Introduction to Quality Management System

A Quality Management System (QMS) is defined as a set of interrelated or interacting elements such as policies, objectives, Aim, procedures, processes, and resources that are established individually or collectively to guide an organization.

Management Responsibility: Senior management is responsible for assigning a management representative to develop and maintain the QMS, acting as representative in all issues concerning quality. Conflicts of interest should be avoided, and the management representative shall be given sufficient authority. The necessary resources shall be available to the management representative, and the responsibilities placed on any one individual shall not be so extensive as to present any risk to product quality. Senior management should ensure:

The QMS takes into account all applicable guidelines and regulations.

Management reviews are performed on a regular basis.

The quality manual, quality policies, and quality objectives are all in place.

Job descriptions, responsibilities, and authorities are clearly understood within the organization.

The Top Ten Responsibilities of the Pharmaceutical Quality Unit are as follows,
➢ To establish the quality system
➢ To audit compliance to the quality system
➢ To establish procedures and specifications
➢ To establish manufacturing controls
➢ To perform laboratory tests or examinations
➢ To review and approve or reject all things cGMP
➢ To ensure investigation of non-conformance
➢ To keep management informed
➢ To describe responsibilities in writing
➢ To remain independent

Elements of Quality Management System

A quality management system typically consists of four facets

Quality Planning: Process of translating quality policy into processes, procedures, and instructions to achieve measurable objectives and requirements

Quality Assurance: Planned and methodical activities executed as part of a quality system to provide confidence that process, product, or service requirements for quality are being satisfied

Quality Control: Act of monitoring, appraising, and correcting a process, product, or service to ensure requirements for quality are being satisfied

Quality Improvement: Process of analyzing performance and taking methodical, systemic actions to improve it

Quality Management System Planning: The organization should take into account applicable regulatory requirements, the size of the company, the complexity of materials and products, and other critical activities when developing the QMS structure.

The QMS should be designed to maintain its robustness, even when changes occur. The quality policy, quality objectives, and quality risk management are essential in developing a QMS and should be defined by senior management.

An appropriate QMS should include, but is not limited to an organizational structure capable of supporting the elements of the quality policy and quality objectives.

➢ Written policies, procedures, records, and agreements that can demonstrate how materials, products, and services will meet established quality specifications

➢ Qualification monitoring and review of outsourced activities

➢ Competence development of personnel through training and promoting awareness of individual job impact on quality

➢ Deviations and complaints handling

➢ Continuous improvement through corrective action and preventative action (CAPA), audits, and management reviews, and QMS planning and commitment

Communication: The organization should establish communication channels that ensure the timely flow of information within the organization and to supply chain partners. Customers should be notified of any changes in packaging, handling, storage, transportation, or documentation (e.g., material safety data sheets or labels).

Communication within the supply chain should be coordinated to determine proper timing of transported and received products, taking into account holiday schedules, weekends, and other interruptions.

Documentation: The organization should have in place a system to control documents and data that are part of the QMS. Since documentation is an essential element of any QMS, having written instructions regarding processes and evidence that activities were completed is essential.

The written instructions should be well-structured and clear in order to facilitate understanding and compliance. Electronic documentation should meet the requirements stated under the Control of documents section and the electronic document control system should be validated.

Control of Documents: The goal is to ensure that all documents in use are updated, approved in a timely manner, and that the current version is in use. These practices prevent obsolete or non -approved documents from being used, which could lead to error. The organization should have a written procedure for controlling documents and establishing formal control regarding identification, revision, approval, distribution, and withdrawal of obsolete copies.

All documents should be approved and training should be performed prior to their use. All documents that relate to product quality and the QMS should be reviewed on a regular basis. The management representative, or a properly qualified designee, should approve these documents. Controlled documents should include a unique identifier, date of issue and revision, and the parties responsible for preparing, approving, and revising the documents.

Employees should have free and timely access to all quality documents that impact their work. The documents should be written in straightforward language that allows full understanding. Documents should be retained for a period required by national and international regulatory bodies (see Control of Records).

At least one obsolete copy should be retained for history after the first revision. External documents such as pharmacopeias, ISO standards, and regulatory acts and guidelines should also be controlled within the QMS.

