Establishing a Quality Management System in your Facility

Guidance, key concepts and first steps

Key messages:

- A quality management system is a formalised system of documenting the activities and responsibilities within a facility for achieving quality objectives.
- Many accreditation standards use a risk-based approach to determine whether the standard has been met. As such, each facility may have a different approach to meet the standard.
- TIA has curated a range of example quality documents (iQDOCs) that can help guide you in establishing your quality management system.

This guide has been written to assist in the establishment of a quality management system in research facilities and new companies. If you are on day one of your journey towards having your facility certified or even accredited according to a quality standard, then this document has been designed to help guide you on best practices and on first steps. It is not fully comprehensive, as each standard has its own requirements and each facility will have its own unique circumstances to be addressed. Therapeutic Innovation Australia (TIA) has curated a wide range of example quality documents (iQDOCs) that can be downloaded according to the relevant quality standard that you are working towards and used in conjunction with this document.

What is a quality management system?

A Quality Management System (QMS) is a formalised system of documenting the activities and responsibilities within a facility for achieving quality objectives, meeting customer and regulatory requirements and improving efficiency on a continuous basis. The purpose of a QMS is to maintain an accurate record of all activities in a facility, including the environment, equipment, processes and personnel. Many facilities opt for an electronic QMS, such as TrackWise, MasterControl, Ace Essentials or Q-Pulse. It is possible to use a paper-based approach in the early stages of development, but for future best practices it will be worth investing in an electronic system. By establishing templates and procedures, demonstrating compliance through forms and documenting deviations from the standard operating procedures (SOPs), it is possible to accurately track a product's manufacture through the facility and ensure that the acceptable quality of the product is achieved.

As you start to build out your QMS you will likely need to introduce a range of new documents. This document aims to provide you with an introduction to the concept of a QMS and will provide links to TIA's iQDOCs, a catalogue of quality documents, indexed by different quality standards. Please do not underestimate how large a task this is – each of the iQDOCs catalogues contains approximately 120-150 documents, not including process-specific SOPs, batch records and individual training records that are specific for the type of manufacturing you perform in your facility. It is therefore important to create a systematic approach to the implementation. All documents will need to have a change/version control

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system in place. From a quality standpoint, it is better to have a "Version 1" of a document published that you can later amend, than to have a Draft version that has never fully been implemented: some level of documentation is always better than none. It is likely that you'll need to make changes to the documents as the QMS develops, but it's important that you only ever have one version of a document in use or "active" at any time.

First you will need to decide which standard you want to implement. Depending on what your facility does, there may be mandatory standards to apply (e.g. for medical products that require compliance by health regulators such as the Therapeutic Goods Administration (TGA)). Or the decision may also be to adopt voluntary standards such as ISO 9001 to ensure your facility is certified and recognised by users to meet standardised quality, customer and business best practices. There are similarities between the different reference standards, and some of the documents are interchangeable or can be adapted from one standard to comply with another, but each of the standards has specific requirements that may be unique. There may also be site specific requirements that need to be incorporated into your documentation. These may be workplace health and safety requirements laid out by the employer or computer systems maintained by the host institution such as hospital, university or parent company.

A risk-based approach is used by many of the accreditation authorities to determine whether the standards have been met. So there are often multiple ways in which a facility can comply with a standard, that allow for site-specific requirements. Therefore, the way that one facility complies may not be an appropriate solution for another, but discussion with other facilities may help inform on a pathway for your facility. Further, it may be possible to discuss implementation with a consultancy firm offering advice

Some quality standards you may consider applying are:

- **ISO 9001:2015** is the internationally recognised quality standard for any organisation (not restricted to labs). It helps businesses monitor and manage quality across all operations. As a service provider, being ISO 9001 certified assures customers that you have a commitment to quality and customer service above that of a standard research lab.
- **ISO 13485** is the internationally recognised quality standard for medical devices.
- Medicinal products supplied in Australia must meet the **Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S) guide to Good Manufacturing Practice (GMP)** except for annexes 4, 5, and 14 which are not adopted in Australia.
- In Australia, the **Therapeutic Goods Administration (TGA) GMP** assesses the implementation of PIC/S GMP, whilst the same role is carried out by the Food and Drug Administration in the United States and the European Medicines Agency in Europe. A commonly used terminology here is current GMP(cGMP), indicating that the codes are continually evolving and the facility must comply with the current code.
- The **Australian Code of Good Manufacturing Practice for human blood and blood components, human tissues and human cellular therapy products (GMP)** describes the manufacturing requirements for biologicals in Australia.
- **FACT-JACIE standard** describe requirements for haematopoietic cell therapies which you can look through to adapt yours if needed.
- The International Conference on Harmonisation (ICH) guidelines for **Good Clinical Practice (GCP)** is an internationally accepted standard for clinical trial design, conduct and reporting. (Note, GCP is not really discussed in this document, rather it focusses more on lab and facility operations.)

in this area or to directly reach out to a technical advisor at the accreditation authority, to ensure your understanding and approach is applicable.

