18 Implementing Quality Systems in the Management of the Animal Care and Use Program

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Abstract

The laboratory animal science community is moving toward increasing the quality of their work. There are two main reasons for that: first, the objective of improving the care and use of the animals to ensure animal well-being; and second, the general trend by animal researchers toward enhancing the quality, reproducibility, and translatability of the research outcome. Therefore, animal care and use program managers are more and more involved, by personal and/or institutional commitment, in the implementation of quality practices in all animal program areas. In addition to internal quality measures, that may or may not be imposed by regulations, there are several external quality systems that can, and have been traditionally applied, to animal care and use programs. The practical aspects of the implementation of the three most common quality systems in the animal research environment (AAALAC International, GLP, and ISO) are described.

Keywords

Quality system · Animal research · AAALAC · GLP · ISO

18.1 Quality Systems in Animal Care and Use Programs

18.1.1 What Is a Quality System?

A Quality System (QS) is a collection of organizational processes defined in policies, standard operational procedures, work instructions, protocols, guidelines, or other documents.

It has the aim to meet an organization's internal and/or external requirements and expectations.

18.1.2 What Are the Quality Systems Applicable for an Animal Program?

The initial action of anyone wanting to introduce a new quality system is an assessment of the added value and the advantage one wants to achieve for an organization.

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Internal requirements are defined by the organization itself. In case of an animal care and use program, these could be internal rules set by program management, responsible veterinarian, Oversight Body (e.g., Animal Welfare Body, Ethics Committee, Institutional Animal Care, and Use Committee), and/or users of the animal services.

External requirements relevant to an animal care and use program can be set by, for example, the government competent authorities and applicable legislation, voluntary organizations such as AAALAC International (AAALAC) (www.aaalac.org), the International Organization for Standardization (ISO; https://www.iso.org/home.html), the Enhancing Quality in Preclinical Data (EQIPD; https://go-eqipd.org/) project, or regulators for the Good Laboratory Practice (GLP) regulations from OECD Principles of Good Laboratory Practice (GLP) and Compliance Monitoring [1], the Food and Drug Administration (FDA; https://www.fda.gov/) in the United States (US) or the European Medicines Agency (EMA; https://www.ema.europa.eu/) in the European Union (EU).

If the focus of your quality management system is animal care and use (institutional policies and responsibilities, animal housing and management, veterinary care, and facilities) then the internationally recognized AAALAC program would apply.

However, if your organization is looking more toward efficacy and efficiencies in the delivery of services or products then a broader, more generic system such as ISO 9001:2015 standards [2] could be considered. Quality standards such as this aim to meet customer satisfaction through continuous evaluation of the processes and systems in place. Animal facilities also involve animal care regimes as one of these processes. Customers in this instance could be any stakeholder within your organization that you provide a service or product to.

There are a number of other quality systems and guidelines that may be relevant for animal care and use program, such as, e.g., Good Manufacturing Practice (GMP) [3, 4] for feed produced and delivered or for veterinary drugs; Enhancing Quality in Preclinical Data (EQIPD: https://go-eqipd.org/) [5]; several FELASA guidelines such as those for health monitoring or genotyping [6]; and AVMA guidelines for euthanasia [7], but for the purpose of this chapter we will focus on AAALAC, ISO, and GLP, which have been already recognized as the most common QS applied in the animal research environment [8].

Whatever decision you take on which type of quality management systems you may pursue, an assessment of how these standards are recognized and respected internationally is also very important.

18.1.3 What Are the Differences and Commonalities Between the Most Commonly Implemented Systems?

A summary of differences and commonalities between the most common systems implemented in animal care and use programs is presented in Table 18.1. Important to note, while some systems have very well-defined scope and applicability (AAALAC, GLP), others (like ISO or internal systems) may be applied at the institutional level or exclusively in the animal unit, which will have implications for the role of the animal program manager in implementing a quality system.

