Report of the FELASA Working Group on evaluation of quality systems for animal units

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Summary

This report compares and considers the merits of existing, internationally available quality management systems suitable for implementation in experimental animal facilities. These are: the Good Laboratory Practice Guidelines, ISO 9000:2000 (International Organization for Standardization) and AAALAC International (Association for Assessment and Accreditation of Laboratory Animal Care International). Good laboratory practice (GLP) is a legal requirement for institutions undertaking non-clinical health and environmental studies for the purpose of registering or licensing for use and which have to be 'GLP-compliant'. GLP guidelines are often only relevant for and obtainable by those institutions. ISO is primarily an external business standard, which provides a management tool to master and optimize a business activity; it aims to implement and enhance 'customer satisfaction'. AAALAC is primarily a peer-reviewed system of accreditation which evaluates the organization and procedures in programmes of animal care and use to ensure the appropriate use of animals, safeguard animal well-being (ensuring state-of-the-art housing, management, procedural techniques, etc.) as well as the management of health and safety of staff. Management needs to determine, on the basis of a facility's specific goals, whether benefits would arise from the introduction of a quality system and, if so, which system is most appropriate. The successful introduction of a quality system confers peer-recognition against an independent standard, thereby providing assurance of standards of animal care and use, improving the quality of animal studies, and contributing to the three Rs—reduction, refinement and replacement.

Keywords Quality; quality system; management; animal unit; animal care; accreditation

The remit of the Working Group was to examine quality and welfare standards for the certification and accreditation of academic or commercial laboratory animal facilities. It is hoped that this will provide guidance on how to select, employ and adapt available accreditation/certification schemes. There are currently several different quality standards which have evolved for specific applications. From one viewpoint these standards embrace a common set of principles, but they appear to differ with regard to the level of

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Accepted 16 October 2003

application-specific interpretation and language that each has acquired.

Probably all facilities at which animals are kept and/or used for scientific purposes are subject to judgement against pre-defined standards, if only to meet national or supranational legislative requirements. An increasing number of facilities are seeking to progress beyond minimal standards and to benchmark the provision by reference to an external standard. A poll by the British Association for Research Quality Assurance in 1999 established that more than half of establishments which had implemented a quality management system considered that it had been a success, when judged on the basis of the impact on documentation, completion and successful training (BARQA, Newsletter 2001).

There is, in consequence, an interest in identifying the particular strengths and weaknesses of different schemes insofar as these relate to laboratory animal science, and, in some cases, to determining whether opportunities exist for harmonization. Areas that are not currently covered by Quality Assurance (QA) standards, cannot provide these opportunities for harmonization. However, the focus of this review is to identify key areas which are covered by existing schemes rather than to propose modifications to the scope or administration of schemes which already exist.

The International Organization for Standardization (ISO) has defined quality as '*the totality of characteristics of an entity that bear on its ability to satisfy stated and implied needs*' (ISO 8402, 1994). The Working Group defined quality as being '*a high standard of performance*', as there was a need for a working definition suitable for evaluating the various quality systems available for animal units. As such, quality systems can be regarded as management tools which provide a means of improving the consistency or effectiveness with which tasks are carried out, thereby benefiting animal studies and researchers. This can be done on a voluntary basis but, in the case of GLP, regulatory requirements are not optional for organizations seeking or planning to seek pre-market approval for products being developed or tested in animals. In the ideal situation a quality system should benefit the animals and their welfare as well. The achievement of a quality standard may also motivate and satisfy personnel and management and may provide reassurance to clients and to the general public.

This paper considers the three most widely used QA schemes applied to laboratory animal facilities in FELASA (Federation of European Laboratory Animal Science Associations) member states:

- Accreditation by the Association for Accreditation of Laboratory Animal Care (AAALAC International)
- Good Laboratory Practice (GLP)
- International Standardization Organization ISO 9000:2000

AAALAC International

The Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International, http://www.aaalac.org/) was founded in 1965 and has conducted a voluntary accreditation programme for laboratory animals for nearly 40 years.

The origins of the programme can be traced to the Animal Care Panel (ACP)—a forum which emerged in the US for exchanging information on the care of laboratory animals. In December 1957, an ACP Committee produced a report addressing the issues of an accreditation programme and in 1960 an Animal Facilities Certification Board (AFCB) was established to determine professional standards for laboratory animal care and develop an accreditation programme.

In 1964, this Board submitted a detailed proposal entitled 'Accreditation of Laboratory Animal Facilities and Care' and this formed the basis for a national, voluntary programme of accreditation of animal care programmes. In the following year the American Association for Accreditation of Laboratory Animal Care was established. Initially, financial support was provided by some of the member

organizations, which comprised a Board of Trustees. In 1996, the Association changed its name to the 'Association for Assessment and Accreditation of Laboratory Animal Care International' (AAALAC International), reflecting the organization's scope of activities in other countries. It remains a private, non-profit organization, the mission of which is to promote high standards of animal care, use and well-being, and to enhance the life sciences, research, testing and education. At present, over 650 companies, universities, hospitals, government agencies and research institutions in 18 different countries have earned AAALAC accreditation.