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At least one obsolete copy should be retained for history after the first revision. External documents such as pharmacopeias, ISO standards, and regulatory acts and guidelines should also be controlled within the QMS. Documentation Categories include, but are not limited to:

Quality Manual

The organization should prepare a quality manual or equivalent documentation, such as a site master file, describing at least:

➢ Brief information on the organization (name, contact information) and its relation to other companies
➢ Activities as licensed by the competent authorities, if applicable
➢ Types of materials, products, and services handled
➢ Scope of the QMS
➢ Overview of the QMS showing the constitutive elements of the system and the structure of documentation used
➢ Quality policy
➢ Quality objectives
➢ Identification of the processes and their sequences, linkages, and interdependences
➢ Organizational chart
➢ Matrix of key personnel responsibilities
➢ Reference to supporting procedures and documents, such as a validation master plan

List of standard operating procedures (SOPs) QUALITY POLICY

Senior management should establish, authorize, and communicate a quality policy. The policy should be suitable for the organization and describe the overall intentions of the organization regarding quality.

The quality policy should be subject to periodic management review in order to maintain its appropriateness. Personnel within the organization should understand the quality policy and how their work affects it.

➢ Responsibilities
➢ Brief description of the processes to be validated

- Equipment, facilities, vehicles, and utilities to be commissioned and qualified and to what extent [installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ)]
- Templates for the protocols and reports
- Requalification and revalidation triggers Change control

Standard Operating Procedures (SOPS)

Written procedures should ensure that materials and products are held in accordance with their labeling instructions and associated regulatory requirements. The written procedures should provide all the steps needed to complete a process and ensure consistency and standard outcomes.

Organizations should establish written procedures for all processes within the organization relating to product or material handling and the QMS, including but not limited to:

- How the material or product is stored, and the controls necessary to ensure the appropriateness of the storage conditions.
- How and when a material or product should be moved from one transport container or vehicle to another.
- How materials and products are handled when equipment malfunctions or when there are delays in distribution due to customs holds, weather, etc.
- How to communicate to necessary supply chain partners.

Product Specification and Material Safety Data Sheet (MSDS)

The organization should have written specifications for incoming materials and outgoing finished materials or products. Specifications can be used for procuring, selling, and quality control analysis. An MSDS should be prepared according to national or international requirements and should be provided with the shipment for transportation, importation, or export.

Protocols

Protocols are applicable for commissioning, qualification, and validation studies. The management representative or an authorized designee should approve them.

Schedules

Organizations should have approved schedules for preventive maintenance, calibration, training, and requalification or revalidation studies.

Forms

Forms required for the operation of the QMS and the provision of the material, product, or service should be part of the document control system.

Labels

Labels are fundamental to material identification. For this reason, any label change should be communicated to down-stream supply chain partners. Label-generating systems and processes should be secure, controlled, documented, and validated.

Suitable verification records should be maintained and each container should be appropriately identified and labeled. Labels applied, even to small containers, should be clear, indelible, unambiguous, and permanently fixed in the format established by the manufacturer, packager, or re-packager.

The label should include wording or icons to emphasize storage and transportation conditions, handling requirements, and hazards. The use of symbols that are recognized by international organizations is strongly recommended.

Labeling

In the context of GDP, labeling is not limited to manufacturing information but may also include shipping and exporting information added to product tertiary packaging.

Control of Records

Records are special kinds of documents that provide evidence of activities performed. For this reason, they should be legible, clear, indelible, identifiable, traceable, and established immediately after performing an activity. The organization should have a written procedure for the control of records

These procedures should establish ways for identifying, storing, and protecting records, in order to avoid deterioration and damage. Electronic records and automated data-capture systems should meet the requirements for the control of records and should be validated. Records should be signed and dated by the person who performed the activity. Corrections to entries should be signed and dated, leaving the original entry legible with an explanation for the change, if applicable, especially if this may not be obvious to subsequent reviewers. Examples of records include: shipment receipts, invoices, packing or repacking batch records, temperature and relative humidity monitoring logs, etc.

Records should be retained for purchases and sales. They should show the date of purchase or supply, the material, product identification (name, batch or serial number, if applicable), product amount, the name and address of the supplier or consignee, and the name and address of the carrier

> ### Resources of Firm Management

Senior management should provide appropriate resources (personnel, facilities, equipment, material, and time) to implement and remain in compliance with GDPs.

1. Personnel Responsibilities and Authorities

The organization should have an organizational chart showing the organizational structure. There should be an appropriate number of personnel to avoid excessive duties being placed on one individual, which can compromise quality. Third parties may be contracted, but they should be audited for competency in executing the duties for which they are to be contracted.

The organization should establish job descriptions, with clearly defined responsibilities and authorities, that are clearly understood by personnel. Personnel should not be subjected to conflicts of interest that can adversely affect the quality of products within the supply chain.

