to generate consistent technically valid results that meet the needs of its customers. The need for mutual recognition of test results for international trade and the acceptance of international standards such as ISO/IEC[1] 1702 5:2005 General Requirements for the Competence of Testing and Calibration Laboratories (ISO/IEC, 2005) requires good laboratory quality management systems. This chapter is not intended to reiterate the requirements of these two documents, nor has it been endorsed by accreditation bodies. Rather, it outlines the important issues and considerations a laboratory should address in the design and maintenance of its quality management system, whether or not it has been formally accredited. Chapter 1.1.1 Management of Veterinary Laboratories of the Terrestrial Manual gives an introduction to the components of governance and management of veterinary laboratories that are necessary for the effective delivery of diagnostic services, and highlights the critical elements that should be established as minimum requirements.

KEY CONSIDERATIONS FOR THE DESIGN AND MAINTENANCE OF A LABORATORY QUALITY MANAGEMENT SYSTEM

In order to ensure that the quality management system is appropriate and effective, the design must be carefully thought out and, where accreditation is sought, must address all criteria of the appropriate quality standard. The major categories of consideration and the key issues and activities within each of these categories are outlined in the following eight sections of this chapter.

1. The work, responsibilities, and goals of the laboratory

Many factors affect the necessary elements and requirements of a quality management system. These factors include:

i) The type of testing done, e.g. research versus diagnostic work;

ii) The purpose and requirements of the test results, e.g. for import or export, quarantine;

iii) The impact of a questionable or erroneous result, e.g. acute hepatopancreatic necrosis disease (AHPND) in an AHPND-free country;

iv) The tolerance level of risk and liability, e.g. vaccination vs culling or slaughter;

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1   ISO/IEC - International Organization for Standardization/International Electrochemical Commission.

v)   Customer needs (e.g. sensitivity and specificity of the test method, cost, turnaround time, strain/genotype characterisation), e.g. for surveillance, or declaration of freedom after outbreak;

vi)   The role of the laboratory in legal work or in regulatory programmes, e.g. for disease eradication and declaration of disease freedom to the OIE;

vii)   The role of the laboratory in assisting with, confirming, or overseeing the work of other laboratories (e.g. as a reference laboratory);

viii)   The business goals of the laboratory, including the need for any third party recognition and/or accreditation.

2.   Standards, guides, and references

The laboratory should choose reputable and accepted standards and guides to assist in designing the quality management system. For laboratories seeking accreditation of testing, and for all OIE Reference Laboratories, the use of ISO/IEC 17025 (ISO/IEC, 2005) or equivalent will be essential. This standard includes managerial and technical requirements and laboratories that are compliant are regarded as competent. Further information on standards may be obtained from the national standards body of each country, from the International Laboratory Accreditation Cooperation (ILAC)[2], and from accreditation bodies, e.g. the National Association of Testing Authorities (NATA), Australia, the United Kingdom Accreditation Service (UKAS), the American Association for Laboratory Accreditation (A2LA), etc. Technical and international organisations such as AOAC International (The Scientific Association Dedicated to Analytical Excellence; formerly the Association of Official Analytical Chemists) and the International Organization for Standardization (ISO) publish useful references, guides, application documents and standards that supplement the general requirements of ISO/IEC 17025. Other relevant documents may include guides and application documents providing interpretative criteria and recommendations for the application of ISO/IEC 17025 in the field of veterinary testing for both applicant and accredited facilities, e.g. http://www.nata.com.au/nata/phocadownload/publications/Accreditation_criteria/ISO-IEC-17025/VET/Veterinary-Testing-ISO-IEC-17025-Application-Document.pdf.

The ISO International Standard 9001 (ISO, 2015), is a certification standard for quality management systems and while it may be a useful supplement to a quality system, its requirements do not necessarily ensure or imply technical competence (in the areas listed Section 3 below). ISO 9001 is assessed by a certification body, which is accredited to undertake such assessments by the national accreditation body. When a laboratory meets the requirements of ISO 9001, the term *registration* or *certification* is used to indicate conformity, not *accreditation*.

With the advent of stronger alliances between medical and veterinary diagnostic testing under initiatives such as «One Health», some laboratories may wish to choose other ISO standards such as ISO 15189 (ISO/IEC, 2012), which include testing of human samples, e.g. for zoonotic diseases.