18.1.4 Can Different Quality Systems Coexist in Our Animal Program?

The short answer is yes, different QS can coexist in an animal program. In fact, this is the norm rather than the exception. For example, animal facilities must comply with their national legal requirements and this is overseen by the government in most countries. This really represents nothing else than a QS. In addition to these basic legal requirements on quality, the unit may have any of the other QSs in place. Institutions can have AAALAC accreditation, which is more focused on animal welfare and/

Table 18.1 Differences and commonalities between most commonly implemented systems

	AAALAC	GLP	ISO	Institutional systems	
				Internal quality system	Compliance with ethical/legal legislation
Applicability	All kinds of animal research and breeder institutions	Institutions performing safety-regulated studies	Any kind of institution	Own institution	Own animal care and use program
Voluntary vs. Mandatory	Voluntary	Mandatory for certain safety-regulated studies	Voluntary	Voluntary	Mandatory
Accrediting/ Certifying Body	Independent organization	Government Body	National approved agencies	No external	Government
Inspectors/site visitors' specialty	Independent Lab animal professionals	Variable, government inspectors	Organization of processes	Internal quality personnel	Government
Main focus	Animal care and use program	Preclinical studies[a]	Organization of processes and customer satisfaction	Organization of processes	Animal welfare
Institutional Quality Assurance Unit	Not needed	Needed	Needed	Not needed, but usually present	Not needed
International recognition	Animal Research community/ Funding agencies/Potential collaborators	Regulatory Agencies/ Private Sector[c]	Commercial/Potential collaborators	Potential collaborators	Potential collaborators
Confidentiality	Very high	Very high	Very high	Internal	Depends on legislation
Support from upper management	Needed	Needed	Needed	Needed	Needed
Role of animal program team[b]	Principal role in the implementation	Support of the process	Support of the process unless applied in animal unit exclusively (principal role)	Support of the process unless applied in animal unit exclusively (principal role)	Principal role in implementation

[a]Reference elements
[b]Manager, veterinarians, technicians, etc.
[c]Purchase of a service (e.g., CRO)

or can hold GLP (Good Laboratory Practice) to comply with regulatory requirements, and/or they may be ISO certified (mostly ISO 9001).

But why should different QS coexist? Animal facilities may have two or three of these QSs established because there will be approaches unique for each QS (see Question 18.1.3 on similarities/differences). Institutions may see value in running different QSs, either because they need to comply with regulatory requirements or because they voluntarily wish to improve their way of working. Naturally, there are also overlapping aspects among the different QSs, but those usually do not conflict with each other. Rather, having experience with one QS facilitates the implementation of another QS, although the workload to establish a new QS can be substantial and should not be underestimated.

18.1.5 What Are the Challenges and Opportunities When Developing and Implementing a Quality System?

There are a number of challenges and opportunities when implementing a QS, for example:

Challenges:

- Buy in from all staff, including senior management and researchers, agreeing that developing and maintaining the QS provides value and the best use of resources.
- Engagement of animal care personnel is needed as they will be first-in-line in the implementation.
- Likely, information from different departments needs to be assembled and someone should have an overarching view to bring all information together.
- Time will be required to identify and evaluate all processes.
- Time will also be required to develop documentation, whether this means new standard operating procedures (SOPs), process maps, training, and/or competency records.
- Resources will be required, including manpower and time commitment, to start up and maintain the QS, in addition to the direct application fees that a QS may have.
- A decision must be taken on which QS provides the best value; for example, for an animal care program AAALAC may provide more value than a process-based system looking at preventive measures and continuous improvement such as ISO9001:2015.
- Maintaining requirements of the QS and a need to meet the standards required, e.g., via annual reports that may have to be provided to an external organization or external audits that may have to be hosted.

Opportunities:

- You are probably already carrying out many of the QS practices anyway and following the QS provides further confidence in the high standards already in place.
- Challenge some long-term established practices and evaluate your processes against best practices and current legislation and compliance.
- In the case of GLP, market the ability to perform regulated studies.
- To evaluate the efficiency and effectiveness of already established and new procedures.
- Gaining confidence that processes are being carried out and meet the current institution QS and industry standards, as well as in how this is implemented.
- Get engaged in a continuous improvement process.
- Establish a better research environment for the research community at the institution.
- Foster team building.
- Motivate animal care staff by bringing them together to discuss QS and explain the key role they play within the organization. Pride in the workplace once the QS implementation has been achieved, all people working in the animal facility can feel they have contributed to the achievement and be recognized by the institution.

- Provide confidence to stakeholders including clients, researchers, and regulatory authority that processes are being managed well and are in line with independent national and international standards.
- Implementing a QS (especially AAALAC) can demonstrate to the public the institutional commitment to animal welfare.