2. Training

The organization should establish written procedures for training. These procedures should describe at least the following: who can be a trainer, competencies of a trainer, how training needs are identified, types of training practices (e.g., self-instructional, classes, on-the-job training, web-based training), and how training effectiveness will be evaluated.

Initial and ongoing training should be given based on an approved training schedule. Training needs should be identified and linked to job description, complexity of duties and types of material handled (e.g., narcotics, radiopharmaceuticals), management reviews, and any kind of human resources program for competence development.

Basic training on GDP should be given to all employees, with the goal of developing awareness outside of related job functions. Records of all training should be kept, and effectiveness of training should be assessed.

3. Hygiene, Occupational Health, and Safety

Written procedures related to hygiene and apparel should be provided, and their use should be enforced. Appropriate apparel should be provided to personnel in order to avoid contamination of both product and personnel.

The organization should be responsible for apparel cleaning. Personal protective equipment should be provided and training in its use given. Any source of product contamination or occupational hazard should be prohibited, including but not limited to: jewelry, food, medicines, or tobacco products.

These can be sources of contamination and occupational hazards, and they should be prohibited in product storage and handling areas.

Premises and Equipment Premises should be designed to maintain the quality and integrity of the materials and products stored.

Buildings should be constructed in such a way that they are appropriate for the intended operations, taking into account:

- Security and safety
- Product characteristics
- Ease of cleaning and maintenance
- Logical flow of personnel and material
- Means of preventing mix-ups and cross-contamination
- Ergonomic measures
- Any local, national, or international requirements
- Necessary environmental controls
- Facilities should be of adequate size for their intended use to prevent overcrowding. Storage should be orderly and provide segregation of quarantined, approved, rejected, returned, recalled, and adulterated products.

Receiving, sampling, and shipping areas should be segregated. Facilities should protect products and materials from inclement weather as necessary. Products with special-handling authorization, such as narcotics, should be segregated and locked in a secure area. Radiopharmaceuticals and radiolabeled materials should be contained in dedicated locked storage areas.

Products with fire or explosion risks should also be kept in dedicated areas specially constructed for this purpose. Products that require special storage conditions with regard to temperature and humidity should also be segregated.

Restrooms, lunchrooms, and social amenities for employees should be separated from the storage and shipping areas. Smoking, eating, and drinking should not be allowed in any storage or shipping area. Access control systems should be in place to prevent unauthorized access to storage areas.

Alarm systems should also be in place. Adequate precautions should be taken to prevent theft and diversion of products. Facilities should have controls and contingency plans to mitigate risks of fire, water, explosion, and terrorism.

Written procedures should be established for cleaning, sanitation, pest control, receiving, storing, and shipping activities. Cleaning and sanitation procedures should indicate the frequency of cleaning as well as the materials and methods used.

Pest control procedures should ensure the prevention of contamination as well as the safe use of pesticides. Records should be kept. All equipment and monitoring devices used to hold and move products within the supply chain

should be appropriate for their intended use. Written procedures on how to operate the equipment should be established and approved.

Organizations should establish written procedures for calibration, repair, and preventive maintenance, taking into account at least the following:

➢ Responsibilities of the in-house staff and third parties, if applicable

➢ Calibration and maintenance agreements

➢ Change control, requalification, or recalibration needs

➢ Calibration and preventive maintenance schedules

➢ Spare parts, equipment, and monitoring device management Actions to be taken if equipment or monitoring devices are found out of specification prior to recalibration

➢ Protections against damage during handling, calibration, and maintenance

Forms for recording calibration, repair, and preventive maintenance activities:

If any change is made to the equipment after repair, the organization should evaluate whether a requalification or recalibration is necessary. Calibration should be performed against traceable standards (national or international) and according to an approved schedule.

Monitoring devices should be safeguarded from actions that can invalidate the calibration. Risk assessment should be used to determine the frequency of calibration.

Commissioning and qualification should also be completed. The extent of these efforts should be determined in the validation master plan. Work Environment Organizations should ensure that appropriate work environments and conditions are provided for the products to be handled and for the personnel handling them.

A written procedure should be established by the organization determining the requirements for cleanliness, luminosity, temperature, relative humidity, pest control, personal garments, and health. Any contaminated or potentially contaminated product (e.g., complaint samples, returns, used medical devices sent for repair) should be carefully handled to avoid contamination of other products and personnel.

Material

All material handled within the supply chain or used to ensure the quality and integrity along the supply chain (e.g., reagents, growth media, transport vehicles, lubricants, HVAC spare parts) should have a written specification, which should be used for purchasing, selling, and quality control, where applicable.