AAALAC International is a voluntary, non-profit corporation, the activities of which are overseen by a Board of Trustees comprising representatives from more than 60 scientific, professional, educational and patient advocacy societies; these include ICLAS (International Council for Laboratory Animal Science) and FELASA, and several international scientific societies. The accreditation scheme is overseen by the 32-member 'Council on Accreditation'—from the US (30) and Europe (2); this consists of highly-qualified individuals, knowledgeable about laboratory animal programme and management issues. Members of Council are appointed by the AAALAC International Board of Trustees and serve for 3 years. *Ad hoc* consultants with veterinary, research and administrative backgrounds and from around the world, may be recommended by the scientific community and are appointed by the Council for 3-year terms; they assist Council members with site visits.

An important function of the accreditation process is to provide an opportunity for the self-assessment of animal programmes. Independent peer review helps facilities to highlight strengths and identify potential weaknesses of its programme. Accreditation provides programme managers, and institutional ethical or care and use committees, with a means of demonstrating the quality of their operational performance, and ensures that researchers provide the highest quality of care for animals and that the three Rs are considered and implemented. Accreditation is particularly valuable in situations where there is no national legislation as it provides a ready-made standard which is internationally recognized. It is also of benefit to institutions engaging in international collaborations (e.g. universities), multinational corporations and contract research organizations with a multinational clientele.

AAALAC International accredits animal care and use programmes throughout the world. It also serves as a valuable resource for information on laboratory animal issues and emerging trends in animal care and use. Within the US, the organization also assists accredited units by interpreting the Guide for the Care and Use of Laboratory Animals (National Research Council (NRC) 1996) and apprising programme managers of changes in federal regulations. Accreditation is open to any private or public institution, organization, or agency maintaining, importing, breeding, or using animals in research, teaching, and testing. Such facilities must maintain an active animal care and use programme. Accredited units may vary in size and complexity—from small laboratories to large multi-site programmes, using farm animals, exotic and traditional laboratory species.

The accreditation system operated by AAALAC International relies on the Guide for the Care and Use of Laboratory Animals (NRC 1996) as its primary standard for evaluating laboratory animal care and use programmes, as well as regulations and standards of the institution's country. The Guide has been translated into seven languages. The principles of the Guide are outcome-based, and their interpretation allows for the use of sound professional judgement in the interpretation of performance standards. If a programme deviates from the standards of the Guide, there must be compelling reasons with strong rationales for this to be acceptable, although full account is taken of local legislation and other regulatory requirements.

The Council on Accreditation also uses a number of 'Reference Resources' when

evaluating animal care and use programmes including the OECD guidelines on humane endpoints, the UKCCR guidelines for the welfare of animals in experimental neoplasia and the EFPIA and ECVAM guidelines on the administration of substances and removal of blood. These resources also refer to other speciality publications for supplemental information about procedures or techniques related to the care and use of laboratory animals. All vertebrate animals used or to be used in research, teaching or testing at facilities seeking accreditation are included in such evaluations. This includes traditional laboratory animals, farm animals, wildlife, and aquatic animals.

The management of an animal facility which wishes to apply for accreditation must compile a dossier of information which fully describes the characteristics of the facility and its management processes. The content and layout of this dossier (the Programme Description) is specified in some detail in an application package available from the AAALAC International office. The Programme Description is used as a guide by the site visit team to evaluate both the programme and facilities. This document is the first step in the accreditation process and is retained subsequently as a resource document.

After submission of an application, the AAALAC International office reviews the dossier to ensure that it meets AAALAC's criteria, and a fee is requested (in North America and Europe) based on the size of the animal facility to cover the costs associated with the site visit. Following this, a site-visit team, comprising two or more AAALAC representatives, is appointed and arranges to review the establishment's animal care and use programme. This includes a visit, the duration of which depends on the size and complexity of the unit and which is conducted by a Member of Council and at least one *ad hoc* consultant. The expertise of the site-visit team is customized to match the needs of the institution (animal species, research mission, language, etc.). Revisits are scheduled at 3-year intervals and an annual report that reflects changes in the programme is required.

Having reviewed the written application, the site-visit team assesses the practices of the institution against the principles of the Guide for the Care and Use of Laboratory Animals (NRC 1996), taking account of local regulatory requirements. A list of additional published sources describing accepted practices is available from the AAALAC International website (http:www.aaalac.org). Site visits commence with an in-briefing, during which members of the facility seeking accreditation meet with the site-visit team to discuss the accreditation process.

After the in-briefing, the site-visit team discusses the Programme Description with institutional representatives. This provides team members with an opportunity to ask specific questions or request additional documents for review. Next, the team tours the facility. Typically, members of the animal care and use or ethical committee are interviewed at some point to determine the committee's activities and other pertinent issues. After the tour, the team may seek additional information on specific protocols or procedures.

The site-visit team then holds a private review session, during which key observations are discussed and a preliminary view established of matters which require additional scrutiny. This is followed by an exit briefing open to all members of the institution. During the exit briefing, the team outlines key findings (as mandatory issues and/or suggestions for improvement), and in some cases may indicate the proposed recommendation to the Council regarding accreditation status. The briefing provides immediate feedback, affords an opportunity to clarify concerns, discuss issues and, where necessary, allows opportunities for correction of deficiencies in advance of submitting the written report to the Council.

