FELASA guidance paper for the accreditation of laboratory animal diagnostic laboratories

Report of the Federation of European Laboratory Animal Science Associations (FELASA) Working Group on Accreditation of Diagnostic Laboratories

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Introduction

Health monitoring

The use of microbiologically defined animals in biomedical research has become standard practice in the last few decades. Microbiological standardization has reduced the numbers of animals used by reducing the variation within and between test groups. It has also improved the overall health of laboratory animals, thus improving their welfare, and has reduced human health risks due to zoonotic diseases. Microbiological standardization is based upon routine testing of the animals at regular intervals (health monitoring).

What is accreditation?

Accreditation means that an impartial outside agency has reviewed the operation of a laboratory and found it to be in accordance to the specifications set forth by the laboratory itself. Most laboratories choose to be accredited according to the European Norm (EN) 45001 or the International Standards Organization (ISO) Guide 25 (both documents are virtually identical). Accreditation is on a voluntary basis. It states that the laboratory is sufficiently competent to perform the diagnostic tests it is offering. In the case of laboratory animal diagnostic special emphasis is placed on competency of the staff, validation of in-house test methods, the establishing of a European Reference Centre and the participation in inter-laboratory testing (ring-testing). Accreditation increases the trustworthiness of a laboratory.

How does it work?

Laboratories are audited and accredited by national accreditation bodies, which are members of the European Cooperation for Accreditation of Laboratories (EAL). EAL guarantees that the same standards are used in all member countries. The laboratory has to provide proof that a quality assessment system is in place. This usually consists of a framework of documents, which describe the essential operations of the laboratories. The norms are frequently very ambiguous and the laboratory itself will have to decide how extensive this documentation needs to be. All incidences where errors, which could affect the result of the test, could occur must be identified. The extent of this quality assessment documentation depends on the complexity of the laboratory. Once the laboratory can document that the testing is done according to the specifications, the accreditation body holds the audit and if everything is in order the accreditation is granted. Otherwise a list of items that need to be corrected will be issued to the laboratory. Accreditation is usually for a period of three years, after which the accreditation body will audit the laboratory again.

Why should a laboratory get accredited?

The quality of health monitoring relies heavily upon the quality of the testing and the correctness of the results. Specialized

laboratories have evolved offering monitoring for pathogens specific to rodents and rabbits. Most tests employed are in-house assays since commercial tests are often not available in this field. Accreditation is a way for the laboratory to show to its clients that it is operating under internationally acceptable standards.

Who needs accreditation?

The Laboratory Accreditation for the laboratory is a seal of approval and can be a marketing tool. It also offers the chance to review the operation, streamline it and improve not only quality but also efficiency of the testing. Interaction with other laboratories during inter-laboratory comparisons can help identify problems and keep the laboratory abreast with new developments.

The Animal Facility Manager Accreditation offers an impartial opinion about the performance of a laboratory, which laymen could otherwise not get. It helps a facility manager to decide which laboratory offers the best service.

The Researcher Knowing that the health monitoring of the experimental animals is conducted in an accredited laboratory increases the confidence in the results of the research conducted with these animals.

How much does it cost?

Cost varies greatly depending on the complexity of the laboratory. When setting up a quality assessment scheme care must be taken only to include essential components. A one-person operation requires much less documentation than a larger laboratory. Cost also depends on how well the laboratory has been organized previously. If all the testing protocols are available and up to date, very little additional documentation is needed. In a laboratory where everything is done without written protocols the efforts to reach accreditation are much greater.

What is FELASA's role in this?

In the past, reproducibility of test results from different laboratories using different test methods has not always been possible (Baneux & LeNet 1997). The laboratories in the field of laboratory animal diagnostics have addressed these issues by organizing ring-testing on a voluntary basis. FELASA has welcomed such efforts and has decided to promote harmonization of laboratory animal diagnostic by recommending that the laboratories operating in this field seek accreditation. Thus FELASA strongly believes that the overall quality of health monitoring and animal experimentation can be further improved.

Why this guideline and who should read it?

As mentioned before the norms are in many ways very ambiguous since they address a wide variety of testing laboratories. Laboratories that engage in laboratory animal diagnostics, however, have very specific needs. To facilitate the accreditation of these laboratories, FELASA has prepared the following guidelines, which are specifically tailored to the needs of laboratories in this field. It is intended to be the main document that will guide a laboratory through the accreditation process. It should also offer assistance to the auditors and experts engaged by the accreditation bodies when auditing a laboratory performing laboratory animal testing. It should provide interpretation of the norms, which are considered appropriate in the field.

This introduction is not part of the guidelines.

Reference

Baneux PJR, LeNet JL (1997). An interlaboratory comparison of serologic test results for *Encephalitozoon cuniculi* infection in rabbits points to the need for accreditation of laboratory animal diagnostic laboratories. *Contemporary Topics in Laboratory Animal Science* **36**(4), 44

Preamble

The following document was written by the Federation of European Laboratory Animal Science Associations (FELASA) in consultation with the European Cooperation for Accreditation of Laboratories (EAL) to provide guidance on the interpretation of the European Norm 45001 for laboratories engaged in laboratory animal diagnostics. This is only a transitory document which in time will be replaced by a set of documents issued by the EAL, which will cover all issues dealt with in this document. Until such time, the document is supported by the EAL who will use it in their evaluation of laboratories in this specific field. Laboratories wishing to use this document for their own accreditation are advised to check back with their national accreditation body or with FELASA to see if this document is still in use.

To form a stand-alone document this guidance paper contains passages adopted from the joint guidance document of EAL and EURACHEM 'Accreditation for laboratories performing microbiological testing' (EAL-G18).

1 Introduction and scope of document

1.1 The general requirements for accreditation are laid down in the European Standard 'General criteria for the operation of testing laboratories' (EN 45001:1989) and 'General requirements for the competence of calibration and testing laboratories' (ISO/IEC Guide 25, 3rd edn. 1990), hereafter referred to as EN 45001 and ISO Guide 25 respectively. Laboratories seeking accreditation must meet all of these requirements.

