Development and Maintenance of a Quality Program

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1 Major Regulatory Requirements of a Quality Program

The Food and Drug Administration's (FDA) concept of quality is based on a number of systems [1–6]. These are shown in Table 1, which also details the elements of each system. The European Medicines Agency has published quality information as part of its guideline on human cell-based medicinal products [7]. This requires the use of release criteria, stability testing, and special requirements for cells that have been genetically modified and for combination products.

The FDA regulations indicate that the quality program must be under a member of management who will, irrespective of his/her other duties, establish and maintain quality system requirements, or the quality plan (QP), and who will report its performance to senior management. Documented reviews of the QP must be at defined intervals, e.g., annually. The plan should define quality practices, resources, and activities and indicate how these requirements will be met and what documentation practices will be used. In addition, it must contain a provision for audits to ensure that the quality system is in compliance and to determine its efficacy. The audit program should include a requirement for documentation of corrective actions and reaudits to determine their effectiveness.

Other components include requirements for sufficient staff with the required education, training, and experience to ensure that all activities are correctly performed. There must be established training procedures, and training must be documented. There must be a system to control documentation, and documents must be reviewed for adequacy before issue. This review will be documented by the date and signature of the individual responsible for review. Approved documents must be readily available, and obsolete documents must be removed from use. Similarly, all

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Table 1 FDA concept of modern quality systems

Parameter	Elements
Quality	Product identity, strength, purity required for safety and efficacy
Quality by design	Product consistently attains pre-defined quality, by design appropriate manufacturing processes
Quality risk management	Helps guide setting of specifications and process parameters for manufacturing and assesses and mitigates the risk of changing a process and/or specification
Corrective and preventative action (CAPA)	Investigation, understanding, and correction of discrepancies while attempting to prevent recurrence
Change control	Managing change to prevent unintended consequences
The quality unit	Usually responsible for the quality control (QC) and quality assurance (QA) units. **QC** assesses suitability of incoming products; evaluates performance of manufacturing to ensure adherence to specifications, and determines acceptability of each product for release **QA** reviews and approves all procedures related to product, associated records, and audits and performs trend analysis
Six System Inspection Model	Consists of production, facilities and equipment, laboratory control, materials, and packaging and labeling

changes to a document must be reviewed, and the changes communicated to the staff. Records of changes must be documented.

There should be procedures in place to ensure that all suppliers conform to specified requirements. This procedure should include an evaluation and selection procedure for vendors. There should be a provision for vendors to inform the manufacturer of product changes.

There must be written standard operating procedures (SOPs) in place to define and control the methods of production. The environment must be adequately controlled, and the control systems must be inspected to verify that system(s) are functioning properly. The facility must also establish requirements for health, cleanliness, personal practices, and clothing of staff. Procedures must be in place to prevent contamination of equipment or products.

Buildings must be of suitable design to perform the proposed operations, prevent mix-ups, and ensure orderly handling. Equipment must meet specified requirements, and there must be maintenance schedules and periodic inspections. Equipment must be calibrated, and calibration procedures must include directions for the calibration procedure and limits of accuracy and precision. Calibration standards that are used must be traceable to national or international standards, and the calibration must be documented.

Procedures must be validated, and validation records must be signed and dated by the reviewing individual. Validated procedures must be performed by qualified individuals who must document their performance of that procedure. When changes are made, the procedure should be revalidated.

There must be acceptance criteria for products and for incoming supplies. Acceptance or rejection must be documented. Product acceptance records must include a description of the activities performed, the dates of those activities, and the signature of the individual performing these activities. There must be procedures for dealing with nonconforming products. An investigation should be performed for nonconformance and actions documented.

There must be procedure to control labeling activities, and labels must remain legible and affixed to products during all stages of manufacturing, distribution, and use. Labels must be examined before use for accuracy, and there must be a system to prevent mix-ups. Packaging must be designed to protect the product, and it must be stored under conditions that prevent mix-ups, damage, and deterioration. There must be a system to document distribution.

All documents and records must be maintained using a system that is readily accessible to the facility and to FDA inspectors. If stored electronically, there must be a backup system. There must be a system to handle complaints and procedures for their receipt, review, and evaluation. There must be a system to evaluate whether or not an investigation must be performed.