Following the visit, site visitors prepare a written report. Other Council members review this and may comment in relation to the Programme Description, before the report is submitted to the next meeting of

the Council on Accreditation. Final decisions regarding accreditation are made by the Council, which meets three times annually (January, May and September). Site-visit reports are considered during the first Council meeting following the visit. During the meeting, the Council member who participated in the site visit describes the programme, shares observations concerning the facility and other programme elements, and serves as an advocate for the organization. Based on the discussion that follows, the organization is notified in writing of its accreditation status, usually within one to two months following the Council meeting. Everyone involved in the accreditation process, including the Board of Trustees, Council members, *ad hoc* consultants/specialists and staff representing AAALAC International, are required to treat all materials they encounter as confidential.

Facilities are given every opportunity to achieve and maintain full accreditation. Categories of accreditation allow flexibility for maintaining accreditation while correcting deficiencies. Most deficiencies noted during site visits can be corrected in a short period of time. Deficiencies rarely pose serious threats to accreditation status. Revocation of accreditation occurs, but is uncommon.

For institutions that apply for the first time, these are the following possible outcomes of the accreditation process:

- *Award full accreditation*
  New applicants with animal care and use programmes that conform with AAALAC International standards are awarded full accreditation.
- *Award accreditation with condition*
  The institution is accredited, but correction of the mandatory item(s) are to be reported in the next annual report or at the discretion of the Council.
- *Award provisional status*
  New applicants that do not meet AAALAC International standards but, in the opinion of the Council, have deficiencies that can be corrected within a period not longer than 24 months, are awarded provisional status. Facilities having a provisional status actively participate in the AAALAC International accreditation programme, but are not considered AAALAC accredited. At the conclusion of the provisional period, the unit must either achieve accreditation or accreditation is withheld.
- *Withhold accreditation*
  Accreditation is withheld from a new applicant if, in the opinion of the Council, deficiencies in the animal care and use programme are so extensive that there is little likelihood that accreditation could be achieved within 24 months. Such deficiencies may involve major programme issues and/or concerns over the physical plant. The institution has the opportunity to appeal this decision.

For accredited institutions these are the following outcome possibilities:

- *Continued full accreditation*
  Following a site revisit, accredited units that continue to conform with AAALAC International standards are awarded continued full accreditation.
- *Conditional accreditation*
  The institution is accredited, but correction of mandatory item(s) is to be reported in the next annual report or at the discretion of the Council.
- *Deferred accreditation*
  If the site revisit to a fully accredited unit reveals serious but short-term, correctable deficiencies in its animal care and use programme, continued full accreditation is deferred. While maintaining accreditation, a 2-month period is allowed for fully correcting deficiencies identified in the written report. Unsatisfactory or non-correction of the identified deficiencies in the allotted time will result in probationary accreditation for a period of 6 months from the date of deferred continued accreditation.
- *Probation*
  A fully accredited unit is placed on probation if the site revisit reveals that serious but correctable deficiencies have developed or at the end of the deferred

continued accreditation period. Probationary periods may be up to 12 months to allow time to fully correct deficiencies. In case adequate correction of the mandatory item(s) is not achieved within the allotted time, proceedings to revoke accreditation are initiated.

- *Revoke accreditation*
  At the time of a site revisit or at the end of a probationary period, accreditation may be revoked if serious deficiencies in the animal care and use programme are discovered. Revocation of accreditation may be appealed to the Council on Accreditation and the Board of Trustees. The institution remains accredited during the appeal process. Should the institution's appeal be unsuccessful, then it will no longer be accredited.

Institutions awarded accreditation by AAALAC International must submit a report each year and notify any significant changes to the programme or the facility as they occur. The annual report should include information on current staffing, and explain any changes made to the animal care and use programme during the previous year. To maintain accreditation, additional site visits take place every 3 years and follow the same process described above.

Good Laboratory Practice (GLP)

The concept of GLP was established in 1978 in order to promote the quality and validity of test data used for determining the safety of chemicals and chemical products. It is concerned with the organizational process and the conditions under which laboratory studies are planned, performed, monitored, recorded and reported, and provides a means of assuring the quality and integrity of research (safety) data by guaranteeing the ability to conduct a retrospective check on these data.

Good laboratory practice was introduced in response to procedural irregularities identified at several pharmaceutical testing companies in the mid 1970s. The Food and Drug Administration of the USA subsequently introduced regulations governing the conduct of safety tests on certain products (www.fda.gov, Code of Federal Regulations, 21 CFR part 58), designed to ensure that studies were carefully conducted and reported so that governments can arrive at sound regulatory decisions. The primary objective of the Organization for Economic Co-operation and Development (OECD) Principles of GLP is to ensure the generation of high-quality and reliable test data related to the safety of industrial chemical substances and preparations in the framework of harmonizing testing procedures for the mutual acceptance of data (www.oecd.org/env/glp). The regulations can be applied by facilities undertaking non-clinical health and environmental safety studies, for the purpose of registering or licensing for use, like pharmaceuticals, pesticides, veterinary drug products and similar products and industrial chemicals. The application of GLP to such studies enables the findings to be used by national regulatory authorities for the purpose of hazard and risk assessments. Test data generated in a participating country in accordance with OECD Test Guidelines and the Principles of Good Laboratory Practice must be accepted by other OECD member countries for purposes relating to the protection of man and the environment. Not only does this constitute national and international harmonization and standardization, but it also provides a means of avoiding repetition of regulatory studies involving animals and therefore contributes to the three Rs.