To define approaches or some facility operations it may be possible to include a paragraph within a larger document, while in a different facility this may be best separated out into multiple documents. Keeping the documents short, specific and simple can help with training, reviewing and amendments, but the more files you have, the harder it is to manage. There is a fine balance between how much should be covered in each document and how many documents you have. As a rule of thumb, many facilities have identified that documents over 20 pages may warrant consideration for separation.

You should always start with the documentation and guidance provided by the quality standard or Accreditation/Regulatory body that you are considering. Most will post guidelines, reviews and changes on their websites. It's important to sign up for any notifications, as you will need to maintain compliance and amend your documents if there is an update to their published standards.

Similar features across most standards

Many of the features of a QMS are universal, but there will be specific requirements for each, so it's important that you always refer to the standard when implementing your QMS.

The documents can fall into a range of categories, but for ease it is worth considering four main pillars for your QMS:

- Facility
- Quality
- Personnel
- Manufacturing

Within each of these will be different levels of documentation such as policies, procedures, forms, lists and templates.

- A policy is a directive or framework under which the activities occur.
- Procedures or standard operating procedures (SOPs) describe the way in which activities are carried out.
- Forms are a way to track that the activities have occurred according to the assigned procedure.
- Lists are ways of maintaining order for each facet of the facility.
- Templates allow for addition of new documents as needed and according to the correct document controls.

As an example, for each piece of equipment there will be a policy that describes the activities that it can be used for, SOPs for how to perform these activities and forms to fill in for each manufacturing run that ensure that the SOPs have been adhered to (and any deviations from this). The lists are a way to track the operations in a facility, such as materials and equipment lists, manufactured products and deviations throughout the year. Templates are useful for ensuring that all your document and forms follow the same format. Each template should contain a header/footer with the document/form name, unique identification number, revision number, active date, author and owner.

Key documents to be found in each pillar are outlined below:

Facility:

- Policy to identify all rooms, buildings, warehouses etc included in the QMS. May be called a Site Master File (SMF). May include a site map, organisation chart, an explanation of the people, equipment and quality environment as well as a description of the activities that occur on site and list of approved contract manufacturers and laboratories for any outsourced activities. Include what standards are being adhered to for maintaining the facility & equipment
- Procedures for cleaning, evacuation, maintenance, mitigating contaminations and visitor access
- Forms for cleaning and maintenance
- Lists of acceptable visitors as well as a visitor log
- Environmental monitoring procedures and forms
- Register of all critical equipment and selected schematics drawings such as the purified water system for example

Quality:

- Policy describing the quality standards to which the facility adheres, the scope, inclusions and exclusions. May be called a Quality Manual
- Procedures for managing risk, performing audits, non-conformances, management of suppliers and materials, document and change control
- An audit schedule and checklists for each type of internal audit
- Forms for non-conformances/deviations, attendance at training, etc
- Templates for all procedures, validations, forms, lists, training assessment forms, etc and changes
- List of all documents included in the QMS (including version number)
- Log of personnel signatures

Personnel:

- Policy describing the expectations of all members of staff. May be called an Orientation Manual
- Procedures for training, assessing and maintaining competency. Each competency will likely need a separate procedure e.g. clean room behaviour, gowning requirements
- A training matrix that identifies all the training requirements for each role
- Training records (such as assessments or attendance forms) for each member of staff for each procedure

Manufacturing:

- Policy describing the manufacturing that occurs in the facility, expectations and standards by which the manufacturing must adhere
- Procedures for every piece of equipment, SOPs for manufacturing processes and for material management and storage
- Batch records for each product manufacture identifying that the SOPs have been followed
- Layouts of production areas including material and personnel flows, general flowcharts of manufacturing processes of each product type produced on site
- Lists of all manufacturing runs
- Lists of critical materials and equipment
- Qualification procedures including for equipment and processes

What does validation mean?