1.2 This document only supplements EN 45001 and ISO Guide 25. It provides guidance for both assessors and for laboratories working in laboratory animal diagnostics. It gives detailed information on interpreting EN 45001 and ISO Guide 25 for the field of laboratory animal diagnostics. The guidance is applicable for laboratories performing routine testing of samples originating from laboratory animals. EN 45001 and ISO Guide 25 remain the authoritative documents.

1.3 Laboratory animal diagnostic includes the bacteriological, mycological, parasitological, virological and pathological examination of laboratory animals or of samples collected from laboratory animals or of samples collected from the environment of laboratory animals for the purpose of assessing the health status of an individual animal or an animal colony (routine health monitoring). The term laboratory animal may include any animal used in animal experimentation but emphasis is placed on rodents and lagomorphs. Laboratories examining mainly samples from farm or companion animals should seek accreditation in their respective field.

1.4 This document is based on the document 'Accreditation for laboratories performing microbiological testing' issued by EAL and EURACHEM (EAL-G18) referred to as EAL-G18 hereafter.

1.5 This document is concerned with the quality of test results. However, it is here noted that laboratory practice should conform to national and international regulation concerning safety, human and animal health and animal welfare.

2 Scope of accreditation

(EN 45003, paragraph 6.6)

2.1 The scope of accreditation of a laboratory is the formal statement of the range of activities for which the laboratory has been accredited. The scope is recorded on an accreditation schedule, which is issued together with the accreditation certificate. In laboratory animal diagnostics the laboratory's scope has to be defined on three levels:

(1) The field of testing: one or more of the four basic categories in laboratory animal diagnostics (**pathology**, **bacteriology**, **parasitology** and **virology**).
(2) The range of animal species from which the tested samples originate from.

(3) The basic methodology employed:

- culture (bacteria)
- tissue culture (virus isolation)
- visual methods (e.g. microscopy) (parasites, pathology)
- immunoassays (ELISA, IFA, HI, immunohistochemistry, Western blot)
- molecular biology methods (PCR, in situ hybridization, Southern blot)

2.2 The range of tests employed by the laboratory may be any or all of those listed in the latest versions of the recommendations issued by FELASA for the respective species. Additional test may be performed if required. A health status of an animal or an animal colony may only be issued if the testing was done according to the recommendations issued by FELASA. Currently existing documents include 'Recommendations for the health monitoring of mouse, rat, hamster, guineapig and rabbit breeding colonies', 'FELASA recommendations for the health monitoring of mouse, rat, hamster, gerbil, guineapig and rabbit experimental units' and 'FELASA recommendations for the health monitoring of breeding colonies and experimental units of cats, dogs and pigs'.

3 Staff

(EN 45001, paragraph 5.2; ISO Guide 25, paragraph 6)

3.1 The laboratory management should define the minimum levels of qualification and experience necessary for all posts within the laboratory.

3.2 All procedures must be performed or supervised by a person carrying an academic degree in veterinary medicine, medicine, microbiology or equivalent. This person needs additional experience in laboratory animal diagnostic of at least three years in the categories and species the laboratory is accredited for. Experience in laboratory animal science comparable with at least the level of FELASA category C is also required. Two of these years may be substituted by four years experience in general medical or veterinary diagnostics. Technical staff needs to have an adequate education and relevant practical experience of at least two years before being allowed to perform accredited work without direct supervision. Specific national regulations may override the guidance given in this document.

3.3 Persons performing tests under direct supervision need not be continuously monitored, but the progress of the testing should be checked at key points during the procedure by the supervisor. The supervisor should at the end directly determine the result of the testing. Persons under indirect supervision may independently perform a test and afterwards report the result to the supervisor.

3.4 The laboratory management should ensure that all staff has received adequate training for the competent performance of tests and operation of equipment. This should include training in basic techniques, e.g. plate pouring, counting of colonies, aseptic technique, serological tests, tissue culture, histological technique, microscopy etc., where this has not previously been undertaken. Objective measures as determined by, e.g. replicate analysis, should be recorded and used to assess the attainment of competence during training. Staff may only perform tests on samples if they are either recognized as competent to do so, or if they do so under adequate supervision. Continued competence should be monitored and, where this is not achieved, the need to retrain staff should be considered. Where a method or technique is not in regular use, verification of staff performance before they undertake tests may be necessary. The critical interval between performance of tests should be established and documented.

3.5 Persons carrying an academic degree and all staff members allowed to carry out test without direct supervision have to document adequate continuous education. This may be in the form of training courses, workshops or scientific meetings relevant to the scope of accreditation of the laboratory.

4 Environment

(EN 45001, paragraph 5.3.2; ISO Guide 25, paragraph 7)

4.1 General arrangement of the premises

4.1.1 There are generally two types of premises in laboratories; **ancillary premises** (entrances, corridors, administration blocks, cloak rooms and toilets, storage rooms, archives, etc.); and the **test premises** (where specific testing and associated activities are carried out) for which, generally, there are specified environmental requirements.

4.1.2 The laboratory must be arranged so as to minimize risks of cross-contamination, where this is significant to the type of test being performed. The ways to achieve this objective are, for example:

(a) to construct the laboratory to the 'no way back layout' principle;
(b) to carry out procedures in a sequential manner using appropriate precautions to ensure test and sample integrity (e.g. use of sealed containers);
(c) to segregate activities by time or space.

4.1.3 It is generally considered as good practice to have separate locations, or clearly designated areas, for the following:

- sample receipt and storage;
- animal short-term housing;
- necropsy;
- sample preparation;
- examination of samples, including incubation;
- maintenance of reference organisms;
- media and equipment preparation, including sterilization;
- sterility assessment;
- decontamination;
- polymerase chain reaction (PCR).

The area for washing (after decontamination) may be shared with other parts of the laboratory providing that the necessary precautions are taken to prevent transfer of traces of substances which could adversely interfere with testing. The need for physical separation should be judged on the basis of the activities specific to the laboratory (e.g. number and type of tests carried out).

4.2 Environment and monitoring

4.2.1 Laboratories must be aware of the potential for contamination of areas both inside and outside the laboratory, and should demonstrate that they have taken appropriate measures to avoid any such occurrence. For example, the laboratory may need to construct physical barriers to isolate the test premises.

4.2.2 The environment within which the analyses are carried out shall be such that results are not invalidated. Depending on the type of testing activities carried out, the laboratory shall define and document the particular arrangements in place for minimizing the risks of contamination.