The OECD comprises 30 member countries, committed to democratic government and the market economy. It plays a role in fostering good management in both public and in business sectors and helps governments to ensure their responsiveness to key economic areas. It provides a framework for developing policies to produce international agreements and other measures to promote free trade. The basic document describing GLP is 'The OECD Principles of Good Laboratory Practice', published by the Organization's Environment Directorate; this document was most recently revised in 1998. The OECD is governed by a council

which consists of representatives of member countries; it oversees the work of the Organization's committees and decides on the annual budget. The Working Group on GLP oversees GLP and compliance monitoring and provides a forum for international liaison among the countries concerned. It has been responsible for the publication of a series of documents related to specific aspects of GLP and compliance monitoring.

The European Community (Article 1.1 of Council Directive 87/18/EEC 1986) adopted the GLP principles published by the Organization for Economic Co-operation and Development in 1982. An OECD Expert Group is working on a revised version of the Principles of GLP and once this has been completed, the revised set of principles will be presented to the OECD Council for adoption. It is anticipated that the European Community will then endorse them. Compliance with the Principles of GLP in laboratories, including those involved in the health and environmental safety testing of pharmaceuticals, agrochemicals, cosmetics and food additives is the responsibility of National Authorities. In the United States, the Environmental Protection Agency (www.epa.gov) and the Food and Drug Administration have developed separate GLP standards. Other national monitoring authorities issue their own versions of GLP but these are based on OECD principles.

Good laboratory practice is a process-oriented, study-based approach to assure the quality of an organization's management, including personnel, levels of competence, the provision and operation of facilities, equipment, test and control articles, and the conditions under which non-clinical studies are planned, performed, recorded, archived and reported. The study director has ultimate responsibility for the overall scientific conduct of studies and compliance with regulations. The standard requires description of the premises, equipment and organizational structure in all parts of the institution which are involved in the type of study concerned to be declared in compliance with the OECD Principles of GLP. When the use of animals is involved the organization of the animal facility is included. The regulations contain 144 requirements, some of which are quite prescriptive about the manner in which studies are carried out. There is particular emphasis on the role of the study director (and any principal investigators), the role of the QA unit, the documenting of standard operating procedures (SOPs), the content of study plans (protocols) and reports, and the way in which data related to each study are generated and archived.

The key focus of GLP is the scientific process, and in particular, the study protocol. The standard is not concerned with the technical validity of studies nor specifically with animal welfare, but rather with the rigour with which they are conducted. In consequence, the result of a GLP study is not required to have an outcome which satisfies the customer's aspirations. For example, a tested substance can be shown to be toxic, even though this was not the result which the customer hoped for. Moreover, considerable emphasis is placed on confidentiality, mainly because most GLP studies are concerned with pre-clinical investigations or safety testing and can be commercially sensitive.

The Principles of GLP do not apply to clinical studies (including pharmacokinetic and efficacy studies), which are covered by various other good practice codes such as Good Clinical (Research) Practice or Good Manufacturing Practice. However, some registration authorities, such as the Food and Drug Administration in USA, require proof of the quality of test data obtained from clinical studies before they will permit registration.

The manager of each test facility is responsible for ensuring compliance with the Principles of GLP and for preparing a statement identifying person(s) who fulfil the responsibilities of management. GLP also defines closely the attributes of people involved in the studies, such as their curriculum vitae (CV), job description, training, etc. The manager must ensure that there are sufficient qualified and competent personnel, appropriate facilities, equipment, and materials for the timely and proper conduct of the study.

Management is also required to keep a master schedule, which lists studies recently completed or in progress, so that if the laboratory were to be disqualified, suspect studies could be immediately identified.

Test facilities should be of adequate size, construction and location for the requirements of studies and so managed as to minimize interference with their validity. Apparatus used to generate, store and retrieve data, and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity. It should be periodically inspected, cleaned, maintained, and calibrated according to SOPs. The receipt, handling, sampling and storage of test and reference items, including food, litter materials, medicines and test compounds must be documented to record their identity, the dates of receipt and expiry, quantities received and used and specific storage instructions.

Managers of test facilities are required to approve written SOPs to ensure the quality of data generated. SOPs should be periodically reviewed and updated where appropriate; any changes must be authorized. Each separate test facility unit or area should make accessible current SOPs relating to activities performed there; and these may be supplemented by textbooks, analytical methods, articles and manuals. This is a good point for GLP, because the standard requires provision of closely defined conditions for the sourcing, housing, handling and care of test animals and for the maintenance of equipment, veterinary care, etc. All processes must be rigorously defined in specific SOPs. The disadvantage of this degree of precision is the need to provide a secure audit trail of activities, which may slow procedures and adversely affect productivity. All documents must be subject to periodic audit, which is often perceived as very bureaucratic.

Each investigation is overseen by a study director, who is the single point of study control, responsible for its overall conduct and for reporting the outcomes, in accordance with a study plan. The study director should approve this plan prior to initiation of the study; it must be verified for GLP compliance by QA personnel and may also need to be approved by the manager of the test facility and possibly by the sponsor. The report prepared on completion of each study is signed and dated by the study director to indicate compliance with these Principles of GLP and to show that he or she accepts responsibility for the validity of the data. The following should be retained in the archives for an appropriate period: the study plan, raw data, samples of test and reference items, specimens, and the final report of each study.