Most quality standards and specifically regulatory bodies will set an expectation that the production process is controlled and appropriately defined (or "validated") to ensure the output or products are consistent in their safety and efficacy. This is a fundamental term for quality systems and generally means that you've tested the equipment, analytical test methods and procedures to ensure they are fit for purpose within the expected parameters. For some items or processes there will be defined protocols available from the provider, for others you may need to adapt them or write from first principles, so they are more specific to your needs.

Glossary:

Audit	An internal or external assessment of any aspect of the facility & manufacturing. It may focus on the training documents or the materials management. It should be based on the standards adhered to in your facility. It is designed to identify gaps and continuous improvements and should be performed routinely (at least quarterly)
CAPA	Corrective and Preventative Action Plan is a way to improve the operations of a facility after a non-conformance is found during tasks, processing or in an audit
cGMP	Current good manufacturing practice, generally use the term current to acknowledge that the requirements to maintain GMP are continually evolving and a facility must maintain the current standard.
Facility	Any laboratories or office space that falls under the remit of the quality management system. Includes manufacturing, production and storage areas.
Form	Documentation that shows that a procedure has been followed. It is signed & dated by the individuals performing each stage of the task, and identifies any deviations from the procedure
Non-conformance	Any instance of operations not following the approved SOP or regulatory standards applicable to your facility & manufacturing
Procedures	Detailed instructions for how to perform each task, may also be called standard operating procedures (SOPs) or work instructions (WI).
Qualification	Falls into installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). All equipment must have documented evidence that it is correctly installed (IQ), operates according to requirements (OQ) and performs safely (PQ).
Validation	The equipment or process has been tested against defined the expected parameters and is accepted for use by the facility.

For equipment, there are methodical risk assessments to determine the appropriate level of validation. This may be only a simple commissioning process, while others may require a more comprehensive installation (IQ), operational (OQ) and performance (PQ) qualifications. IQ is how you determine that the equipment has been installed correctly in a suitable location. Some suppliers will be able to perform IQ when the equipment is delivered, others you will have to perform internally. OQ determines that the equipment operates as specified by the manufacturer within approved operating limits. The PQ ensures that the processes performed are stable over time (usually yearly at least) and is used to verify acceptable equipment performance in intended processes under specific operating conditions.

A key requirement for setting up cGMP facilities is to have a validation master plan (VMP). The VMP is a foundational document that outlines the principles, scope, responsibilities and structured approach for all validation activities to ensure a risk-based strategy for achieving and maintaining a qualified facility with validated processes. The VMP should also address or point to supporting validation policies that cover the equipment, processes, cleaning, analytical methods, utilities and computer system validation.

Quality control

A large aspect of the transition to a QMS is controlling the quality of any products produced in that facility. According to the TGA, quality must be built into each batch of product during all stages of the manufacturing process. Associated with this is ensuring you have the appropriate quality assurance assays that you have clearly defined parameters for successful release. Some of these assays will be compendial, and performed routinely in several facilities (e.g. mycoplasma, endotoxin) whilst others will be bespoke (e.g. number of CAR positive cells). These assays may need to be developed, but you should be considering the documentation requirements throughout your assay design, to ensure that quality is built into the manufacturing process.

How to carry out and document changes to procedures

A key component of any QMS is the method you use to make changes to any policies, procedures or forms, generally called the Change Control Plan (CCP). Within a quality framework it is not possible to tinker or deviate from the documented protocol. Amendments take time to implement and must be actively managed, controlled and documented. This is a fundamental difference between a research laboratory and an environment operating to a QMS.

When changing a procedure, form, template, or other QMS controlled document for a minor reason that does not impact the product being manufactured, a change control plan may not be required, however it is important to supersede the current document to a new version of the document and to record what changes occurred. This can be accomplished through establishing a “version history” into the document or through the electronic QMS as an attachment to the new document version.

In the case that changing a procedure will impact either the product being manufactured, the facility, or your regulatory compliance process, then you will need to create and follow a CCP as laid out within your quality management system. This will contain standard methodology and assessment of risks and mitigation steps, but in general, will include:

1. Description of the change and scope
2. Risk analysis
   Impacts on financial, IT, product, regulatory, equipment, material, documentation, personnel, facility aspects
3. Validation plan and report
   Method, expected results and review
   Results against user requirements
4. List of document changes required
   SOPS, forms, training, templates, lists
5. Training requirements
6. Implementation plan
7. Follow up evaluation

8. Management review

In carrying out a change control plan, it's important to ensure that all relevant staff have received training on any new protocols which may include hands on training and updated training records. All documents in a QMS are version controlled, such that everyone is trained upon and uses the same version at all times. Upon implementation of a change, it is crucial that any out-of-date printed versions be retrieved and removed to ensure that they are out of reach of users. A copy of old document versions should be kept and stored in a site master archive.