4.2.3 Space should be sufficient to allow work areas to be kept clean and tidy. The space required should be commensurate with the volume of analyses handled and the overall internal organization of the laboratory.

4.2.4 Workrooms should be appropriately ventilated. This may be done by natural (where permitted by type of testing performed) or forced ventilation, or by the use of an air-conditioner. Where air-conditioners are used, filters should be appropriate, inspected, maintained and replaced according to the type of work being carried out.

4.3 Access

4.3.1 Depending on the type of testing being carried out, access to the laboratory should be restricted to authorized personnel. Where such restrictions are in force, staff should be made aware of:

(a) the intended use of a particular area;
(b) the restrictions imposed on working within such areas;
(c) the reasons for imposing such restrictions.

4.4 Hygiene

4.4.1 Clothing appropriate to the type of testing being performed (including, if neces-

sary protection for hair, beard, hands, shoes, etc.) should be worn in the laboratory and removed before leaving the area. In many laboratories a laboratory coat may suffice.

4.4.2 Depending on the type of the diagnostic activities being undertaken, the design and fittings of the laboratory must be such as to minimize potential contamination from the surroundings and from substances handled in the laboratory.

4.4.3 Walls, floors, ceilings and work surfaces should be non-absorbent and easy to clean and disinfect. Wooden surfaces of fixtures and fittings shall be adequately sealed. Measures should be taken to avoid accumulation of dust, by the provision of sufficient storage space, by having minimal paperwork in the laboratory and by prohibiting plants and personal possessions from the laboratory work area.

4.4.4 Reduction of contamination can be achieved by having:

- smooth surfaces on walls, ceilings, floors and benches (the smoothness of a surface is judged on how easily it may be cleaned). Tiles are not recommended as bench covering material;
- concave joints between the floor, walls and ceiling;
- minimal opening of windows and doors while tests are being carried out;
- sunshades placed on the outside;
- easy access for cleaning of internal sunshades if it is impossible to fit them outside;
- fluid conveying pipes not passing above work surfaces unless placed in hermetically sealed casings;
- a dust-filtered air inlet for the ventilation system;
- separate hand-washing arrangements, preferably non-manually controlled;
- cupboards up to the ceiling;
- no rough and bare wood;
- stored items and equipment arranged to facilitate easy cleaning;
- no furniture, documents or other items other than those strictly necessary for testing activities.

This list is not exhaustive, and not all examples will apply in every situation.

Ceilings, ideally, should have a smooth surface with flush lighting. When this is not possible (as with suspended ceilings and hanging lights), the laboratory should have documented evidence that they control any resulting risks to hygiene and have effective means of overcoming them, e.g. a surface-cleaning and inspection programme.

4.4.5 The computer equipment ventilation system should be arranged to prevent contamination, i.e. the airflow should not be directed onto the workbenches.

4.4.6 In cases where work under sterile conditions is limited or takes place only occasionally, it may be sufficient to use a clean bench provided that stringent aseptic techniques are used.

5 Equipment

(EN 45001, paragraph 5.3.3; ISO Guide 25, paragraphs 7 and 9)

5.1 As part of its quality system, a laboratory is required to operate a documented programme for the maintenance, calibration and performance verification of its equipment. The basic principles are described in the document 'Calibration and Maintenance of Measuring and Test Equipment in Testing Laboratories (EAL-G19)' issued by the EAL.

5.2 Maintenance

(Guidance on maintenance of equipment can be found in ISO 7218)

5.2.1 Maintenance of essential equipment shall be carried out at specified intervals as determined by factors such as the rate of use and the manufacturer's recommendations. Detailed records shall be kept.

5.2.2 Attention should be paid to the avoidance of cross-contamination arising from equipment, e.g.:

- disposable equipment should be clean and sterile;
- re-used glassware should be properly cleaned;

- ideally, laboratories should have more than one autoclave. However, one autoclave is acceptable provided that adequate precautions are taken to separate decontamination and sterilization loads, and a documented cleaning programme is in place to address both the internal and external environment of the autoclave.

5.2.3 Typically, the following items of equipment will be maintained by cleaning and servicing, inspecting for damage, general verification and, where relevant, sterilizing:

- general service equipment—filtration apparatus, glass or plastic containers (bottles, test tubes), glass or plastic Petri dishes, sampling instruments, wires or loops of platinum, nickel/chromium or disposable plastic;
- water baths, incubators, microbiological cabinets, autoclaves, homogenizers, fridges, freezers;
- centrifuges;
- tissue processor, inclusion centre, microtome, automatic stainer, paraffin bath, thermostated flotation bath;
- volumetric equipment—pipettes, automatic dispensers, spiral platers;
- measuring instruments—thermometers, timers, balances, pH meters, colony counters;
- optical instruments—microscopes, photometer.

5.3 Calibration and performance verification

5.3.1 The laboratory must establish a programme for the calibration and performance verification of equipment which has a direct influence on the test results. The frequency of such calibration and performance verification will be determined by documented experience and will be based on need, type and previous performance of the equipment. Intervals between calibration and verification shall be shorter than the time the equipment has been found to take to drift outside acceptable limits. Examples of calibration intervals and typical performance checks for various laboratory instruments are given in Appendix A and Appendix B.

5.3.2 Where the concept is applicable, all measurements having a significant effect upon test results must be traceable to national or international standards. Evidence of traceability shall be through certificates issued by a national standards laboratory or by a laboratory accredited for calibration. In the case where traceability is not available through either of these routes, it shall be provided by a body recognized by the accreditation organization for the measurement concerned.

5.3.3 Temperature measurement devices

(a) Where the accuracy of temperature measurement has a direct effect on the result of an analysis, temperature measuring devices, e.g. liquid-in-glass thermometers, thermocouples, platinum resistance thermometers (PRTs) used in incubators and autoclaves shall be of the appropriate quality to achieve the specification in the test method. The graduation of the temperature measuring devices must be appropriate for the required accuracy of measurement. They shall also be calibrated to national or international standards for temperature.

(b) Acceptable traceability of measurement for thermometers may be achieved by in-house calibration against calibrated reference thermometers, thermocouples or platinum resistance thermometers in accordance with a documented procedure, provided that the overall uncertainty of measurement of the reference device is appropriate to the calibration.