In multi-site studies, a principal investigator has to be appointed for each test site to ensure that each phase of the study that is not under direct supervision of the study director is appropriately conducted and that all those involved in its conduct understand the relevant parts of the Principles of GLP. Although the study director does not have all phases of the study in a multi-site study under his/her direct supervision, he or she remains responsible for all phases of the study. The same goes for the QA aspects of a multi-site study. Study personnel must have access to the study plan, study amendments and appropriate SOPs, and must comply with the instructions given in these documents. Any deviation from these instructions should be documented and communicated directly to the study director.

In addition, each test facility must have a documented QA programme to provide assurance that studies are performed in accordance with GLP. The underlying characteristic of GLP is the ability to fully audit scientific investigations. The programme is implemented by an individual or by individuals familiar with the test procedures and designated by and directly responsible to management. These QA personnel conduct inspections to determine that study plans and SOPs are being followed by study personnel and that studies are conducted in accordance with the Principles of GLP. This periodic examination of evidence relating to conduct of studies is one of the strongest characteristics of GLP as it guarantees the rigour with which the

study was conducted. The disadvantage is that the implementation of assurance requires a great deal of documentation; and this is often based on paperwork and so is very demanding of both time and personnel. Compliance with GLP ensures that investigations are conducted to a high level of quality. Also, because GLP requires compliance with the national law, it addresses the issue of animal welfare, at least to the minimum which that law requires. Environmental enrichment is also possible within GLP studies, provided that a sound scientific justification is given, such as the provision of certificates of analyses which indicate that no interference with the experimental results is likely to occur. The cost of the endorsement of compliance itself is very low.

A facility seeking recognition for compliance with the OECD Principles of GLP applies to the National Authority, identifying the proposed scope of the accreditation, for example the types of investigations to be conducted. At least one GLP compliant study must have been completed prior to the initial assessment, to enable audit of completed studies. There are two categories of award—full membership and prospective membership. Prospective membership is granted once an applicant has informed the National Authority of the intention to conduct safety studies at particular premises. The Authority inspects the laboratory within 12 weeks and full membership may then be confirmed or withheld. This assessment is done to determine compliance with the principles.

There are several different types of inspection:

- A GLP inspection which is undertaken periodically (generally once every 2 years) to determine a laboratory's compliance; it includes examination of ongoing studies as well as completed studies;
- A data audit to verify that information contained in a final report is accurate and reflected by the raw data;
- A directed inspection which is any inspection conducted where there is a likelihood of non-compliance, for example following submission of questionable data in a final report, tips from informers, etc.;
- A follow-up inspection, made after a GLP inspection has revealed shortcomings. Its purpose is to assure that proper corrective actions have been taken.

If inspection reveals areas of non-compliances, a written notice is presented at the time, or occasionally subsequently. The issues identified are discussed with the laboratory management, at which stage the management can either agree or disagree and can propose possible corrective actions. Alternatively, the management may respond after it has had sufficient time to properly study the report. A follow-up inspection will be arranged to ensure that appropriate changes have been introduced.

ISO 9000:2000

Following a meeting in London in 1946, delegates from 25 countries decided to create a new international organization to facilitate international coordination and unification of industrial standards. The new organization, ISO, commenced operation in 1947 and the first ISO standard was published in 1951. The name is taken from the Greek *isos*, meaning 'equal'. There are now many ISO standards, covering all technical fields except electrical and electronic engineering. All standards are reviewed at least every 5 years to determine whether they should be confirmed, revised or withdrawn.

The International Organization for Standardization is a non-governmental, worldwide organization of national standard bodies from about 140 countries, each of which nominates a member body which represents national approaches to standardization. Only one such body for each country is accepted for membership of ISO. The Organization's mission is to promote the development of standardization and related activities so as to help international trade, and to promote cooperation in intellectual, scientific, technological and economic activities.

The activities of ISO are governed by a Council, consisting of Officers and 18 elected member bodies. There is also a General Assembly, constituted by a meeting of the Officers and delegates nominated by the member bodies. It generally meets once a year.

ISO 9000 was introduced to provide a framework for organizations to improve products or services which they provide. Following a period of worldwide consultation, a Committee of Council published in December 2000, a proposal for changes to the ISO 9000 standard. ISO 9000:2000 describes the fundamentals and vocabulary of the quality management system and ISO 9001:2000 describes the requirements of the quality management system and addresses customer satisfaction. ISO 9004:2000 provides guidelines for performance improvements. In particular, the Committee had argued that the standard should be easier to use and it should be compatible with other management systems (e.g. Business Process Re-engineering, etc). A new emphasis on continuous improvement was envisaged, with the standard structured to reflect 'processes' rather than outcomes. This new scheme requires establishment of a quality management system, demonstrable customer focus, effective management of resources and enhanced product realization, analysis and improvement. Management must monitor and track improvements, focusing on the purpose of the process, the possible impact of failure and the needs of customers. For example, the emphasis is now upon ensuring that staff are suitably trained to conduct processes which affects the quality of what they perform, rather than relying on regular reference to written procedures. The key to raising standards is considered to be a formal training system, based on the previous experience and/or training and competence of staff and the abilities required to accomplish the various tasks within the organization. Management should ascertain and record the previous experience, competencies and/or training of staff and determine the abilities necessary to accomplish the various tasks within the organization. Account should also be taken of any proposed changes to operations which may involve a requirement for new skills (new equipment, new products, etc.). By combining these assessments, it is possible to determine a programme for further training, which will ensure that staff are able to conduct the required tasks. Records should be maintained of any training provided, whether on-the-job, in-house or external courses, etc. The level of competence required depends on the risk assessment of the impact of failure of the process. Job design is required to ensure that there are motivated people in clearly defined jobs.