The International Standards Organization (ISO) [8] is an independent, nongovernmental international organization that sets standards. It has 164 national standard bodies as members. The ISO 9001 standard [9] deals with quality management. It addresses customer focus, leadership, engagement of people, process approach, quality improvement, evidence-based decision-making, and relationship to management. ISO does not provide certification. This is done through accredited certification bodies after an extensive audit of the company's quality management system. The audit is performed annually. The components required for ISO 9001 certification are shown in Table 2 [10].

The International Council of Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving global harmonization to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained while meeting the highest standards. It publishes an extensive series of guidelines for quality, safety, and efficacy and seeks buy-in from national organizations. One of these is the ICH guidance Q10 on pharmaceutical quality systems [7]. It is largely based upon the ICH Q7 guideline "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" [11] and the ISO quality management system (see above). It augments these by describing specific quality system elements and management responsibilities. The guideline largely conforms to the FDA and ISO proposals in structure but also includes an annex on potential opportunities to enhance science and risk-based regulatory approaches [12]. These opportunities include compliance with GMP and demonstration of (1) an effective quality system (including the use of risk-based management principles), (2) product and process understanding, and (3) pharmaceutical quality systems.

Table 2 Components of ISO 9001 certification

Element	Component
Process approach: a process is the set of work steps that transform inputs into a more complete form – the product	Controls and checkpoints: Source of inputs Inputs – materials, information, and resources required to produce product Actions performed to create products Outputs – quality of the deliverable Receivers of outputs – customers for products
Risk-based thinking	Identify plan and implement actions to address potential risks and rewards Should be applied to product requirements review, contract negotiations, operations management, design and development, purchasing and work transfer
Leadership	Commitment to the QP Leadership defines measurable quality objectives and delegates tasks and assigns adequate resources
Planning of quality management system	Actions should be proportionate to the risk and the impact on product Planning should be results-driven All actions must be documented
Support and resources	Provide sufficient human resources and ensure competency through training Effective methods for awareness of QP and communication of changes in relevant documentation Maintain needed infrastructure, e.g., equipment and facilities Maintain and calibrate equipment
Customer focus	Monitor customer perception of the degree to which their needs and expectations have been met QP should address customer, statutory and regulatory requirements Establish processes to protect customer from receiving nonconforming products Specify objectives for product quality and delivery times Utilize customer feedback
Operations control	Plan, implement, and control processes needed for provision of product Control planned changes and review the consequences of unintended changes
Key business processes	Control product development steps and consider obsolescence Control external providers Control release and delivery of products Provide post-delivery support

(continued)

Table 2 (continued)

Element	Component
Performance evaluation improvement	Monitor, measure, analyze, and evaluate processes Use trained internal auditors to maintain QP Implement new systems for continued improvement