18.2 Elements and Implementation of a Quality System in Practice

18.2.1 What Are the Basic Practical Elements of a Quality System?

The implementation of a QS entails putting order in and defining all the activities that have to be performed, ensuring the personnel who perform the activities understand their role in the program and have the necessary competence to perform them, and ensuring the tools used to perform the activities are fit for purpose. To achieve this, a certain amount of documentation, variable in extent and level of confidentiality across the quality systems, is needed. Basic elements to consider are:

- Standard Operating Procedures (SOPs). The SOPs are written instructions on how a process or procedure is performed. They serve to define and standardize the way the activities are performed. They should be clear, concise, and easily available, and ideally should be detailed in a way that a new person could perform every task following the respective SOP.
- Personnel management. Responsibilities and reporting lines of personnel involved should be clear, known by everybody, and documented (i.e., organizational chart, job descriptions and updated curriculum vitae (CV)).
- Training and competency assessment. Standards for how staff are trained and how competency is assessed and reassessed as appropriate.
- Equipment and facilities management. Equipment and facilities used are expected to be under a maintenance program appropriate for the specific characteristics and use (see more in the specific question on equipment and facilities below).
- Self-evaluation and continuous improvement. Once a quality system is implemented, it requires an active mechanism to self-evaluate the progress of the implementation. This self-evaluation, which can be conducted via internal audits, should also focus on continuous improvement, since the quality standards will evolve over time.
- External evaluation. The quality principles may be implemented by an institution without external help, and tailored to the institutional needs as an internal quality system. However, external independent evaluation is needed to obtain official recognition of the implementation of the most widely recognized quality systems, through inspections, audits, or site visits performed by the certifying/accrediting bodies.
- Quality Assurance Unit (QAU). Although not obligatory in all systems (e.g., AAALAC), a QAU with personnel specifically qualified will be necessary for the more "formal" quality systems, especially the GLP, that involve a higher level of documentation and coordination with other areas of the institution.
- Documentation management. How documents are reviewed, managed, changed, disseminated, and archived. The administrative work is one critical aspect to consider when considering the implementation of a quality system.

18.2.2 What Program Topics Does the Quality System (QS) Need to Cover?

A QS can cover many topics but will be based on the commitment and the decision made by an establishment on what QS to implement. This will also be heavily influenced by the standards of the QS which they are going to follow (i.e., whether this is

to acquire certification or accreditation or as a guide to implementing their own in-house system).

These are Questions about the topics to consider when developing a QS:

- How are you going to meet the needs of the stakeholders and ensure assurance to all statutory and regulatory requirements?
- What is the purpose of the work and the strategic direction that may affect its ability to achieve the QS?
- What are the organizations objectives, risks, and opportunities, how have these been considered and how are they being addressed?
- Within an organizational structure, who are the key representatives and what are their responsibilities? How will they deliver the resources required for the implementation, maintenance, and continual improvement of the QS?
- How does the institutional management demonstrate leadership and commitment to the QS?
- Does the type of research being carried out require a specific QS to meet client requirements or is this covered by local rules and regulations?
- How is training and competency delivered and assessed?
- Within Health and Safety, what are the programs for identifying hazards, managing risk, and the maintenance of occupational health and safety of personnel?
- How are the animal facilities' environment controls managed and maintained?
- What housing and management is specific to each of the species held?
- How can an effective veterinary care program be implemented during all phases of animal care and use?
- What types of records are kept to demonstrate all aspects of the QS are in place and being managed?
- What systems are in place to allow an open culture for reporting and managing welfare concerns?
- How does the ethical review process, through the work by the Oversight Body (e.g., AWB, Ethics Committee, IACUC, and relation with the competent authority), comply with legal requirements including harm benefit analysis and the 3Rs, and be effective?
- What type of management system is in place for crisis management planning and implementation?
- How is security and plant maintenance managed and what systems are in place to deal quickly with breakdowns that may affect animal welfare or legislative requirements?
- How is performance monitored, evaluated, analyzed and evaluated, and how are opportunities for improvement identified and managed?

18.2.3 What SOPs Are More Important to Consider?

The most important factor to consider when embarking on SOP writing is to be clear about the requirements, what process are you describing and whether it is likely to be misinterpreted if you do not include a detailed procedure to follow. Moreover, it is important to include evidence of processes that may be required during audits of the quality management system, including calibration and training records.

For many animal facilities the most important SOPs are:

- Husbandry SOPs providing instructions about the care of animals, including, for example, SOPs for animal management such as acquisition, acclimatization, housing, feeding, sexing and breeding, euthanasia, as well as sanitization practices.
- Training and competency of animal care and research staff.
- Environmental SOPs outlining the process for recording temperature, humidity, noise, lighting, and the systems for alerting and remedying issues of non-compliance with expected environmental conditions.
- SOPs for the most common experimental procedures (e.g., blood sampling) providing details on how research experiments are car-

ried out, such as procedures authorized under national legislation, including those involving anesthesia, analgesia, and euthanasia techniques. This may include data management, animal welfare, and outline the scientific requirements.
- Facility Management SOPs for the calibration and servicing of equipment will provide evidence for the quality system audits and that suitable controls are being maintained for safety and collecting experimental data.