The new ISO standard—9000:2000—now focuses on actions which the organization takes to enhance customer satisfaction, to improve efficiency, to meet regulatory requirements and continually to improve performance in these respects. This includes developing and enhancing processes for the care of animals, provision of services, purchasing activities, staff training, improvement of operational processes, etc. In other words ISO 9000:2000 certification is concerned with 'quality management'. It is based on eight quality management principles: customer focus, leadership, involvement of people, process approval, a systematic approach to management, continual improvement, a factual approach to decision making and the establishment of mutually beneficial supplier relationships. The first thing to be done when applying the standards to an existing management system is the analysis of the current status of the facility with respect to these indicators so as to identify any gaps between the current system and the requirements of ISO 9000:2000. An ISO certified facility must have a defined organizational structure, within which the authorities and responsibilities of individuals are clearly laid down. Managers must identify which processes are needed to supply products to the facility's customers and must determine how much each is influenced by the existing quality management system. These may include processes related to customers (e.g. those to whom the animals or services are supplied), breeding and/or husbandry or applied procedures, purchasing and sales arrangements,

etc. There may well be regular senior management meetings, etc. but the standard requires that at such meetings, problems are brought to the manager's attention and solutions are determined. These need not be considered individually—an analysis of trends may well be sufficient. After this, the solution is implemented and then the result is reviewed at the next meeting, where the matter can be dropped or further solutions determined.

Appropriate resources must be allocated, responsibilities assigned and a schedule established to implement the identified actions and track progress. In particular, arrangements must be made for periodic, objective review of procedures by an auditor appointed by management. ISO 9000:2000 provides guidance on auditing, auditor qualification and managing audit programmes. This procedure is known as internal quality auditing and must be conducted regularly and systematically by a person who is completely independent of the process being assessed. The auditor must establish whether activities being conducted accord with the description in the documented system, and are sufficient to meet the requirements of ISO. The findings are recorded and solutions to any problems are agreed by whoever is responsible for the activity in question. At an agreed time, a re-audit is conducted. Where problems are found, the documented system or the activity itself must be altered. Meetings of senior management are held regularly (e.g. each 3 or 6 months) at which recurring or intractable problems are considered and solutions determined. From this point onwards, the process of auditing, review, determination of changes and then re-audits followed by review, etc. is a never-ending cycle, which should lead to continual incremental improvements. After the processes required by the scheme have been operating for sufficient time, the activities must be inspected and certified by an independent certification body (e.g. Lloyds in UK) that inspects and certifies the unit. The assessor may recommend acceptance, may recommend changes which will facilitate compliance (when a further external audit will be necessary), or may refuse to recommend acceptance. It is important that the certification body is accredited according to the ISO/IEC Guide 62 by the government-approved national body, in order to assure that a high-quality assurance is provided. The International Electrotechnical Commission (IEC) is the leading global organization that prepares and publishes international standards for all electrical, electronic and related technologies (http://www.iec.ch). Joint ISO/IEC standards and guides for conformity assessment (process of evaluation and approval) encourage best practice and consistency when products, services, systems, processes and materials need to be evaluated against standards, regulations or other specifications.

Emphasis is placed on the effectiveness of management and on the monitoring and tracking of improvements throughout the production cycle, but the new ISO standard is less prescriptive than the old one in terms of documentation requirements. It may be sufficient to demonstrate that the process is robust and that the activity is driven by customer requirements. The determination of, and satisfaction of, customer needs must be central and the impact of possible failure must be assessed and minimized.

Much importance is attached to determining what customers require and expect, and then continually improving the system and products/services, so as to better meet their requirements. This prompts the organization to direct its energies to enhancing customer satisfaction, to meeting applicable regulatory requirements and continually monitoring and improving these. For example, this may include introducing strategies to raise standards of animal care, the provision of services, purchasing activities, and staff training, and to ensure customer (scientist) satisfaction.

Comparison of schemes

Each of the three schemes reviewed here offers recognition to an internationally recognized standard; in the case of

AAALAC, the need to accommodate different national regulatory frameworks may provide a little more flexibility than either of the other two schemes. All three schemes address issues relating to the training, performance and competence of staff, and conduct reviews with due consideration to the needs of confidentiality.

ISO 9000 has been available in Europe since 1951. GLP has been available since 1982. The first European organization was accredited by AAALAC in 1986.

The principal difference between the three schemes is the focus of the quality assurance process:

- AAALAC principally addresses the quality of the broad environment within which animal care and use takes place;
- GLP addresses the reliability and reproducibility of experimental data which is generated by the use of animals; and
- ISO 9000:2000 focuses on customers—the persons to whom the animals and their products or services are provided.