2 Development of a Quality Program

2.1 Initial Activities

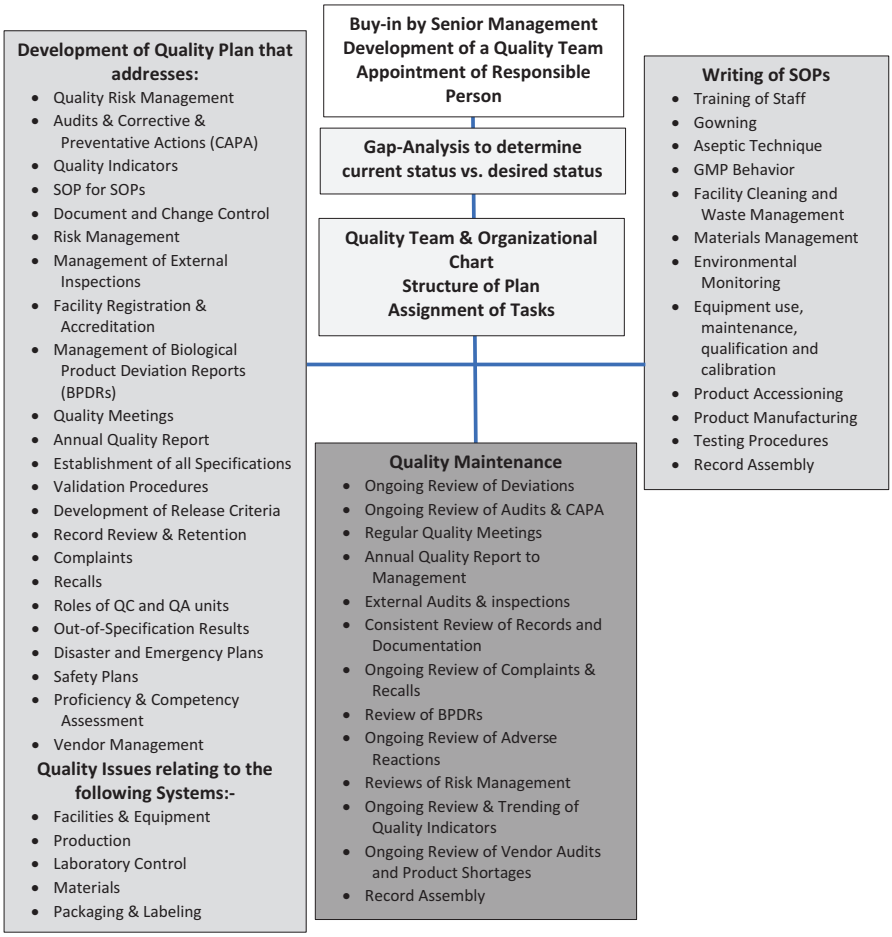
The major aims of a QP are continual improvement of processes, lowest overall cost, and maximizing customer satisfaction. The plan is usually developed in phases which include the architecture of the QP, an analysis of the current state of quality at the facility, preparation of the required documentation, implementation of the plan, and post-follow-up [13–15]. The stages of development of a QP are shown in Table 3.

It is important that upper management is seen as fully committed to quality, by actively participating in the QP design, implementation, and monitoring. They should also be advocates of quality improvement and should commit adequate resources to these activities. There must be a documented structure to the QP with clearly assigned responsibilities and authorities. When designing the QP, it is also important to determine the requirements of what needs to be documented and controlled and how policies and procedures will be organized and managed.

The next step is to perform a current state analysis. This identifies and maps the core products, as well as identifying the gaps in various processes and policies. It should include the prioritization for new or redesigned processes and any updated project plans. This should result in the development of the quality policy and its objectives and writing of the QP and related procedures. In the QP, the organizational structure should be defined and presented in the form of an organizational chart. Staff responsible for overseeing quality should not be involved in manufacturing activities, or, in the case of very small facilities, there may be external quality review by an institutional representative, or an internal review with a separation of time between manufacturing and records review. The individual responsible for overseeing the QP and reporting its activities to upper management must be identified. This individual (and designees) should also have sign-off authority to changes in processes, documents audits, etc.

The next stage is to write the SOPs that will comprise all activities performed by the facility, including those performed by the quality staff. SOPs must be written so that they provide adequate instructions for a staff member with relevant education and experience (see the chapter on SOP writing).

Table 3 Major steps in development and maintenance of a quality program



2.2 Quality Plan SOPs

It is suggested that there should be specific quality SOPs. These should include the SOP for writing SOPs, role of the quality assurance and quality control groups, document control and retention, risk management, deviation reporting, annual quality report, validation and qualification procedures, product accessioning and management, product release and distribution, environmental monitoring, management of external inspections, audits and CAPA, quality improvement, facility accreditation and registration, complaints, recalls, out-of-specification results, disaster and emergency plans, training, proficiency and competency assessment, vendor management and materials management, calibration, cleaning, pest control, and waste management.

Responsibility for defining the facility and equipment requirements falls to technical experts who understand the pharmaceutical science, risk factors, and manufacturing procedures. The quality unit should review and approve all of the initial facility design criteria and procedures pertaining to facilities and equipment.

Material management SOPs should include either testing or the use of a certificate of analysis plus an identity analysis of incoming materials. Identity analysis is not required for products made for phase 1 clinical trials [16]. Vendors should be periodically audited based on a risk assessment. Where appropriate, materials must be obtained from qualified sources. Changes to materials should be implemented through a change control system.