A written procedure for identification and storage of all material should be in place. Quality control analysis for incoming materials should be performed (e.g., imported materials and products). Written procedures should be in place for sampling, analysis, and disposition of the products, and records kept. Quality control laboratories, where applicable, should be constructed for this purpose and based on national or international requirements. Written procedures should be established for handling controlled drug substances and drug products prior to, during, and after analysis. Obsolete materials should be destroyed according to written procedures and documented.

Transport Vehicles

All vehicles used in supply chain activities, such as semitrailer trucks, vans, trucks, tanker trucks, trains, airplanes, sea vessels, mail delivery vehicles, motorcycles, emergency medical services, and industry representatives' automobiles, should be suitable for their intended purpose. They can be considered in-transit storage and require the precautions needed to maintain product quality and integrity.

Dedicated temperature-controlled transport vehicles should be qualified. For other vehicles, shipment monitoring is required as appropriate to demonstrate the protection of the drug product or material of any storage area.

Organizations owning or leasing their transportation vehicles should have a written plan for the purchase, maintenance, and replacement of vehicles used to transport products. They should also have a transport vehicle log listing at least: vehicle identification, chassis, age, condition, mileage, operational status, and insurance policy number, if applicable.

Vehicle cleaning procedures should be written and records kept. Preventive maintenance and pest control should be done according to approved schedules, and written procedures and records kept.

Cleaning validation should be performed if the product is in contact with the transportation vehicle (e.g., tanker trucks for excipients). If there are problems with vehicles during the transportation process (e.g., breakdowns, accidents, loss of fuel), cargo should be protected against environmental factors, thefts, and diversions, and a nonconformance report should be opened. Such provisions should be included in the service level agreement.

Operations

Procurement Organizations should establish written procedures for procurement, taking into account at least:

- Purchase based on material and product specification
- Supplier qualification
- Responsibilities

- Purchase approvals
- Purchase forms and records

All intended activities and services should also comply with all local laws and regulations. The organization should establish a written procedure for how suppliers are selected and evaluated, and the criteria for qualification.

Supplier qualification audits should be handled as established in the Audits section. Records should be kept. A list of all qualified suppliers should be in place. Shipping and Receiving Organizations should establish a written procedure for receiving goods and determining the appropriate checks for this process.

A checklist can be utilized as a reminder of what to inspect and what to record, taking into account: purchase order, material or product name, amount ordered, amount received, batches or serial numbers received, expiry date, manufacturer name, marketing authorization holder name, carrier name, date and hour of receiving, cargo conditions, appearance, and whether the supplier or carrier is licensed to handle the material or product. If computerized systems are used to control orders, materials, products in stock, supplier and customer files, and carriers, the organization should record material or product item codes and internal lot numbers, if applicable.

Where appropriate, the transport vehicle should be inspected before unloading to verify that adequate protection from contamination was maintained during transit. Deliveries should be verified at receipt in order to check that containers were not damaged and that the consignment corresponds to the order.

Appropriate delivery records (e.g., transport vehicle movement documents, receiving and delivery records, data logging records, temperature records and similar devices, bills of lading, house air waybills, master air waybills) should be reviewed by each receiving organization in the supply chain to determine if the product has been subjected to any transportation delays or other events that could have exposed the product to undesirable conditions.

Each supply chain partner should ensure that its respective service level agreements and supporting documents cover delivery and receiving responsibilities of the transactional parties. All incoming materials and products should be quarantined. After disposition is confirmed, products should be transferred to their respective storage areas, according to their classification and storage specification. When products arrive at warehouse loading docks and other arrival areas, they should be transferred as quickly as possible to a designated storage area within a time period that is consistent with the risk assessment in place.

Sampling

Sampling should be performed if analytical control is required on incoming materials. The organization should establish a written procedure for sampling, including at least: sample identification, quantity, protection and safety procedures for the sample and remaining product, method for communicating results, and changes in product status and location.

Storage

Organizations should establish a written procedure for material and product storage. Each material and product should have a storage specification regarding temperature, relative humidity, and other special requirements (e.g., controlled substances and drug products and radiopharmaceuticals).

No material or product should be stored directly on the floor. Pallets should be used to hold material and products and should not cause contamination. If wood pallets or packages are used, they should comply with international requirements (e.g., International Standards for Phytosanitary Measures).

Storage areas should be qualified and a temperature mapping and monitoring program should be in place (see 1083.2). Organizations should establish a written procedure for inventory control, which should be checked periodically. If any inventory deviation is found, a nonconformance report should be opened and the appropriate authorities informed, if applicable (e.g., controlled products and radiopharmaceuticals).