18.2.4 How Is Training/Competence of Personnel to Be Addressed Under a Quality System?

Ensuring trained and competent staff is key to a QS and providing suitable and sufficient evidence of this will be required within any internal or external audit process.

Key questions to consider are:

- Are staff in all functions following a training program? These may include animal care staff, veterinarians, researchers, Animal Welfare Officers, and Oversight Body members.
- The scope and type of training required to carry out a task/process and attain the standards required. This could range from reading a document, online training, taught courses, or individual practical one-to-one training.
- Is the person carrying out the training the most suitable and experienced person to deliver the training? Do they have an understanding of the process in enough depth to answer questions and provide additional support if further training is required?
- How is competency going to be assessed? For example, a written assessment, observational assessment, or a combination of all of these methods?
- Is the individual assessing competency independent enough to the person carrying out the training so that they can do this in a standard, non-biased way? Do they understand the level of competency required to sign an individual off as competent?
- How often does competency need to be reassessed?
- What training documents are needed? This could be a whole range of different formats including SOPs, competency documents, and observation recordings.
- Is the training program in compliance with applicable legal requirements?

All training and competency records are required to be in a format that can provide assurance to any internal or external auditor that the training has been undertaken and competency has been assessed including all dates this occurred.

18.2.5 How Are Equipment and Facilities Management (e.g., Calibration/Verification/Maintenance) to Be Addressed Under a Quality System?

Equipment and facility management are essential to produce accurate and consistent research data and reduce unwanted effects on animals, thus are an integral part of any laboratory animal operation and are vital for both maintaining animal welfare as well as data quality assurance.

Equipment may require verification (which ensures correct operation according to its stated operating specifications), and/or calibration (which ensures measurement accuracy compared to a known standard) and/or validation (which ensures that a system satisfies the stated functional intent of the system).

Key points to consider are:

- Type of equipment related to animal use.
- Level of management required (calibration/verification/validation). For example, under GLP, full validation may be required for certain types of equipment (e.g., software), whereas it may not be required under other QS (e.g., AAALAC).
- Frequency of use.
- Competence of responsible personnel.
- Records of management activities.

Most common equipment and facilities on which to perform some of these activities will include:

- Heating, ventilation and air conditioning (HVAC) system, including environmental conditions (temperature and relative humidity) and air pressure difference between areas.
- Lighting system (intensity levels, on/off).
- Watering system (microbiological monitoring, decontamination systems).
- Sterilization equipment.
- Cage washing equipment.
- Anesthesia equipment.
- Health and safety equipment (e.g., eye wash stations and safety hoods).
- Housing systems (e.g., ventilated racks).
- Surfaces of animal facility.
- Laboratory research equipment (e.g., balances): this will apply at least to the equipment directly involved in animal procedures. When applying a QS that covers the entire laboratory work, and not only the animal use (i.e., GLP and ISO), these processes will be implemented also for the equipment of the entire laboratory, and the entire facility.

All records are required to be in a format that can provide assurance to any internal or external auditor that the procedures have taken place, including all dates this occurred. In many cases, this may involve the use of stickers directly applied on equipment.

18.2.6 What Level of Documentation Is Necessary?

Most external QS have specific standards that outline the documentation required for assistance and evidence that you have reached the QS standards. Such documentation can also serve for any kind of audit. With an internal based QS, the decision on the amount of documentation and the duration of archiving can be made by that individual establishment, whereas external QS may have specific requirements.

In general, most of the documentation will refer to:

- Standard operating procedures/work instructions
- Personnel (training, competence)
- Husbandry and veterinary records
- Oversight Body meeting minutes
- Equipment/facilities (calibration/verification/maintenance)
- Occupational health and safety

It is important to ensure that the documentation being kept reflects actual practices and the requirements of the QS in place. For example, if work is being carried out using equipment that needs to be calibrated, the documentation should show evidence that this is being carried out. Or if you have a system in place for training staff and assessing competence, it should demonstrate that this is being carried out.

The records can be in any format but would need to be accessible, archived where necessary and disposed of securely once the archive period has been reached.

18.2.7 Why Consider a Quality System for an Animal Care and Use Program?

The objective of a QS is to satisfy the needs or requirements of stakeholders, either internal and/or external. The stakeholders can include:

- The institutional management.
- The research community.
- The competent authority (regulatory agency).
- The buyer of a product (e.g., animals) or service (e.g., studies) offered by the institution.
- The institutional Oversight Body (EC/IACUC/AWB…).
- External collaborators.
- Funding agencies.
- The public.
- Publishers.