3.   Accreditation

If the laboratory decides to proceed with formal recognition of its quality management system and testing, then third party verification of its conformity with the selected standard(s) will be necessary. ILAC has published specific requirements and guides for laboratories and accreditation bodies. Under the ILAC system, ISO/IEC 17025 is to be used for laboratory accreditation of testing and/or calibration activities. Definitions regarding laboratory accreditation may be found in ISO/IEC International Standard 17000: Conformity Assessment – Vocabulary and Principles (ISO/IEC, 2004a). Accreditation is tied to demonstrated competence, which is significantly more than having and following documented procedures. Providing a competent and customer-oriented service also means that the laboratory:

i)   Has technically valid and validated test methods, procedures and specifications that are documented in accordance with the requirements of the applicable standard or guidelines, e.g. Chapter 1.1.2 *Principles and methods of validation of diagnostic assays for infectious diseases* and *Terrestrial Manual* chapters 3.6.1 to 3.6.8 *Recommendations for validation of diagnostic tests*;

ii)   Has appropriately qualified and trained personnel with a depth of technical knowledge commensurate with appropriate levels of authority;

iii)   Has appropriate equipment with planned maintenance/calibration schedules;

iv)   Has adequate facilities and environmental control;

v)   Has procedures and specifications that ensure accurate and reliable results;

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2   ILAC: The ILAC Secretariat, PO Box 7507, Silverwater, NSW 2128, Australia; http://ilac.org/

vi)   Implements continual improvements in testing and quality management;

vii)   Can assess the need for and implement appropriate corrective or preventive actions, e.g. customer satisfaction;

viii) Accurately assesses and controls uncertainty in testing;

ix)   Demonstrates proficiency in the test methods used (e.g. by participation in proficiency tests on a regular basis);

x)   Has demonstrated competence to generate technically valid results.

4.   Selection of an accreditation body

To facilitate the acceptance of the laboratory's test results for trade, the accreditation standard used must be recognised by the international community and the accreditation body recognised as competent to accredit laboratories. Programmes for the recognition of accreditation bodies are, in the ILAC scheme, based on the requirements of ISO/IEC International Standard 17011: General Requirements for Accreditation Bodies Accrediting Conformity Assessment Bodies (ISO/IEC, 2004b). Information on recognised accreditation bodies may be obtained from the organisations that recognise them, such as the Asia-Pacific Laboratory Accreditation Cooperation (APLAC), the Interamerican Accreditation Cooperation (IAAC), and the European Co-operation for Accreditation (EA).

Accreditation bodies may also be signatory to the ILAC and regional (e.g. APLAC) mutual recognition arrangements (MRAs). These MRAs are designed to reduce technical barriers to trade and further facilitate the acceptance of a laboratory's test results in foreign markets. Further information on the ILAC MRA may be obtained from the www.ilac.org

5.   Determination of the scope of the quality management system and/or of the laboratory's accreditation

The quality management system should cover all areas of activity affecting all testing that is done at the laboratory. While accredited laboratories are obliged to meet the requirements of the standard as detailed below, these principles are relevant to all testing laboratories.

Laboratories accredited to ISO/IEC 17025 have a specific list of those tests that are accredited, called the schedule of accreditation or the scope. Veterinary testing facilities include government and private facilities, veterinary practices, university veterinary schools, and other laboratories for the testing of animals and animal products for the diagnosis, monitoring and treatment of disease. In principle, if new testing methods are introduced these must be assessed and accredited before they can be added to the scope, however a flexible scope can be implemented that assesses the laboratory as competent to add tests to scope, which are then formally added at the next accreditation visit. The quality management system should ideally cover all areas of activity affecting all testing that is done at the laboratory. However, it is up to the laboratory to decide which tests are to be accredited and included in the scope. If an accredited laboratory also offers unaccredited tests, these must be clearly indicated as such on any reports that claim or make reference to accreditation. Factors that might affect the laboratory's choice of tests for scope of accreditation include:

i)   The impact of initial accreditation on resources within a given deadline;

ii)   A contractual requirement for accredited testing (e.g. for international trade, research projects);

iii)   The importance of the test and the impact of an incorrect result;

iv)   The cost of maintaining an accredited test;

v)   Availability of personnel, facilities and equipment;

vi)   Availability of reference standards (e.g. standardised reagents, internal quality control samples, reference cultures) and proficiency testing schemes;

vii)   The quality assurance necessary for materials, reagents and media;

viii) The validation, technical complexity and reliability of the test method;

ix)   The potential for subcontracting of accredited tests;

6.   Quality Assurance, Quality Control and Proficiency testing

Quality assurance (QA) is the part of quality management focused on providing confidence that quality requirements will be fulfilled systematic and planned process of ensuring that the service offered meets the stated requirements in all areas. The requirements may be internal or defined in an accreditation or certification standard. QA is process orientated and ensures the right things are being done in the right way.