(c) When the accuracy of the temperature measurement does not have a direct effect on the test result, e.g. in the case of fridges, freezers and paraffin baths, laboratories may meet accreditation requirements by using, throughout the laboratory, working thermometers manufactured to acceptable national/international specifications. Verification of the performance of these devices will need to be carried out.

(d) An independent verification of the integral thermometer-sand recorders in media preparators and autoclaves shall be carried out to demonstrate their accuracy.

Where it is not possible to use devices such as thermocouples, maximum thermometers that have been calibrated within the required temperature range may be used to monitor the autoclave chamber temperatures. A comparison between temperatures indicated externally and the maximum reached inside the autoclave may be made. Records of such checks and details of any corrective action taken shall be recorded.

5.3.4 Uniformity of temperature

The stability of temperature, uniformity of temperature distribution and time required to achieve equilibrium conditions in incubators, water baths, ovens and temperature-controlled rooms shall be established initially and documented, in particular with respect to typical uses (e.g. position, space between, and height of, stacks of Petri dishes). The constancy of the characteristics recorded during initial verification of the equipment shall be checked and recorded after each significant repair or modification. Laboratories shall monitor and retain temperature records of equipment used for testing.

5.3.5 Autoclaves

(a) Autoclaves shall be capable of meeting specified temperature tolerances. Pressure cookers fitted only with a pressure gauge are not recommended for sterilization of media or decontamination of wastes.
(b) The performance of each autoclave shall be initially evaluated by establishing its functional properties, e.g. heat distribution characteristics with respect to typical uses. This process must be repeated after significant repair or modification (e.g. replacement of thermo-regulator probe or programmer, loading arrangements, operating cycle). The sterilization/decontamination cycle must take account of the heating profile of the load. Clear operating instructions shall be given based on the heating profiles determined for typical uses.
(c) Records of autoclave operations, including temperature and time, shall be maintained. This should be done for every cycle, acceptance/rejection criteria set and records maintained. Monitoring shall be achieved by one of the following:

(i) using a thermocouple and recorder to produce a chart or printout;
(ii) using a maximum thermometer;
(iii) direct observation and recording of maximum temperature achieved.

In addition to directly monitoring the temperature of an autoclave, the effectiveness of its operation during each cycle may be checked by the use of chemical or biological indicators for sterilization/decontamination purposes. Autoclave tape should be used to indicate that a load has been processed, but not as an indicator to demonstrate completion of an acceptable sterilization cycle.

5.3.6 Weights

Weights shall be calibrated and balances verified at regular intervals by a documented procedure (according to their intended use). All weights shall be calibrated and traceable to national or international standards.

5.3.7 Volumetric equipment

(a) Volumetric equipment such as automatic dispensers, dispenser/diluters, mechanical hand pipettes, multichannel pipettes and disposable pipettes may all be used in the diagnostic laboratory. Laboratories should carry out initial verification of volumetric equipment and then make regular checks to ensure that the equipment is performing within the required specification. Verification should not be necessary for glassware which has been certified to a specific tolerance.
(b) Equipment should be verified for the accuracy of the delivered volume against the set volume (for several different settings in the case of variable volume instruments) and the precision of the repeat deliveries should be measured. For 'one-use' disposable volumetric equipment, laboratories should obtain supplies from companies with relevant ISO 9000 registration. After initial verification of the suitability of the equipment, it is

recommended that random checks on accuracy are carried out. Where companies do not have ISO 9000 registration, laboratories should check each batch of equipment for suitability.

5.3.8 Conductivity meters, pH meters
Conductivity meters, oxygen meters, pH meters and other similar instruments shall be verified regularly or before each use. The buffers used to calibrate the instrument shall be stored in appropriate conditions and shall be marked with an expiration date.

5.3.9 Hygrometers
Where humidity is important to the outcome of the test, hygrometers shall be calibrated and the calibration shall be traceable to national or international standards.

5.3.10 Timers
Timers, including the autoclave timer, shall be verified using a calibrated timer or national time signal.

5.3.11 Photometers (ELISA readers as well as single cuvette photometers) and refractometers
Photometers should be checked regularly for the proper function of automatic procedures, lamp function, light direction etc. by either an in-built self-check or by a manual procedure. The accuracy of the estimation of the optical density or refraction should be monitored regularly against a reference standard in order to document that the deviation from the standard value is within the accepted variation range of the instrument. For instruments having an automatic calibration of results each type of test must be regularly validated against a standard or a sample tested by another method or another laboratory.

5.3.12 Thermocycler (PCR)
Temperature and timing in thermocyclers should be checked regularly by internal self-check or by using external control devices.

6 Reagents and culture media

(ISO Guide 25, paragraph 8.1)

6.1 The laboratory should ensure that the quality of the reagents used is appropriate for the tests concerned. The grade of any reagents used (including water) should be as stated in the method together with guidance on any particular precautions which should be observed in its preparation or use. Preferably, reagents (including ready-to-use media, Petri dishes, slides, microtitre-plates, conjugated antibodies, enzymes and substrates) should be obtained from manufacturers who have a quality certification system certified to ISO 9000. Laboratories should ensure that certification covers all relevant activities including supply/delivery, where this has a bearing on the performance of the goods. Laboratories should initially verify the suitability of the product by using

- For (tissue) culture and microscopy methods positive and negative control organisms which are traceable to recognized national culture collections or an organization recognized by the accreditation body.
- For immunoassays positive and negative control sera which are derived from international reference material or which previously have been tested by at least two different methods at the laboratory or at two different laboratories.
- For molecular biology positive and negative control samples containing either:
  - specific nucleic acid which are derived from international reference material;
  - specific nucleic acid which previously have been tested by at least two different methods at the laboratory or at two different laboratories;
  - control organisms which are traceable to recognized microbiological/national culture collections or an organization recognized by the accreditation body.

6.2 Each batch received should include an assurance that it is supplied in accordance with the quality specification. In the event of any changes, the manufacturer should supply a revised specification. Distilled water, deionized water or reverse osmosis produced water, free from bactericidal and inhibitory substances, should be used in the preparation of media, solutions and buffers.