With an animal care and use program it is an expectation from all stakeholders that:

1. Refined animal husbandry and welfare is an integral part of scientific programs.
2. The establishment is carrying out current best practices according to established procedures.
3. All animal use has undergone an effective ethical review and required authorization.
4. Staff are highly trained and competent.
5. A culture of care is implemented throughout the establishment.

A QS during initial discussion, implementation, and maintenance assists an establishment to reflect on the five areas highlighted above and to look for continuous improvement. This is essential to demonstrate to stakeholders and auditors/inspectors that you have a robust animal care and use program in place.

18.2.8 How Can We Use What We Already Have in Our Program Relating to Quality, Such as the Oversight Body (EC/AWB/IACUC)?

A good place to start when deciding to implement a QS is to highlight what is already available within the establishment, especially controls and processes required to cover any legal obligations. These will help develop a foundation to build your quality program and identify areas that need additional information and or processes to be put into place.

The *legal requirements* an animal care and use program must adhere to will also be—to different levels of detail—evaluated by agencies such as AAALAC, GLP, and ISO.

Also, a functional institutional Oversight Body is a legal requirement in many countries including the European Union member states, the UK, and the USA. The *roles of an institutional Oversight Body* such as oversight and evaluation of the animal care and use programs are key contributors to a QS and usually cover aspects such as:

- The establishment of animal welfare policies towards a culture of care.
- The inclusion of the 3Rs in programs of work.
- The review of standard operational procedures/work instructions.
- The review of animal research projects.
- The periodic review of the animal program and facilities.
- Additional activities such as retrospective assessments of projects and advising on rehoming schemes.

Additional useful, quality-related guidance can be obtained from documents such as implemented legislation (e.g., Directive 2010/63/EU in the European Union) [9] or other guidance documents such as the Guide for the Care and Use of Laboratory Animals [10] and FELASA recommendations [7].

Thus, a functional institutional Oversight Body and adherence to legal and guiding documents will cover at least part of the animal care and use requirements of the three external quality systems mentioned above.

The external quality systems, in particular, the accreditation process of AAALAC, in return will ensure the proper implementation of the processes mentioned in the guidance documents, including those to be executed by the institutional Oversight Body. They thus facilitate the management of the requirements imposed by legislation and recognized standards, and address additional quality aspects relevant to an animal program.

There is a close interrelationship between the legally mandated infrastructure of an animal facility and the requirements of the external QS. But importantly, the already existing infrastructure imposed by legal requirements can be used to implement and manage the quality requirements of AAALAC, GLP and ISO.

In essence, there are already a lot of good practices and processes being carried out within animal facilities that can be utilized directly into a QS. The real challenge when adding current practices in a QS is in auditing the processes regularly and looking for continuous improvements.

18.3 Institutional and Personal Responsibilities

18.3.1 Where Can the Initiative to Implement a Quality System Come from Within the Institution?

There is not only one potential source within the institution to promote a QS.

A QS is very often implemented to protect the brand, organization processes, and the customers' interest. In these cases, the normal process would be coming from institutional management. This situation can happen for all applicable quality systems and has the practical advantage of management making the necessary resources available, which can have a positive impact on the animal program.

When the reason for the implementation is compliance with legal requirements (i.e., Ethical regulatory bodies such as AWBs or IACUCs, GLP for regulated studies), or customer requirements, the process is also normally the same.

However, when the intention is focused more on reducing concerns about the reproducibility and translatability of animal studies and/or assuring animal welfare and the 3Rs, the initial interest may come from other institutional representatives, such as veterinarians, investigators (i.e., internal customers), and/or animal program responsible persons. This case is usually more related to AAALAC, ISO, or EQIPD. When this occurs, the success will depend on if/how/when the interested parties convince top management to dedicate the resources needed. Not easy, but not impossible.

18.3.2 Does the Type of Institution Make a Difference in the Type of Quality System and Way of Implementation?

Yes, it does. Whereas all institutions must have, to some extent, some kind of internal QS due to compliance with legal requirements and their own commitment to quality, the nature of the institution, type of research, and relation with external customers make a difference when considering the more standard systems such as AAALAC, GLP, or ISO.

Institutions performing regulated preclinical research will implement GLP as a legal requirement. This is more common in the field of contract research organizations (CRO) where this type of work is mostly conducted, but GLP will have to be implemented in any type of institution conducting regulated preclinical research, for example, in pharmaceutical companies and, albeit with less frequency, in academic institutions.