AAALAC accreditation is a statement that institutional policies and practices for the care and use of animals comply with recognized standards. The process of achieving accreditation requires demonstration of this fact to expert peer reviewers. In comparison with this, GLP requires detailed, formal documentation describing precisely how animals are cared for and how they will be used. Internal auditing arrangements must be in place and demonstrate that the processes described have been adhered to. Although there is considerable flexibility in identifying how tasks will be performed, it is generally recognized as being the most bureaucratically demanding of the three schemes. As subjectivity may be introduced by individual site visitors, the accreditation of the AAALAC scheme by the ISO/IEC Guide 65—as is done for farm assurance schemes in Europe and the US—may contribute to a high-quality standard accreditation process, although the review by the 32-Member Council already minimizes the risk that inconsistencies will occur. ISO 9000:2000 requires the facility to produce evidence that its business is conducted in such a way as to identify and enhance customer satisfaction. The customer here is not the animal itself but the person(s) who will use it or its products. GLP compliance is focused on a study, so that unless the animals held or bred in a facility are to be used for investigations to which GLP will be applied, the facility cannot be registered under GLP. In contrast, ISO 9000:2000 certification can be used to certify arrangements for the breeding and care of experimental animals regardless of their eventual use, and may be extended to include the scientific use of the animals. AAALAC accreditation does extend to animal care and use in research, and deals directly and specifically with animal welfare, in contrast to ISO and GLP.

Table 1 summarizes the principal characteristics of the three schemes and may prove helpful in allowing a facility to identify a scheme most appropriate for its requirements. There is of course no reason why a facility should only seek recognition under one quality standard, and one of the challenges of the future is to develop means by which the format of evidence presented for recognition against one standard can be made appropriate for recognition against the others.

Whichever scheme is introduced, it is likely that greater attention will be paid to procedures and practices and that this will contribute to the three Rs. It is likely too that greater clarity of what is expected from animal care staff and Category B persons (those carrying out animal experiments) and Category C persons (those responsible for directing animal experiments) will improve their performance and that improved training will offer greater job satisfaction and flexibility within the workplace. The AAALAC programme includes a specific focus on improved animal welfare conditions, and the reviewers are specialists in these fields. Therefore a better welfare assurance is expected to be obtained than by ISO and GLP certification. ISO is a business-oriented process, and as such it can be weighed whether the improvements in management processes will pay off against the costs in time and money to introduce ISO certification. GLP is mandatory when pre-market approval for

Table 1 Comparisons of the strengths and weaknesses of the various quality systems for animal units

	AAALAC	GLP	ISO 9000:2000
Subject	Strengths		
Principal focus	The animal care and use programme	The consistency of studies	The customer
Applicability	An animal facility alone can be accredited. Peer review of animal units	Details of studies for which GLP compliance is claimed are documented	Customer focused—i.e. business friendly. ISO standards are available for a wide range of businesses so the philosophy is transferable
Animal welfare and law	Heightens awareness of laboratory animal welfare globally. Where there is no existing law, the ILAR Guide is the minimum standard	GLP requires compliance with National law—animal welfare is assured to this extent	Meets regulatory requirements concerning animal welfare
External consideration	Well respected in institutions conducting experiments on live animals, including US agencies	Assures sponsors and regulatory bodies that work is rigorously carried out and documented	Gives customer confidence that quality is provided
Internal quality assurance	A facility manager can introduce it without seeking specialist assistance	Quality assurance unit is obligatory and leads to better consistency	Obliges internal review of the management system
Working processes	Support processes are reviewed	All steps in the process are described in SOPs and legal documents	Principally a management tool to ensure processes are coordinated and effective
Inspection	Site inspections are carried out by external visitors	External independent (government-appointed) inspectors	External inspectors
Direct costs	No costs except for the annual fee	Inspections are free of charge	Cost of certification is relatively low
Ongoing costs	Annual report, annual fee. Ongoing quality assurance reports and SOPs are not obligatory, so relatively inexpensive	Costs are associated with the QA unit and setting-up and maintaining SOPs; there is a continuing need for documentation (expensive)	No major expenditure required. Maintenance of an established accreditation is relatively cheap
Flexibility (1)	Flexibility towards local situation—if local legislation is more stringent than the ILAR-Guide, then that becomes the standard	Mandatory government requirement for certain studies. SOPs are prepared by the establishment and so can reflect its needs	Facility specifies its own procedures providing these raise overall performance
Flexibility (2)	Working standards can be changed whenever you wish, providing they meet the minimum defined standard	High-quality working standards may positively influence other, 'non-GLP' studies in the same unit	The need to retain and adhere to policy documents assures consistency of management. Facilities are encouraged to continually innovate and improve

(*Continued*)

Table 1 (*Continued*)

	AAALAC	GLP	ISO 9000:2000
Subject	Weaknesses		
Bureaucracy	It is necessary to describe and adhere to a detailed, programme description	Slowness of procedures due to the bureaucratic nature of the process. Needs for paperwork and confidentiality may make procedures appear rigid	There may be a large amount of paperwork at the beginning of the process, depending on the 'starting position'
Resources	High initial demands on time and resources, even if a different QA system is already in place. Less to maintain the system	High ongoing costs in terms of personnel and time. Animal care staff, analytical staff and directors are subordinated to the QA process	Once the system is in place, ongoing maintenance needs are minimal and principally address improvements
Standards and applicability	In some respects ILAR Guide standards differ from EU standards. Standards also differ between European countries. In all cases, the requirements of national legislation have to be met, although if the AAALAC standards exceed other requirements, the highest standard is applicable	A study-based system, not primarily directed at the animal facility. Animal facility can only be accredited as part of a larger establishment conducting regulatory work (e.g. pre-clinical safety studies) or as a CRO for in-life parts of studies	The customer and final product count, rather than the way the process works. The management framework is less rigidly defined, so operational standards are less critical than production settings
Subjectivity	Subjectivity may be introduced by individual site visitors; review by 32-Member Council minimizes inconsistencies	Each facility determines its own working practices but needs to ensure that these are audited. Approval is by the inspectors; policies may vary between countries	Provides no detailed guidelines for implementation. Variability between business types, certifying bodies and auditors, means that subjective differences may lead to inconsistencies in quality