6.3 Laboratories shall ensure that all reagents (including stock solutions) are ade-

quately labelled to indicate identity, concentration, storage conditions, expiration date and/or recommended storage periods. The person responsible for the preparation of the reagent should be identifiable either from the label or from the records.

6.4 Culture methods

6.4.1 Culture media may be prepared in the laboratory from the individual chemicals, from commercially available dehydrated powders, or may be purchased ready to use.

6.4.2 Reagents and commercial dehydrated powders shall be consumed within the shelf-life of the product. The date of receipt, expiration date and opening date should be recorded. The stock should be rotated so that the older media and reagents are used first. Storage should be under appropriate conditions, e.g. cool, dry and dark. All containers, especially those for dehydrated media, should seal tightly. Dehydrated media that are caked or cracked or show a colour change should not be used.

6.4.3 Where laboratories are making use of pre-prepared media and reagents, they should obtain a copy of the ISO 9000 registration certificate from the suppliers of the goods. It is recommended that further checks should be made on products on a random basis to ensure continued compliance with the required specification. These checks may be encompassed by a laboratory's in-house regular quality control (QC) programme. The manufacturer should initially supply a 'quality specification' which will include at least the following:

(a) shelf life of the product;
(b) storage conditions;
(c) sampling regime/rate;
(d) sterility check, including acceptability criteria;
(e) efficacy checks including the organism used, their culture collection reference and acceptability criteria;
(f) date of issue of specification.

6.4.4 Media, solutions and reagents should be prepared, used and stored in accordance with a documented procedure following the instructions of the manufacturer/author. Guidance on the preparation and sterilization of media, and recommended storage times can be found in ISO 7218.

6.4.5 All laboratory prepared batches of media should be checked to ensure they support the growth of specific microbial cultures. In addition, selective media should be checked to ensure they suppress the growth of non-target organisms. In preference to using the commonly used streak method, it is better to use a quantitative procedure, where a known (often low) number of relevant organisms are inoculated onto the medium under test and the recovery evaluated. This can be used to establish a recovery level below which a batch will not be accepted.

6.5 Non-culture methods

6.5.1 Antigens may be purchased from external manufacturers according to article 6.1. They may as well be propagated and prepared in the laboratory. All laboratory prepared batches of reagents (e.g. antisera, antigen, culture, primers, probes) (if relevant) should be checked for absence of cross-contamination by other reagents prepared in the laboratory. Information like batch number (or equivalent), date of production, the protocol of the actual production procedure as well as all information of the original quality control test should be documented.

6.5.2 Commercially obtained antigens, antibodies and other reagents must not be used after the expiration date given by the manufacturer. Date of receipt, expiration date and opening date should be recorded. The stock should be rotated so that older antigens, antibodies and reagents are used first. Antigens, antibodies and reagents produced in the laboratory, as well as commercially obtained antigens, antibodies and reagents with no expiration date must be given an expiration date by the laboratory based upon the laboratory's own judgement.

6.5.3 Where laboratories are making use of pre-prepared antigens, antibodies and other reagents, they should obtain a copy of the ISO 9000 registration certificate from the suppliers of the goods. It is recommended that

further checks should be made on products on a random basis to ensure continued compliance with the required specification. Purity tests must be made on each batch of in-house antigens or commercially obtained antigens not being tested by the manufacturer. These checks may be encompassed by a laboratory's in-house regular QC programme. The manufacturer should initially supply a 'quality specification' which will include at least the following:

(a) shelf life of the product;
(b) storage conditions;
(c) purity checks including the sera used;
(d) efficacy checks using sera of known titres previously being tested by two different methods or the same method at two different laboratories;
(e) date of issue of specification.

Each batch received should include an assurance that it is supplied in accordance with the quality specification. In the event of any changes, the manufacturer should supply a revised specification.

7 Test methods and procedures

(EN 45001, paragraph 5.4; ISO Guide 25, paragraph 10)

7.1 Laboratories may use sectorial, official, national, and international standard methods and in-house methods. The laboratory should not feel constrained to use a standard method if it has an in-house method which has equivalent or superior performance, more modern technology and a degree of validation adequate for the purpose. The laboratory should satisfy itself that each particular method is adequate for its intended purpose.

7.2 The trueness, repeatability/reproducibility, specificity, sensitivity, limit of determination, matrix effects and ease of use must be taken into account before selecting a particular test method. Laboratories should select methods which are suitable for their purposes (see Section 9).

7.3 Methods used by a laboratory shall be fully documented. A recommendation for these procedures is given in ISO 78/2, Layouts for Standards: Part 2.

8 Validation methods and verification of performance

8.1 Each laboratory will have particular requirements for the performance characteristics of a particular method in order to demonstrate suitability for the intended purpose. However, the essential feature of any method is that it should give the 'correct' answer with respect to specified limits of detection, selectivity, repeatability and reproducibility.

8.2 For official methods, or methods from recognized national or international standard organizations, a full validation may not be necessary but, before using such a method for the first time, the laboratory should introduce it by a documented training programme. Basic parameters like variation, selectivity, sensitivity and specificity can generally be found in scientific publications, books and manuals for microbiological media.

8.3 Commercialized test systems (kits) may not require further validation if validation data from alternate sources, e.g. based on collaborative testing, is available. Laboratories should seek from manufacturers validation data and evidence of operation to a recognized quality assurance system. Where full validation data are not available, the laboratory is responsible for completing the validation of the method before using it routinely.

8.4 For all other methods, validation must be performed to assure the reliability of the obtained results and, if possible, to establish the results dispersion.

8.5 All validation data must be recorded and stored for at least as long as the method is in force and as long as necessary to ensure adequate traceability of raw data and results.

8.6 Participation in, or organization of, collaborative trials, proficiency testing, or interlaboratory comparisons, whether formal or informal, is also a means of checking the validity of methods but it is recognized that

this is not always feasible. The analysis of samples using both the proposed new method and existing methods for the same determination would assist in establishing the efficacy of a method.

8.7 If a modified version of a method is required to meet the same specification as the original method, then comparisons should be carried out using replicates to ensure that this is the case. A statistically acceptable number of samples should be analysed by each procedure to ascertain whether any difference in the results is statistically significant.