Quality Control (QC) is the systematic and planned monitoring of output to ensure the minimum levels of quality have been met. For a testing laboratory, this is to ensure test processes are working correctly and results are within the expected parameters and limits. QC is test orientated and ensures the results are as expected.

Proficiency Testing (PT), sometimes referred to as External Quality Assurance or EQA, is the determination of a laboratory's performance by testing specimens of undisclosed content. Ideally, PT schemes should be run by an external independent provider. Participation in proficiency testing enables the laboratory to assess and demonstrate the reliability results by comparison with those from other participating laboratories.

All laboratories should, where possible, participate in external proficiency testing schemes appropriate to their testing. Participation in such schemes is a requirement for accredited laboratories. This provides an independent assessment of the testing methods used and the level of staff competence. If such schemes are not available, valid alternatives may be used, such as ring trials organised by reference laboratories, inter-laboratory testing, use of certified reference materials or internal quality control samples, replicate testing using the same or different methods, retesting of retained items, and correlation of results for different characteristics of a specimen.

Providers and operators of proficiency testing programmes should be accredited to ISO/IEC 17043 – Conformity assessment – General requirements for proficiency testing (ISO/IEC, 2010).

Proficiency testing material from accredited providers has been well characterised and any spare material, once the proficiency testing has been completed, can be useful to demonstrate staff competence or for test validation. Information about selection and use of reference samples and panels is available in *Terrestrial Manual* Chapter 3.6.6 *Selection and use of reference samples and panels.*

7. Test methods

ISO/IEC 17025 requires the use of appropriate test methods and has requirements for their selection, development, and validation to show fitness for purpose.

This *Aquatic Manual* provides recommendations on the selection of test methods for trade, diagnostic and surveillance purposes in the chapters on specific diseases. The fact that a test is recommended does not necessarily mean that a laboratory is competent to perform it. The laboratory quality system should incorporate provision of evidence of competency.

In the veterinary profession, other standard methods (published in international, regional, or national standards) or fully validated methods (having undergone a full collaborative study and that are published or issued by an authoritative technical body such as the AOAC International) may be preferable to use, but may not be available. Many veterinary laboratories develop or modify methods, and most laboratories have test systems that use non-standard methods, or a combination of standard and non-standard methods. In veterinary laboratories, even with the use of standard methods, some in-house evaluation, optimisation, and/or validation generally must be done to ensure valid results.

Customers and laboratory staff must have a clear understanding of the performance characteristics of the test, and customers should be informed if the method is non-standard. Many veterinary testing laboratories will therefore need to demonstrate competence in the development, adaptation, and validation of test methods.

This *Aquatic Manual* provides more detailed and specific guidance on test selection, optimisation, standardisation, and validation in Chapter 1.1.2 *Principles and methods of validation of diagnostic assays for infectious diseases*. Chapter 1.1.2 refers to *Terrestrial Manual* chapters 3.6.1-3.6.8 *Recommendations for validation of diagnostic tests* that deal with the development and optimisation of fundamentally different assays such as antibody, antigen and nucleic acid detections tests, measurement uncertainty, statistical approaches to test validation, selection and use of reference samples and panels, validation of diagnostic tests for wildlife and comparability experiments after changes in a validated test method..

The following are key test method issues for those involved in the quality management of the laboratory.