Institutions dealing with external customers may be interested in ISO to offer evidence of consistency of the product or service. This is more typical in breeders and CROs. However, when other types of institutions want to consider their own researchers as customers, they can also consider ISO, which may also be seen in academic and other institutions. However, due to the lack of specialization of this scheme on animal research, the implementation of ISO in animal facilities outside the commercial environment is low.

AAALAC can be implemented in all kinds of institutions, and in fact this is what happens in practice. In addition to the particular commitment to improving the animal care and use program that any institution may have, it offers a visible label of promoting animal welfare, which can be used to gain confidence of customers (e.g., in CROs and breeders), the public (all institutions), and collaborators (academia, pharmaceutical companies, biotechs, etc.).

It is important to note that the cited QSs are not exclusive, and certain types of institutions

implement more than one, or even the three of them together. For example, there are institutions, including a number of CROs, which perform regulated research and must have GLP as a legal need, implemented ISO to focus on the consistency of their processes, and AAALAC to cover better animal welfare, care, and use aspects.

18.3.3 Who Are the Key Institutional Players to Get Engaged in the Implementation Project?

A QS may cover many areas within an establishment, some of which will require specialist knowledge outside of the normal routine working processes, e.g., calibration of temperature and humidity sensors in ductwork will require maintenance service input.

The main point to consider in any change or implementation project is what individual roles need to be involved to ensure success and this will normally include representatives of:

- Senior institutional management, with authority and resources.
- Quality Assurance Unit, as appropriate.
- Research staff.
- Technical and procedural services staff.
- Animal facility manager.
- Animal care staff.
- Veterinary staff.
- Human Resources.
- Health and Safety.
- Maintenance Service.

Input from other professionals related to areas such as security, information technology, or laboratory services may also be needed.

The main point to consider is who should lead and coordinate all the above players. Sufficient authority and backup should be given by management to the project leader responsible for the implementation of the QS.

18.3.4 What Are the Obligations for Researchers Under a Quality System in the Animal Care and Use Program?

Researchers must be engaged in the implementation of the QS in the animal program from the beginning, as they will have to follow the QS requirements. Researchers will have to be involved in any QS, but their level of involvement may differ depending on the QS. For example, their involvement will be higher under GLP, because the research process is the main protagonist (with the Study Director as main responsible), whereas under AAALAC, the main focus is on the animal care and the research involvement is less. Aspects of the researcher's involvement in the QS may include:

- Coordination with the responsible person for the implementation of the QS (e.g., quality assurance unit and facility manager) to define the requirements for researchers.
- Provision of personnel documentation and definition of responsibilities and reporting lines, job descriptions, and training. Common to all QS.
- Preparation of experimental SOPs. Absolutely necessary under GLP for all experimental procedures. Some experimental SOPs can be necessary for other systems too, especially when they are generally used (e.g., blood sampling).
- Keeping detailed records related to research activities with animals and following their clinical signs and welfare status.
- Participation in inspections/audits/site visits. Absolutely necessary under GLP. In other QS, there may be a variable level of interaction with researchers during the onsite assessment to describe certain research processes. For those participating in the institutional Oversight Body (IACUC/EC, AWB, etc.) activities, they may be asked to describe their

role in the oversight and ethical review processes.
- Compliance with institutional health and safety policies relating to animal use. For example, AAALAC thoroughly evaluates the occupational health and safety program, which must apply to all staff relating to animal care and use, including researchers.

To better engage researchers and ensure their effective involvement, it is advisable to explain the QS and the benefits they receive as early as possible and invite them to actively participate during the implementation process. Their perception may also be different depending on the necessity of the QS: whereas they must implement GLP to perform certain types of studies, ISO and AAALAC are voluntary, which may limit their engagement.

18.3.5 What Is the Process of Applying for a Quality System?

After deciding which of the QS you would like to establish, initiating the process within your organization, getting the appropriate approvals, and identifying your key people for the process, you should make contact with the organizations that will accompany you through the process and assist you in achieving the desired quality system.

ISO application: ISO certification is issued by certification/registration bodies that are independent of ISO. The task will be to identify the certification body in the region/country, which will walk you through the standards, documentation to be provided, and the audit process. A list of certification bodies by country can be found at: https://iaf.nu/en/home/

AAALAC application: There is single application process for any institution around the world, accessible at: https://www.aaalac.org/accreditation-program/apply-for-accreditation/. In summary, the applicant must submit an application form and a description of the animal care and use program using the Program Description (PD) template freely available on the website. There is the standard PD, a European version of the PD, and a Thai version. It is also very important to read carefully the instructions on how to complete the PD. In addition to the main office in the USA, AAALAC has a European office that can help applicants from Europe, Latin America, Africa, and the Middle East, and an office in Thailand for the entire Asia Pacific area.