products being developed and tested on animals is performed. In all these cases a considerable amount of hard work is necessary to achieve certification or accreditation; this will require clear communication and tactful handling of any resistance to the additional work-load by those who will be working with it. In the case of successful introduction and management, quality systems can be expected to lead to a more efficient organization with better guarantees for high-quality work and animal welfare in the long term.

Implementation of a scheme

The three QA schemes discussed here differ in very important respects. It is very unlikely that any one scheme will prove of equal value to all facilities affiliated to FELASA. ISO is primarily a business independent management tool—to master and optimize your business, aiming at implementing 'customer satisfaction'. AAALAC is primarily a peer-reviewed system which evaluates the organization and practices in a laboratory animal facility for adequate use of animals, safeguards for animal well-being ('state-of-the-art' housing, techniques, etc.) as well as health and safety risks to staff. AAALAC emphasizes the concept that quality animal care and use yields quality scientific data. GLP is a legally-defined system for institutes and companies which have to be 'GLP-compliant'. It is often relevant only for them. All people involved in the decision to

implement a quality management system must have a basic understanding of what is involved. Typically, when implementing a management system for the first time, senior management will take the initial implementation decisions—both the need to provide a degree of quality assurance and to decide which scheme(s) to adopt. However, a quality management system requires a backbone and structure, and responsibility for overseeing implementation may lie with a designated individual, such as the quality manager. In such cases, provision should be made for management back-up in the event of unforeseen circumstances.

Decisions on how to implement the chosen quality system will normally be made collectively by informed senior management, and their support must be retained throughout its introduction and eventual use. Implementation of the system will involve work by the staff themselves and therefore depends crucially on their knowledge and commitment. It is often necessary to delegate power and responsibility for particular tasks to lower management levels as this will help improve understanding and acceptance.

When starting to implement a quality system, management must be fully committed and must support and motivate personnel within the establishment. Throughout this process, it is important that all staff are familiar with the objectives and with the changes which may need to be made. Junior staff particularly, who will ultimately be required to implement any new measures, must understand them and feel personally involved with and committed to them. They may have concerns over the impact of these new tasks on their day-to-day job, and the personality of the QA officer is of utmost importance in working to help them overcome such fears. Responsibility must be placed firmly where it belongs and rewards may be offered as a means of stimulating competition between those involved in more routine aspects of implementation. Occasionally it may be prudent to initially restrict inclusion to key personnel whose activities impinge directly on the quality of the process; for example researchers may be excluded in the first instance and subsequently brought into the system (where appropriate) in a second phase.

Implementing a management system of any kind involves a number of discrete stages and is a significant undertaking for an organization seeking business improvement. However, good planning and senior management support can significantly ease the process. It is essential that those implementing the scheme are fully conversant with its requirements. All those implementing or working within the proposed system should familiarize themselves with it fully. Copies of standards may be available online, or as hard-copy, from the certifying or accrediting body. An alternative strategy is to use consultants familiar with the standard concerned to help the implementation process. Often it will be found that much of the documentation required has already been written, and incorporates clear descriptions of processes and the involvement of personnel. However, the documents will probably not be process-oriented, are probably unrelated to the organizational structure, and may not be coherent or comprehensive. There may also be several activities which the facility is not at present conducting or which could usefully be altered. Therefore a plan and time schedule must be drawn up for the collation and classification of existing documents. An organizational chart may already exist, but it is important to ensure that the authorities and responsibilities of relevant people are clearly defined so that they can be involved in appropriate activities. The next stage is to analyse how these processes are working in the existing facility and to identify who is involved in which processes. None of these schemes necessarily seek changes to existing working procedures, although employees may decide to press for these if they anticipate improvements.

Finally, the installed QA process must be monitored, maintained and continually improved. A business is a living thing and whatever quality system is adopted, standards need to be continually reviewed and improved in order to lock-in the benefits flowing from it. Achievement of a QA standard may positively influence the morale and self-respect of users and staff

working within a facility. The award represents peer-recognition against an independent standard and may provide assurance concerning standards of animal care and use, thereby improving the quality of animal studies and contributing to the three Rs. However, after all the hard work of getting the management system implemented and registered, the benefits are not just internal. Informing customers and other stakeholders of the fact that the facility has achieved such recognition can have significant commercial and promotional benefits. Applying one or more of these three quality standards in an animal unit will, in principle, be of benefit, i.e. it improves scientific working methods and animal welfare. However, in order to prove that this is indeed the case, the effectiveness of these schemes should be assessed scientifically.

Acknowledgment The support of the charity Laboratory Animals Ltd is gratefully acknowledged.

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