7.1. Selection of the test method

Valid results begin with the selection of a test method that meets the needs of the laboratory's customers in addressing their specific requirements (fitness for purpose). Some issues relate directly to the laboratory, others to the customer. Considerations for the selection of a test method include:

i)   International acceptance;

ii)   Scientific acceptance;

iii)   Appropriate or current technology;

iv)   Suitable performance characteristics (e.g. analytical and diagnostic sensitivity and specificity, repeatability, reproducibility, isolation rate, limits of detection, precision, trueness, and uncertainty);

v)   Suitability of the test in the species and population of interest;

vi)   Sample type (e.g. serum, tissue, milk) and its expected quality/state on arrival at the laboratory;

vii)   Test target (e.g. antibody, antigen, live pathogen, nucleic acid sequence);

viii)   Test turnaround time;

ix)   Resources and time available for development, adaptation, evaluation;

x)   Intended use (e.g. export, import, surveillance, screening, diagnostic, confirmatory);

xi)   Safety factors;

xii)   Customer expectations;

xiii)   Throughput of test samples required;

xiv)   Cost of test, per sample;

xv)   Availability of reference standards, reference materials and proficiency testing schemes (see also *Terrestrial Manual* chapter 3.6.6).

7.2. Optimisation and standardisation of the test method

Once the method has been selected, it must be set up at the laboratory. Additional optimisation is necessary, whether the method was developed in-house or imported from an outside source. Optimisation establishes critical specifications and performance standards for the test process as used in a specific laboratory. Optimisation should determine:

i)   Critical specifications for equipment and instruments;

ii)   Critical specifications for reagents (e.g. chemicals, biologicals), reference standards, reference materials, and internal controls;

iii)   Robustness - critical control points and acceptable ranges, attributes or behaviour at critical control points, using statistically acceptable procedures;

iv)   Quality control activities necessary to monitor critical control points;

v)   The type, number, range, frequency, and arrangement of test run controls;

vi)   Criteria for non-subjective acceptance or rejection of a batch of test results;

vii)   Criteria for the interpretation and reporting of test results;

viii)   A documented test method and reporting procedure for use by laboratory staff;

ix)   Evidence of technical competence for those who perform the test processes and interpret results.

7.3. Validation of the test method

Validation evaluates the test for its fitness for a given use by establishing test performance characteristics, such as sensitivity, specificity, and isolation rate; and diagnostic parameters such as positive/negative cut-off, and titre of interest or significance. Validation should be done using an optimised, documented, and fixed procedure. The extent and depth of the validation process will depend on logistical and risk factors. It may involve any number of

activities and amount of data, with subsequent data analysis using appropriate statistical methods. Validation activities might include:

i)   Field and/or epidemiological studies, including disease outbreak investigations;

ii)   Development of testing algorithms for specific purposes, e.g. surveillance, outbreak investigations, etc.;

iii)   Repeat testing to establish the effect of variables such as operator, reagents, equipment;

iv)   Comparison with other, preferably standard, methods and with reference standards (if available);

v)   Collaborative studies with other laboratories using the same documented method. Ideally organised by a reference laboratory and including testing a panel samples of undisclosed composition or titre with expert evaluation of results and feedback to the participants;

vi)   Reproduction of data from an accepted standard method, or from a reputable publication;

vii)   Experimental infection or disease outbreak studies;

viii)   Analysis of internal quality control data.

Validation is always a balance between cost, risk, and technical possibilities. There may be cases where quantities such as accuracy and precision can only be given in a simplified way. Criteria and procedures for the correlation of test results for diagnosis of disease status or for regulatory action must be developed. The criteria and procedures developed should account for screening methods, retesting and confirmatory testing.

Test validation is covered in Chapter 1.1.2.

7.4. Uncertainty of the test method

Measurement of Uncertainty (MU) is «a parameter associated with the result of a measurement that characterises the dispersion of values that could reasonably be attributed to the measure» (Eurachem, 2012). Uncertainty of measurement does not imply doubt about a result but rather increases confidence in its validity. It is not the equivalent to error, as it may be applied to all test results derived from a particular procedure.

Laboratories must estimate the MU for each test method resulting in a measurement included in their scope of accreditation and for any methods used to calibrate equipment (ISO/IEC, 2005).

Tests can be broadly divided into two groups: quantitative (biochemical assays, enzyme-linked immunosorbent assays ELISA, titrations, real-time polymerase chain reactions PCR, pathogen enumeration, etc.); and qualitative (bacterial culture, parasite identification, virus isolation, endpoint PCR, immunofluorescence, etc.).