GLP application: GLP certification is issued by national government GLP compliance programs which are in place to ensure compliance with GLP by the institutions that conduct the tests. Furthermore, the signing of Mutual Recognition Agreements (MRA) on data ensures that the results of these tests are recognized by other countries. The applicant has to contact the government office (in some countries this may be at the regional level) responsible for this certification, who will coordinate with the institution the submission of documentation and inspection procedure. Links to National Web Sites on Good Laboratory Practice can be found at: https://www.oecd.org/chemicalsafety/testing/linkstonationalwebsitesongoodlaboratorypractice.htm

18.3.6 Have Quality Systems Regulatory Implications?

Out of the QS reviewed in this chapter, only GLP has direct regulatory implications. Certain safety and efficacy studies have to be performed following GLP requirements as defined by regulators. Details of regulations vary across geographical regions (for example, based on EMA in the European Union or FDA in the USA) [11, 12]. Certification of GLP requirements is performed by inspectors from the applicable government authorities, at regional or national level. The results of the studies are officially informed and registered as part, for example, of the preclinical development of medicinal products.

AAALAC and ISO represent voluntary systems with no direct regulatory implications. However, it can be argued that AAALAC may

have an indirect impact on certain activities. For example, it can facilitate the application process for funding by government agencies (such as the NIH in the USA). Also, it is mentioned as a risk-mitigating factor in the working document for guidance on inspections and enforcement to fulfil the requirements under Articles 34 and 60 of Directive 2010/63/EU [7] when evaluating the risk and deciding on the frequency of inspections of institutions by competent authorities in the European Union [13].

18.3.7 Is a Quality Assurance Unit Needed for the Implementation of a Quality System?

A Quality Assurance Unit can be defined as a group of people in a QS that is focused on providing confidence that all quality requirements will be fulfilled both internally and externally. Assurance relates to how a process is performed.

Overall a QAU provides evidence-based confidence to management, regulators, and other stakeholders. It evidences that high-quality work is being carried out in an organization and that the organization addresses key areas such as best practices and evaluation of essential metrics to identify continued delivery and engagement in quality. By addressing different units of assurance you are in effect building up and maintaining a QS. For example, when assessing competency, the quality assurance units would encompass areas such as training of the learner and trainer, documents used for training and assessment, examples of assessment criteria, retraining, user feedback, and record keeping of all relevant stages.

Under ISO and GLP, the work and auditing of a QAU is a necessary part of the quality standards in place, not only for the internal implementation but also to prepare the external audit/inspection by the respective certification bodies. However, a QAU may not be necessary if the QS has no external certification criteria (i.e., internal systems), or the level of documentation can be managed by the animal care and use management (i.e., AAALAC). Although not required in all cases, developing an auditing QAU would in essence help to ensure no area had been missed and help to identify strengths, weaknesses, threats, and opportunities within the system.

18.3.8 What Is the Time Commitment Needed for the Implementation of a Quality System?

The time commitment required for a quality system is dependent on the resources available and whether a QS is going to be implemented in its entirety or parts of an already defined standard used as a reference for improvement. When considering a QS you need to think about the following time constraints:

- Commitment from senior staff as there are needs to be top management buy-in to discuss scope, mission statements, and organizational objectives.
- Processes already in place, changes required, and potential hurdles to change.
- Time requirements by others that need to be involved.
- Frequency of group meetings needed to develop the QS and the best use of resources to be productive at each meeting.
- Evaluation and auditing of how items are calibrated and records maintained.
- Development of process maps and/or standard operating procedures to highlight and standards to maintain.
- Development of training programs and assessing both training and competency.
- Audit of the QS system once in place.
- Ongoing time commitments in establishment of a quality culture framework and maintaining it.

In summary, implementing a QS requires a significant time investment (from several months to a few years) that has to be considered in the initial planning.

18.3.9 What Are the Financial Costs of Implementing a Quality System?

There are two types of financial costs associated to the QS:

(a) The costs associated with the organization (e.g., staffing) and potential necessary updates in the animal program (e.g., facility or equipment improvements) to get ready for the implementation. This cost can be very variable and will be inversely related to the initial baseline quality of the animal program. The size and complexity of the program will be a significant factor in the final cost. It is important to note that this cost will significantly be higher than the official fees of the applicable certification process described below, because it will include costs associated with requirements to continuously train people, assure documentation is up-to-date, procedures being compliant with requirements imposed by the QS, run internal audits/assessments, prepare external audits, etc.