8.8 Methods detecting the presence of an organism

8.8.1 Methods that detect the presence of (parts) of the microorganism can be compared directly with each other. Qualitative microbiological test methods (in which the response is expressed in terms of presence/absence) should be validated by estimating, if appropriate, the specificity, relative trueness, positive deviation, negative deviation, limit of detection, matrix effect, repeatability and reproducibility (see EAL-G18 Appendix A for definitions).

8.8.2 For quantitative microbiological test methods, the specificity, sensitivity, relative trueness, positive deviation, negative deviation, repeatability, reproducibility and the limit of determination within a defined variability should be considered and, if necessary, quantitatively determined in assays. The differences due to the matrices must be taken into account when testing different types of samples. The results should be evaluated with appropriate statistical methods.

8.8.3 The validation of microbiological test methods should be performed under the same conditions as those of a real assay. This can be achieved by using a combination of naturally contaminated products and spiked products.

8.9 Serology methods

8.9.1 Serology methods aimed at giving a qualitative response, i.e. positive or negative, should be validated by estimating their relative specificity and sensitivity in comparison with an analogue method using individual samples for comparison. The analogue method could be another in-house test, a commercial kit or a method employed at an accredited laboratory. If available, a method detecting the presence of an organism should be used as reference method for the validation of serology methods.

8.9.2 It is often difficult to assign a true or absolute value to serological systems with no 'gold standard' available with a 100% sensitivity and specificity. In this setting the concepts of sensitivity and specificity of a new test are ill-defined and should not be used. If the true infection status of the animal is not known, results of the new test and reference test should be displayed in tabular or graphic form, and areas of disagreement should, if possible, be investigated by other diagnostic tests (e.g. immunoblot, PCR).

8.9.3 A statistically relevant number of samples, if possible, from colonies with a well defined microbiological status (positive and negative, shown by an alternative method or because the infection has been introduced experimentally) should be analysed. If due to the improvement of the health status of laboratory animals no samples from naturally infected animals are available, validation is limited to the use of samples from experimentally infected animals. The reproducibility of these methods should be estimated.

> **Note:** Methods that detect the presence of (parts) of the microorganism and serological methods will often not agree fully when data on individual animals are compared. Both types of method should however yield the same conclusion as to whether an animal colony is infected or not upon the examination of a statistically valid number of samples

8.10 Even when validation is complete, the user will still need to verify that the documented performance can be met, e.g. by the use of spiked samples prepared from reference cultures or reference material. Participation in inter-laboratory comparisons is

mandatory. This may either be established as a ring test organized by several laboratories, or by the individual laboratory by sending samples tested by the laboratory for other laboratories for comparison.

Note:

- (Diagnostic) sensitivity is the probability that the test will be positive when the animal truly is (or was) infected.
- (Diagnostic) specificity is the probability that the test will be negative when, in fact, the animal is (or was) not infected.

9 Quality assurance of results/quality control

(EN 45001, paragraph 5.4.2 (e) and (f); ISO Guide 25, paragraph 5.6)

9.1 Quality assurance is the programme of activities carried out by a laboratory intending to improve laboratory performance generally. The activities include encouragement of the constant use of internal quality control, support of external assessment schemes, and all measures taken to increase both within and between laboratory reproducibility by means of training courses, conferences, and collaborative studies of laboratory methods.

9.2 Internal quality control

9.2.1 Internal quality control consists of the procedures undertaken by a laboratory for the continual evaluation of the work of the laboratory. The main objective is to ensure that day-to-day consistency of measurement is in agreement with some agreed value, such as by comparison with the agreed characteristics of molecules, cells, organisms or with the assigned values of control materials where these exist. When consistency is not achieved, control must be exercised over the release of results.

9.2.2 Laboratories should operate internal quality control schemes using, whenever appropriate, statistical techniques such as: design of experimental/factorial analyses; variation/regression analyses; safety evaluation/risk analyses; tests of significance; quality control charts; statistical sampling inspection.

9.2.3 For DNA/RNA amplification ((RT-) PCR), suitable controls that allow monitoring the complete sequence of operations, from sample treatment to detection of amplicon, are necessary. Control for false-positive results by contamination should be done by adding negative samples to the panel of test samples. DNA/RNA extraction and inhibition of the enzyme reactions can be controlled by using internal controls (e.g. spiking of test sample). Internal controls should be as similar as possible to the target DNA. To check the specificity the PCR product can be analysed by hybridization with specific probes.

9.3 Reference cultures

(Bacterial or viral strains, parasites)

9.3.1 To demonstrate traceability, laboratories shall use reference cultures of micro-organisms obtained from a recognized national collection or an organization recognized by the accreditation body.

9.3.2 Reference cultures may be sub-cultured once to provide reference stocks. Purity and biochemical checks should be made as appropriate. The reference stocks shall be preserved by a technique (e.g. freeze-drying, liquid nitrogen storage, deep-freezing) which maintains the desired characteristics of the strains. Reference stocks shall be used to prepare working stocks for routine work (see EAL-G18 on preparation of bacterial working stocks). If reference stocks have been thawed, they must not be re-frozen and re-used.

9.3.3 Bacterial working stocks should not normally be sub-cultured. However working stocks may be sub-cultured up to a defined number of sub-cultures when:

(a) it is required by standard methods; or
(b) laboratories can provide documentary evidence demonstrating that there has been no loss of viability (where important), no changes in biochemical activity and/or no change in morphology.

Working stocks shall not be sub-cultured to replace reference stocks.

9.4 Reference material and certified reference material

(used in immunological assays and molecular biology methods)

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

9.4.2 Where no certified reference materials exists (e.g. in serology, PCR, etc.) in-house reference materials should be established. They should be validated by inter-laboratory comparison among different laboratories. The laboratories are encouraged to participate in the establishing and maintenance of an international repository of reference material such as control sera for serology. Reference material should be regularly tested against these 'international standards'.

> **Note:** International reference material consists of cut-off control sera for immunological assays and low-level positive samples containing specific nucleic acid for molecular biology methods. Monospecific control sera may be generated by the following procedure: pathogen-free animals are experimentally infected with an organism, where possible by natural route (nasal, oral or oronasal) to minimize extraneous antibodies. Animals are kept under barrier to prevent external contamination. Positive sera are collected and diluted with negative sera of the same species. Serial dilutions, made in negative serum, are tested and a consensus cut-off value is determined by inter-laboratory comparison. One designated laboratory stores the appropriately diluted cut-off serum and makes it available to other laboratories as reference material. These international reference materials are re-examined at intervals by inter-laboratory comparison to adjust their values to the present situation. Different laboratories may store different international reference materials. FELASA keeps a record where the retainers of all international reference materials are listed.