The determination of MU is well established in *quantitative* measurement sciences (ANSI (American National Standards Institute), 1997). It may be given as a numeric expression of reliability and is commonly shown as a stated range. Standard deviation (SD) and confidence interval (CI) are examples of the expression of MU, for example the Optical Density result of an ELISA expressed as $\pm n$ SD, where n is usually 1, 2 or 3. The Confidence Interval (usually 95%) gives an estimated range in which the result is likely to fall, calculated from a given set of test data.

The application of the principles of MU to *qualitative* testing is less well defined. The determination and expression of MU has not been standardised for veterinary (or medical, food, or environmental) testing laboratories, but sound guidance exists and as accreditation becomes more important, applications are being developed. The ISO/IEC 17025 standard recognises that some test methods may preclude metrologically and statistically valid calculation of uncertainty of measurement. In such cases the laboratory must attempt to identify and estimate all the components of uncertainty based on knowledge of the performance of the method and making use of previous experience, validation data, internal control results etc.

Many technical organisations and accreditation bodies (e.g. AOAC International, ISO, NATA, A2LA, SCC, UKAS, Eurachem, CITAC) teach courses and/or provide guidance on MU for laboratories seeking accreditation.

The ISO/IEC 17025 requirement for «quality control procedures for monitoring the validity of tests» implies that the laboratory must use quality control procedures that cover all major sources of uncertainty. There is no requirement to cover each component separately. Laboratories may establish acceptable specifications, criteria, ranges etc. at critical control points for each component of the test process. The laboratory can then implement appropriate quality control measures at these critical points, or seek to reduce or eliminate the uncertainty effect of each component. Measurement uncertainty is covered in *Terrestrial Manual* chapter 3.6.4.

7.4.1. Components of tests with sources of uncertainty include:

i)   Sampling;

ii)   Contamination;

iii)   Sample transport and storage conditions;

iv)   Sample processing;

v)   Reagent quality, preparation and storage;

vi)   Type of reference material;

vii)   Volumetric and weight manipulations;

viii) Environmental conditions;

ix)   Equipment effects;

x)   Analyst or operator bias;

xi)   Biological variability;

xii)   Unknown or random effects.

Systematic errors or bias determined by validation must be corrected by changes in the method, adjusted for mathematically, or have the bias noted as part of the report statement.

If an adjustment is made to a test or procedure to reduce uncertainty or correct bias then a new source of uncertainty is introduced (the uncertainty of the correction). This must be assessed as part of the MU estimate.

Additional information on the analysis of uncertainty may be found in the Eurachem Guides to Quantifying Uncertainty in Measurement (Eurachem, 2012) and Use of uncertainty information in compliance assessment (Eurachem, 2007).

7.5. Implementation and use of the test method

Training should be a planned and structured activity with steps to ensure adequate supervision is maintained while analysts are being trained. Analysts should be able to demonstrate proficiency in using the test method prior to producing reported results, and on an ongoing basis.

The laboratory must be able to demonstrate traceability for all accredited tests and the principle should apply to all tests whether accredited or not. This covers all activities relating to test selection, development, optimisation, standardisation, validation, implementation, reporting, personnel, quality control and quality assurance. Traceability is achieved by using appropriate documented project management, record keeping, data management and archiving systems.

8.   Strategic planning

Laboratories should have evidence of continual improvement, which is an obligatory requirement for accredited laboratories. The laboratory must be knowledgeable of and stay current with the quality and technical management standards and with methods used to demonstrate laboratory competence and establish and maintain technical validity. Evidence of this may be provided by:

i)   Attendance at conferences, organisation of in-house or external meetings on diagnostics and quality management;

ii)   Participation in local and international organisations;

iii)   Participation in writing national and international standards (e.g. on ILAC and ISO committees);

iv)   Current awareness of publications, writing and reviewing publications about diagnostic methods;

v)   Training programmes, including visits to other laboratories;

vi)   Conducting research;

vii)   Participation in cooperative programmes (e.g. Inter-American Institute for Cooperation in Agriculture);

viii) Exchange of procedures, methods, reagents, samples, personnel, and ideas;

ix)   Planned, continual professional development and technical training;

x)   Management reviews;

xi)   Analysis of customer feedback;

xii) Root cause analysis of anomalies and implementation of corrective, preventive and improvement actions.

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NB: FIRST ADOPTED IN 1996 ENTITLED GOOD LABORATORY PRACTICE, QUALITY CONTROL AND QUALITY ASSURANCE; MOST RECENT UPDATES ADOPTED IN 2017.