(b) The fees charged by the external body responsible for the administration/auditing/certification/accreditation processes:

ISO9001:2015: This is dependent on the quality organization chosen to certificate your program; however, on average a surveillance audit costs in the range of 1000–2000 € per day. The number of site visits will be dependent on the size and complexity of the organization. The average would be one to two visits per year for general auditing purposes with a full recertification visit lasting 2–3 days every 3 years.

AAALAC International: There is an application fee and an annual fee to be paid once the program is accredited. The fees are associated to the size of the program, and can be seen at: https://www.aaalac.org/accreditation-program/fees-and-deadlines/ Most of the application fees are in the range of 5000–10,000 €, with an annual fee in the lower range.

GLP: The daily cost for the certification audit may vary across countries and regulatory bodies. In the European context, it can be estimated in the range of 1000–4000 per day or complete process. As with ISO, the final sum may depend on the complexity of the research unit.

18.3.10 How Is the Quality System to Be Maintained in Time?

Active maintenance of a QS is important to ensure the QS remains functional, fit for purpose, and includes the latest updates and information. This will require time and effort from a team that should be committed to investing in this process. The responsible person(s) for the implementation of the QS should plan and identify all the resources required to maintain the QS, which may be substantial (including finances), e.g., to implement improvements that were identified during the last external inspection, audit or AAALAC site visit. It will ensure that good practices are maintained, ongoing processes (including documents such as SOPs), and existing competences (including training needs and resources) are reviewed and adjusted as required, and new developments in the field are taken into consideration. This is a continuous improvement process and a large part of any QS.

A culture of quality needs to be maintained or even strengthened to keep people engaged, not to lose momentum, and ensure the continuous process is in place to be ready for the requirements of each QS visiting/auditing/inspection procedure. Any important changes in the animal care and use program must be dealt with appropriately and, in case of an AAALAC-accredited organization, should be reported to AAALAC annually. The program description should be revised as needed in preparation for the next AAALAC visit (the process is repeated every 3 years). With other external QS, auditing requirements may vary (e.g., audits performed annually, semi-annually, or ad hoc). Time and effort needed for these activities should not be underestimated, although proper planning with clearly defined responsibili-

ties and timelines will help. Similar efforts should be considered for the maintenance of other QS. A cost-benefit analysis will be useful to better understand whether the benefits that come from the QS justify the investments made into the maintenance of the system or whether an internal system would work, limiting the need to meet an external standard and audit requirements.

18.3.11 How to Ensure and Demonstrate the Value of the Quality System?

Efforts toward quality management not only demonstrate effective and controlled operational systems and processes to external stakeholders but can be invaluable in developing and monitoring progress within your own institution. This is particularly important in areas such as welfare, training, and data management.

External users of services, especially those who are aspiring to reach standards set by regulatory bodies or who are seeking funding and additional resources, may frequently quote the QS of the facility they have or planning to use.

Requesting regular feedback from researchers working within an accredited facility will give an indication of the impact of the QS on the success of services delivered. This also aids continuous improvement and provides feedback to staff on the value they make toward the establishment.

For internal purposes that include staff, welfare, and research, the value of a QS is not limited to times around a periodic audit, but in a sustained effort to meet the standards throughout the year, every year. Regular reviews, meetings of teams, and internal efforts will ensure that changes, and issues which arise between official audits are identified at early stages and corrected appropriately. Monitoring metrics of the QS can be vital in demonstrating the effectiveness and therefore the value of the quality-driven efforts. This information can also be used for root cause analysis to delve deeply into processes to identify more robust systems, if necessary. These can include:

- Registers tracking incidents of non-compliance and subsequent corrective actions.
- Improvement in data accuracy, transparency, traceability, and appropriate data storage.
- Appropriate and fit-for-purpose documentation of processes (including up-to-date SOPs and effective risk assessments).
- Help with the timely and accurate delivery of projects.

Prospective implementation of a QS will help to avoid errors from the start and continuous evaluation of the measurements described above will enable a retrospective assessment of improvements and give a tangible readout of value and service improvements.

The QS should become part of the culture of an establishment where all systems and processes are constantly evaluated and questioning of the effectiveness and efficiency becomes a normal part of any review process. This is not carried out alone by institutional management but by those carrying out the processes to provide additional value and ownership that leads to highly motivated staff.

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