Training SOPs should include the following: evaluation of training needs, provision of training to meet these needs, evaluation of effectiveness of training, and documentation of training and retraining. Training should include both on specific job functions and related cGMP/cGTP regulatory requirements.

Control over the product from its design to its delivery must be defined and approved. Documentation of this control must include the resources and facilities used, procedures used to carry out the process, identification of the investigator who will maintain and update the process as needed, identification and control of important variable, quality control measures, data collection, monitoring and controls for the product and process, validation activities including acceptance criteria, and effects or related process, functions, or personnel.

One method to evaluate quality on an ongoing basis is the use of quality indicators for each operational unit. These provide a series of parameters that can be monitored on a regular basis. Examples of indicators are product sterility, accidents, number of deviations, turnaround times, corrected test reports, failure to meet release specifications, etc.

2.3 Procedure SOPs

Procedure-specific SOPs, which can be written by manufacturing/testing group managers, should include those for testing procedures, product manufacturing, release testing, cryopreservation and storage, transportation and shipment, records assembly, and specific equipment use. Procedures should be subject to (1) risk analysis to identify process weaknesses and to (2) scale-up to demonstrate that the design is fundamentally sound. The SOPs should provide an expected outcome for the procedure, and this should also be validated. The need for a change to a procedure should be based on a review and evaluation of records. All procedure SOPs must be reviewed as part of the QP and released through a documented procedure. There must then be documentation of training of relevant staff members.

3 The Quality Manual

Table 4 shows the major elements that are suggested for inclusion in the quality manual.

Table 4 Suggested major sections in a quality policy manual

Section	Purpose
Introduction	The *introduction* of the quality manual introduces you to both the standards that will be met and the manual itself
Quality management principles	The *quality management principles* section covers the core principles that drive compliance with the standards, in addition to your quality management system
References and definitions	Provides a glossary of terms, definitions, and abbreviations that will be used throughout the manual
Context of the organization	Provides information discussing various types of issues that may arise while implementing or updating the QP and features strategies that can help overcome such issues. These include both internal and external issues that may be identified by the use of a strengths, weaknesses, and opportunities (SWOT) analysis
Leadership	Indicates who is responsible for making sure that the development and implementation of the policies regarding the QP are going according to plan, and who make sure that resources for QP implementation are allocated
Management system planning	Evaluation of internal and external connections, risks/issues, successes, and opportunities that may arise
Support	The goal of *support* is to ensure improvements are made in some of the following areas: Customer satisfaction Employee satisfaction Human resources Financial resources Working area
Operations	Includes: Objectives and requirements for the product or service Verification, validation, monitoring, inspection, and test requirements Documented information to demonstrate conformity Related risks and opportunities Documented information to demonstrate conformity and control of nonconforming products Necessary resources or outsourced processes and their controls Criteria for process performance and product/service acceptance Potential consequences and mitigation to change affecting input requirements Resources necessary to support the ongoing operation and maintenance of the product
Performance evaluation	Routine review of performance to know which aspects of the QP are working correctly – and which are not, so that improvements can be made
Improvement	Analysis of data that is relevant to the QP and relates to both short-term and long-term improvement. Data can include supplier performance, internal and external audit results, and evaluation of risks and opportunities

4 Maintaining the Quality Program

Once the QP has been developed and implemented, it is important to monitor the data that are collected and to act upon the information obtained. This process is part of continuous quality improvement (Fig. 1). The following sources of information can be used:

4.1 Deviations

Deviations from procedures must be documented to provide a history of facility activities. The deviations may be planned or unplanned. Planned deviations should be cleared by QA prior to implementation. Staff must be encouraged to use the