9.4.3 Reference materials and substances and certified reference materials shall be stored and handled under conditions that do not alter their integrity, in accordance with a documented procedure and the relevant test method.

9.5 External quality assessment (proficiency testing)

9.5.1 Externally organized proficiency testing schemes provide an independent means by which a laboratory may objectively assess and demonstrate the reliability of results produced by its analytical methods. Participation provides a means for a laboratory to measure its own performance against that of other laboratories. It is important to monitor proficiency testing results as a means of checking quality assurance and to take appropriate action as necessary.

9.5.2 In the field of laboratory animal diagnostics the majority of methods used are in-house methods. Inter-laboratory comparisons are therefore a crucial scheme in establishing and maintaining test methods in this field. Laboratories should participate in proficiency testing as an important part of their quality assurance protocols. Laboratories should regularly participate in programmes which are relevant to their scope of accreditation.

9.5.3 Requirements of proficiency testing is described in ISO Guide 43. Acceptable inter-laboratory comparison programmes consist of at least three independent laboratories from at least two different countries. Minimal frequency should be four times annually with at least two samples each time. Test samples may include one or more of the following:

- **Bacteriological culture and virus isolation:** reference cultures, clinical samples, spiked samples.
- **Parasitology:** parasites of the life cycle stage(s) to be detected in the individual test.
- **Pathology:** unstained slides for staining, stained histological slides or high-quality

reproduction (e.g. photographs) thereof for interpretation.

- **Immunological methods (serology):** reference material (control sera), sera from experimentally infected animals, sera from naturally infected animals (sera from different animals may be pooled, but care must be taken to assure that the pool is homogeneous).
- **Molecular biology methods (PCR):** reference material, nucleic acid preparations, reference cultures, clinical samples, spiked samples.

10 Laboratory audit and review

(EN 45001, paragraph 5.4.2; ISO Guide 25, paragraphs 5.3–5.5; EAL Information Sheet, EAL-G3)

10.1 The basic principles are described in the document 'Internal Audits and Management Review for Laboratories (EAL-G3)' issued by the EAL.

11 Sample handling and identification

(EN 45001, paragraph 5.4.5; ISO Guide 25, paragraphs 10 and 11)

11.1 Very often in diagnostics of small rodents live animals are submitted to the laboratory for testing. The manner of transport and, if applicable, housing of these animals may influence the outcome of the testing. In addition animal welfare aspects must be taken into consideration.

11.2 When shipping live animals, national and international laws and regulations have to be observed. Animals should be transported in closed, escape-proof, container which protect the animals as much as possible from outside influences. Sufficient ventilation must be provided through adequately sized openings which are covered by filter material to prevent the entry of additional microorganisms during transport. Shipping conditions should ensure that the animals arrive at the laboratory in fit condition. Notably the animals should not suffer from food or water deprivation or from injuries due to transportation, since this may influence the results of the testing.

11.3 Live animals should not be housed in the testing laboratory itself. If they are not euthanized upon arrival they have to be housed in a designated animal room to prevent cross-contamination between animals and testing procedures in the laboratory. Housing conditions must comply with national regulations. Housing conditions should ensure that the animals remain fit and there is no interference with the subsequent testing. Notably animals must be housed in containment (e.g. filter top cages, isolators, ventilated cubicles) to prevent cross-infection between animals from different origins. If a laboratory is only doing serology, animals may be kept without containment for up to five days.

11.4 Live animals must be euthanized prior to necropsy using a method approved by the European Commission 'Recommendations for euthanasia of experimental animals'.

11.5 Sampling activities outside the laboratory are not directly covered by EN 45001 or ISO Guide 25. However, microbial flora may be sensitive to factors like temperature or duration of storage and transport, so it is important to check and record the condition of the sample on receipt by the laboratory.

11.6 The laboratory should have a procedure that covers the delivery of samples. If there is an insufficient sample or the sample is in poor condition due to physical deterioration, incorrect temperature, torn packaging or deficient labelling, the laboratory should either refuse the sample or (if it is possible to carry out the work) should indicate the condition on the test report.

11.7 The following information should be noted:

(a) a unique unambiguous identification that can be used to trace the sample from receipt to the end of the analytical process;
(b) date and, where relevant, the time of receipt;

(c) identity of person/organization providing sample for test;
(d) sample identification number from the sampler (if any);
(e) nature and characteristics of the sample;
(f) list of tests required, and, as far as is necessary;
(g) temperature and condition of the sample on receipt;
(h) characteristics of the sampling operation (sampling date, sampling conditions etc.).

11.8 Samples awaiting test shall be stored under suitable conditions to minimize any modifications to any microbial population present.

11.9 The packaging and labels from samples may be highly contaminated and should be handled and stored with care so as to avoid any spread of contamination.

11.10 The preparation of the laboratory sample and the test portion should follow the national or international standards specific to the tested products (if available) and the general guidance given in ISO 6887 and ISO 7218.

11.11 Sample preparation may simply involve stirring a sample and measuring an aliquot (e.g. liquids) or may require a multi-stage reconstitution and sub-culturing (e.g. dried products). In either case the laboratory should be able to demonstrate that:

(a) the test portion is as representative of the product as possible (when relevant) and suitable for analysis;
(b) contamination of the test portion and the environment has been avoided (see Section 4).

11.12 A procedure for the retention and disposal of samples shall be written. Laboratory sample portions that are known to be highly contaminated shall be decontaminated prior to being discarded. They should be stored until the test results are obtained, or longer if necessary.

12 Disposal of contaminated waste

12.1 The correct disposal of contaminated materials may not directly affect the quality of sample analysis, however it is a matter of good laboratory management and should conform to national/international environmental or health and safety regulations (see also IS0 7218).

13 Uncertainty of measurement

13.1 The international definition for uncertainty of measurement is given in ISO international vocabulary of basic and general terms in metrology: 1993.