How to manage errors

Mistakes happen, and everyone makes mistakes. Within a quality framework these can be called non-conformances, deviations or opportunities for improvement. Non-conformances may arise for multiple reasons including lack of training, incomplete or unclear protocols or factors seemingly outside of your control. Before considering the reason for the error, it's important that the deviation is documented. The mechanisms for documenting the deviation need to be clearly outlined in the QMS.

After accurately documenting the deviation it is time to identify the reasons, generally called a root cause analysis, and then any improvements that can be made to processes/documentation to prevent it happening again, also known as corrective and preventative action (CAPA) plan. As with all errors, it's important to refrain from laying blame, rather the focus should be on preventing the same thing happening again and learning from the mistake. Common reasons for mistakes are listed in Table 1. The errors that initially look like they are outside of your control need to be risk assessed to bring within your control, perhaps by identifying back up equipment options or alternative suppliers.

Common reasons for errors	Ways to mitigate errors
Lack of preparation for the process	Ensure all supplies are available for the process ahead of time, room bookings made, allocate suitable time for the process
Poor training and education	Ensure everyone who is signed off to perform a process has had hands on training (not just read the protocol). Provide regular training sessions
Lack of communication	Establish clear lines of communication across all aspects of the facility
Equipment malfunction	Perform regular maintenance, document all maintenance

Figure 1. Common reasons for deviations to the protocol and how to mitigate.

A CAPA is designed to identify the cause and provide detailed pathway to prevent the deviation from occurring again.

How do I begin the documentation process for a QMS?

Although it seems a daunting task, you will likely already have some documents in place and it will be a case of adapting these for the relevant standard. For example, you may have an SOP for how to use a flow cytometer. But you'll likely need to expand it to be more prescriptive, add cleaning, maintenance and contingency procedures and create a form that documents the activities such as date performed, personnel performing the maintenance, reagents used and their expiry dates.

Your first task is to bring together a facility/site master file (SMF) which provides an overarching explanation of the facility and the manufacturing activities, people, equipment and quality environment. It is likely to include an organisational chart, but you can also keep this as a separate document.

The next will likely be your quality manual which provides an explanation of the quality management within the facility including policies, inclusions and exclusions, regulatory codes, responsibilities and improvement mechanisms. Information required for the SMF and the quality manual can sometimes be incorporated into one document. However, there is a slight difference in focus between the two documents that may necessitate different documents. The key difference between them is that most facilities will have a SMF, whereas only those that work within a quality framework will need the quality manual. Therefore, the SMF may have a broader scope than that of the quality manual.

Throughout the process of adding documents to the QMS it is important to ensure consistency of layout. This will make it easier to read, understand and find the information when someone new starts at the facility or when a change to the documentation is needed or if a new process is added. Using templates in your QMS will provide a framework for all your documents and will facilitate easy implementation of new policies and processes.

Conclusion

This document aims to set you up on the right path for development of a QMS, laying out some of the key principles that you'll need to include and highlighting some of the ways to make the initiation of the project possible. It is not a prescriptive list because the standards can be applied in multiple ways to fit your facility. This guidance therefore follows a similar principle of providing the "what" rather than the "how". Together with the extensive iQDOCs library available on TIA website, this guidance will help you on your journey towards complying with your relevant standard.

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Further information/ Contacts

Please refer to the following websites for current requirements

- ISO9001: https://www.iso.org/iso-9001-quality-management.html
- ISO13485: https://www.iso.org/iso-13485-medical-devices.html
- PIC/S: https://picscheme.org/en/publications?tri=gmp#zone
- TGA cGMP: https://www.tga.gov.au/how-we-regulate/manufacturing/manufacture-medicine/good-manufacturing-practice-gmp
- TGA manufacture of biologicals: https://www.tga.gov.au/resources/resource/guidance/australian-code-good-manufacturing-practice-human-blood-and-blood-components-human-tissues-and-human-cellular-therapy-products
- FACT/JACIE: https://factglobal.org/media/qpvn2kph/sts_5_2_041_fact-jacie-standards-eighth-edition_8_1_r2_12142021_forweb.pdf
- ICH GCP: https://ichgcp.net/