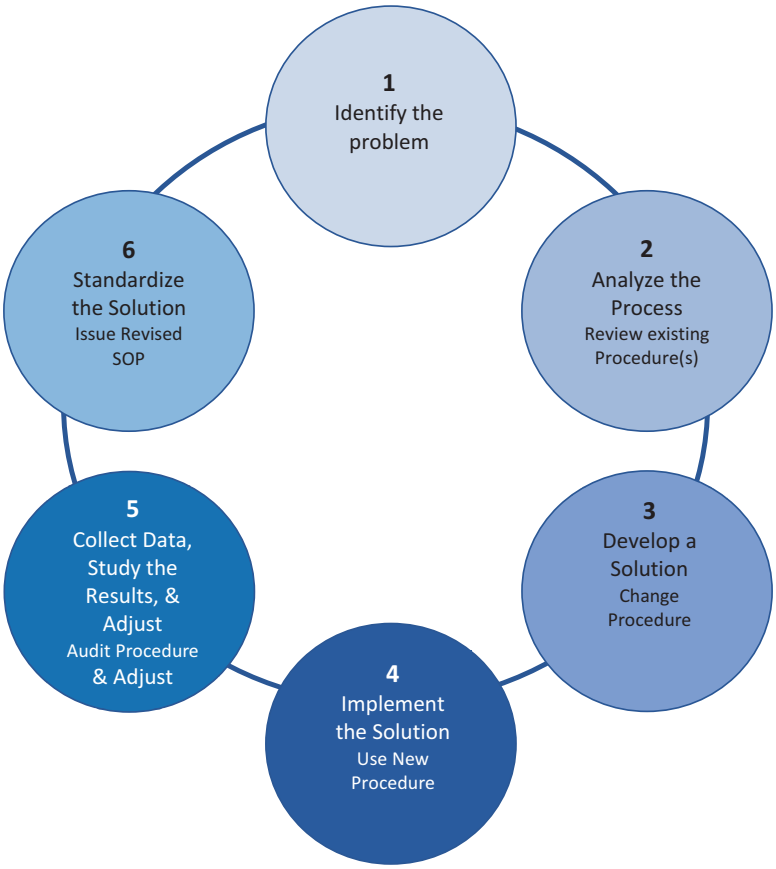


Fig. 1 Maintenance of quality program by continuous quality improvement

deviation system routinely to report any unintended change to a procedure. This should be documented, describing what happened, potential implications, and any corrective actions taken at the time. This report should be forwarded to QA who will assign it a degree of seriousness, review it for implications, and suggest corrective actions. These findings must be communicated to the staff involved in the deviation for review and for implementation of the corrective action. There must be follow-up by QA to determine the efficacy of the corrective actions and to make formal changes to the SOP if required. Deviations should be tracked as a quality indicator.

4.2 Audits and CAPA

Internal audits should be performed at sufficient frequency to enable the prompt detection of problems. Some professional standards require that there should be a calendar available detailing the audits to be performed annually. An audit should consist of a formal, planned check of the elements of the system being audited, following written audit procedures. Deficiencies and determination of whether CAPA is required should be taken in consultation with management. There should be a written description of the CAPA process and the process by which data is input. Issues to be addressed by the CAPA system can include individual or multiple procedure deviations or adverse trends detected in quality indicators. If necessary, statistical analysis should be used to detect such trends. The CAPA investigation is ultimately aimed at determining the root cause of a problem and development of corrective or preventative actions. These actions should be, where necessary, validated and should not adversely affect other product indicators. The efficacy of CAPA activities can be determined in a subsequent reaudit, and, if effective, the changes made must be disseminated to the staff, and retraining performed.

Audits should be performed by staff experienced in the procedure to be audited using a written copy of the SOP and relevant worksheets during observation of the procedure. Other audits may consist of an evaluation of systems, e.g., discard of outdated materials, recording of cleaning procedures, presence of calibration stickers on equipment, etc. These do not require the presence of facility staff during the audit. Audit findings must be documented and summarized and include a list of the issues detected. This report is returned to the audited staff, and they should address each problem with a corrective action and document it on the audit report. The report is then returned to QA for evaluation and potential closure with a scheduled follow-up to determine the efficacy of the actions taken.

4.3 Quality Meetings

Formal quality meetings should be held at regular intervals, usually quarterly, with the facility staff. There should be an attendance list and an agenda. At this meeting, it is normal to report findings for the previous quarter on the selected quality indicators, a review of actions taken as a result of the previous meeting, the numbers of products made and released, upcoming events that may affect the facility, and any other issues raised by the audience. The proceedings must be minuted, and the minutes made generally available to the staff and upper management.