13.2 It is recognized that the current state of knowledge regarding uncertainty of measurement across the full range of microbiological disciplines is variable. For this reason, laboratories may not currently have access to appropriate guidance on estimating uncertainty of measurement in their particular discipline. This situation is currently being addressed within the laboratory community and it is expected that more clearly defined guidance in the field of microbiology will be available in future. However, repeatability and reproducibility data are components of uncertainty of measurement and should be determined as a first step towards producing estimates of this parameter.

13.3 Uncertainty of measurement may be provided as follows:

- **Pathology:**
  - The personal conviction of the person reading the slide as to the correctness of the diagnosis.
- **Serology:**
  - The specificity and sensitivity of the assay as determined by the validation procedure.
- **Bacteriological culture:**
  - Probability of identification as provided by commercial test systems such as panels of biochemical tests for identification.
  - Profiling of chemotaxonomic characteristics (e.g. gas chromatographic cell wall lipid profiling by an automated

microbial identification system, giving a similarity value between 0.0–0.999)

13.4 The basic principles are described in a soon-to-be-released document issued by EAL.

14 Use of computers

(EN 45001, paragraphs 5.3.3 and 5.4; ISO Guide 25, paragraph 10.7)

14.1 Where well established software is used for the purpose of communication or analytical work, no particular validation is necessary.

14.2 Where in-house software is used, complete documentation for validation purposes must be provided. Furthermore, it must be shown that loss or corruption of data does not occur.

14.3 Where software is updated, a record of the revisions must be retained.

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Appendix A
Guidance on calibration and calibration checks

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

Type of equipment	Requirement	Suggested frequency
Reference thermometers & reference thermocouples	Full traceable re-calibration Single point (e.g. ice-point check)	Every 5 years Annually
Working thermometers & working thermocouples	Check against reference thermometer at ice point and/or working temperature range	Annually
Balances	Full traceable calibration	Annually
Photometers	Traceable calibration	Annually
Thermocyclers	Traceable calibration	Annually
Calibration weights	Full traceable calibration	Bi-annually or annually, depending on class
Check weight(s)	Check against calibrated weight or check on balance immediately following traceable calibration	Annually
Timers	Check against national time signal	Annually
Volumetric glassware	Gravimetric calibration to required tolerance	Annually
Microscopes	Traceable calibration of stage micrometer	Initially
Hygrometers	Traceable calibration	Annually

Appendix B
Guidance on commissioning and verification of performance

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

Type of equipment	Requirement	Suggested frequency
Temperature controlled equipment (incubators, baths, fridges, freezers)	(a) Establish stability and uniformity of temperature	(a) Initially, and after repair/modification
	(b) Monitor temperature	(b) Daily/each use
Sterilizing ovens	(a) Establish stability and uniformity of temperature	(a) Initially, and after repair/modification
	(b) Monitor temperature	(b) Each use
Autoclaves	(a) Establish characteristics for typical loads/cycles	(a) Initially, and after repair/modification
	(b) Monitor temperature/time	(b) Each use
Safety cabinets	(a) Establish performance	(a) Initially, and after repair/modification
	(b) Particle count and airflow monitoring	(b) Every 6 months
Laminar airflow cabinets	(a) Establish performance	(a) Initially, and after repair/modification
	(b) Check with sterility plates	(b) Every 6 months
Thermocyclers	Monitor temperature/time	Each use
Microscopes	Check alignment	Daily/each use
pH meters	Calibration check using at least two buffers	Daily/each use
Balances	Check zero, and reading against check weight	Daily/each use
Stills, de-ionizers and reverse osmosis units	(a) Check conductivity	(a) Daily
	(b) Check for microbial contamination	(b) Monthly
Gravimetric diluters	(a) Check weight and volume (weight) dispensed	(a) Daily
	(b) Check dilution ratio	(b) Monthly
Media dispensers	Check volume dispensed	Daily/each use/each adjustment
Pipettors/pipettes	Check accuracy and precision of volume dispensed	Regularly (to be defined by taking account of the frequency and nature of use)
Spiral platers	(a) Establish performance against conventional method	(a) initially and annually
	(b) Check stylus condition and the start and end points	(b) Daily/each use
	(c) Check volume dispensed	(c) Monthly
Colony counters	Check against number counted manually	Annually
Anaerobic jars/incubators	Check with anaerobic indicator	Each use
Laboratory environment	Monitor for airborne and surface microbial contamination using, e.g. air samplers, settle plates, contact plates or swabs	Every 6 months

Appendix C
Guidance on maintenance of equipment

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

Type of equipment	Requirement	Suggested frequency
Incubators, fridges, freezers, ovens	Clean and disinfect internal surfaces	Monthly
Water baths	Empty, clean, disinfect and refill	Monthly, or every 6 months if biocide is used
Centrifuges	(a) Service (b) Clean and disinfect	(a) Annually (b) Each use
Autoclaves	(a) Make visual checks of gasket, clean/drain chamber (b) Full service (c) Safety check of pressure vessel	(a) Regularly, as recommended by manufacturer (b) Annually (c) Annually
Safety cabinets	Full service and mechanical check	Every six months
Laminar flow cabinets	Service and mechanical check	As recommended by manufacturer
Microscopes	(a) Clean, and full maintenance service (b) Check eye-piece graticule	(a) Annually (b) Annually
Photometers	Service	Annually
Thermocyclers	Service	Annually
pH meters	Clean electrode	Each use
Balances, gravimetric diluter	(a) Clean (b) Service	(a) Each use (b) Annually
Stills	Clean and de-scale	As required (e.g. every 3 months)
De-ionizers, reverse osmosis units	Replace cartridge/membrane	As recommended by manufacturer
Anaerobic jars	Clean/disinfect	After each use
Media dispensers, volumetric equipment, pipettes, and general service equipment	Decontaminate, clean and sterilize as appropriate	Each use
Pipettors, multi-channel pipettors, multi-step pipettors Spiral platers	(a) Decontaminate and clean (b) Service (a) Service (b) Decontaminate, clean and sterilise	(a) Each use (b) Annually (a) Annually (b) Each use
Laboratory	(a) Clean and disinfect working surfaces (b) Clean and disinfect floors, sinks and basins (c) Clean and disinfect other surfaces	(a) Daily, and during use (b) Weekly (c) Every 3 months