4.4 Quality Agreements

It is increasingly common for facilities to use quality agreements both to audit potential vendors and in response to implementing contracts to provide manufacturing or testing services to a third party. These agreements usually define the work to be performed, the specifications to be met, timelines, etc. Central to the agreement is a questionnaire that requests information on the quality management system and indicates which party is responsible for performing specified actions. These agreements help as an additional assessment of the QP. Another source of this information can be obtained by review of complaints from customers and any recalls that were necessary.

4.5 Quality Reports

Regulatory authorities generally require that an annual quality report be submitted to upper management (usually the director of the business or academic unit). This should summarize the work of the QP during the previous year, critical findings, trends, and future plans. This report can be based on the minutes of the quarterly quality meetings supplemented with additional information. Management should acknowledge in writing receipt of the report and offered the opportunity to make comments or provide feedback. Annual quality reports are frequently requested at external audits.

4.6 Accreditation

Many facilities apply for accreditation by professional organizations. This provides an evaluation of the quality system as part of its inspection procedure. For general accreditation of the QP, ISO 9001 certification can be sought from a number of third-party organizations, which can be found online.

In the case of cell and gene therapies, accreditation can be performed by the Foundation for the Accreditation of Cellular Therapy (FACT) (predominantly in North and South America, with some additional countries), the Joint Accreditation Committee of the International Society for Cell and Gene Therapy, and the European Bone Marrow Transplant Group (JACIE) (predominantly in Europe and some additional countries) or the AABB (international). These organizations perform on-site inspections to evaluate the facility's compliance with their written standards. Other organizations, such as the College of American Pathologists, perform focused inspections on specific activities, e.g., flow cytometry, and provide accreditation in that specialty. Facilities are encouraged to participate in these programs to provide an additional information on the quality of their operations.

5 Problems Developing and Maintaining a Quality System

The following section is based on the issues confronted by the Center for Cell and Gene Therapy when developing its cGTP and cGMP Quality Systems. The first was managing writing the required SOPs. It rapidly became apparent that production of one SOP resulted in a requirement for multiple others, and a decision had to be made as to when there was a sufficient number to start operation of the facility. The number of documents produced resulted quickly in the need for a clear document control policy and the development of procedures for ensuring that staff were properly trained. The first documents to be written include the QP, the SOP for writing SOPs, and document control. Staff training probably comes next.

Initial training will be on gowning and behavior in the facility and aseptic technique. For new facilities, a facility qualification will be required with associated SOPs on facility cleaning and environmental monitoring. Once the facility is qualified, it is necessary to source order and manage reagents and materials. This will be followed by SOPs for equipment operation, maintenance, and calibration. Equipment will require qualification SOPs to ensure that it operates properly for its intended use. Manufacturing SOPs will then be developed in parallel with those for release testing and assembly of records. The development of these procedures, in turn, required preparation of a validation procedure that would meet regulatory requirements.

Manual documentation of training is extremely time consuming since the training forms have to be circulated to many people and will often sit on an individual's desk for some time, causing often undetected delays. This can be resolved by

implementing an electronic system for documenting training or adapting the e-mail system to provide a somewhat simplistic alternative.

After QP implementation, it is important to monitor the effectiveness of the plan (Table 3), perform audits, and address any detected deficiencies. The review of the QP after implementation should include the appropriateness of the quality policy, the results of audits and inspections, customer feedback and complaints, trend analysis of data, status of actions to prevent a potential problem, and follow-up of actions from previous management reviews. The review should result in improvements to the QP, to manufacturing processes and products, and realignment of resources. Initially, we performed a minimal number of audits, due to a lack of QA staff. This situation has improved, and we now have a staff of seven, with a resulting improvement in QA activities.

An area with which we have struggled is CAPA. In many cases, the deviations which are reported are classified as of low impact and appear to be the result of an isolated simple human error. We have found it difficult to perform an in-depth CAPA review and assign a root cause to such problems. We have now implemented the CAPA element of the Q-pulse quality assurance software. This guides the user through the CAPA procedure and, therefore, provides a more uniform report.

6 Conclusions

The QP provides management and regulatory authorities with the assurance that activities follow the relevant policies and procedures and result in safe and effective products of assured quality. Quality must be seen as a communal activity involving not only all facility staff but also a number of external groups and organizations that provide sources of both input and oversight. It must be seen as an activity that is mutually beneficial rather than punitive.

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