Products beyond their expiry date should be removed from the saleable stock and assigned "rejected" status while awaiting destruction (see 1083.2). Sales Organizations should establish a written procedure for sale and customer qualification. This is applicable only for business-to-business partners, Regulatory authorizations for all intended activities or services (e.g., wholesale, transport) are mandatory except brokering. Copies of authorizations should be requested periodically to ensure that the "qualified" status is maintained. Lists of qualified suppliers and customers should be maintained.

Product Selection and Packaging

A written procedure should be established by the organization ensuring that the correct product was selected, properly packaged, and dispatched. Products should be selected on a first-expired, first-out basis.

Appropriate packages should be in place ensuring that the product will be preserved throughout storage and distribution. Package qualification tests should be performed according to approved protocols.

Transportation Products and materials should be transported in such a way that any specified conditions are maintained and nothing impacts the quality and integrity of the product or material.

A written procedure should be established by the organization, including at least:

- Responsibilities
- Approvals for subcontracting
- Methods for defining transportation routes
- Capacities and limitations of transportation systems, loading patterns (e.g., first- out, last-in), and insurance needs.

Carriers should record, at least: product name, amount, batches or serial numbers, sender name, recipient name, carrier route, receiving and delivery date and hour, duration and condition of transport, vehicle identification, mileage, and operator name. Transportation vehicles should be qualified and maintained. Transportation should be planned in a way that promotes a rational use of resources (e.g., transportation vehicles, fuels) and provides better logistics to avoid delays and product stress. Only licensed drivers, pilots, and operators can conduct transportation vehicles. All national and international (if applicable) regulations should be followed. A global positioning system (GPS) should be used to aid delivery and to track the transportation vehicle

Outsourcing Activities

A written agreement should be developed and signed for all outsourced activities related to the procurement of materials and services. The suitability and competence of the parties to carry out their responsibilities should be investigated.

All duties, information, and responsibilities required for both the service supplier and the customer should be clearly described. Audits should be performed to assess the appropriateness of the contractor.

Subcontractors may be used but only with formal agreements among all parties, such as the service supplier, customer, and the subcontractor. Organizations should establish written procedures to regulate any prospective outsourced activities and the related agreements.

The performance of contractors should be monitored on a regular basis, and improvements should be identified and implemented.

Complaints, Deviations, Returns, Recalls, Counterfeits, and Reprocess and Rework Products

Complaints

A written procedure for complaint handling should be in place, including at least:

Instructions for receiving complaints and communication channels available to the complainant

Complaint log

Complaint investigation form with basic information about the complainant (e.g., name, address, country, contact person, phone number, e-mail), the product or service complaint (e.g., product name, batch number, expiry date, detailed description of complaint, amount of product with alleged problem, order number, carrier name and route, shipping and storage conditions, date of complaint), results of investigation, and conclusion (confirmed, non-confirmed, or adulterated product). Each complaint investigation form should have a unique identification number.

Instructions for recommending CAPA.

The criteria for choosing appropriate CAPA depends on the nature and the frequency of the complaint.

Description of how customer complaints are addressed and resolved, and which types of complaint warrant notification of regulatory authorities

Monthly reports and trend analyses, including times for complaint handling

A complaint officer with comprehensive knowledge of the supply chain should be assigned since this person will be responsible for choosing the most applicable investigation approach.

The complaint officer also acts as a link among other areas within the organization, such as marketing, operations, quality, maintenance, regulatory, and legal affairs. Legal affairs should be notified if a suspicious or counterfeit product is identified or a breach of contract is suspected.

Records should be kept for each complaint. Monthly reports should be compiled in order to allow the evaluation of the number and the nature of complaints received. A trend analysis of complaints should be performed and used as input for management review.

Deviations

A written procedure for handling deviations should be in place. If any deviation occurs, a nonconformance report should be opened and a unique identification number assigned. The investigation should include at least the following:

- Complete description of the deviation

- Where, when, and how the deviation was found
- Actions taken to prevent non authorized use of the nonconforming product or nonconforming service
- Frequency of deviation

  Description of how the deviation impacts quality

  Necessity to trigger a corrective action

The management representative should approve all decisions concerning products or services with deviations. Records should be kept.

Returns

A written procedure for handling returns should be in place. A return form should be opened for each product that is sent back to the organization. A risk-based evaluation should be performed to determine if the product will be accepted for restocking and resale or if it will be destroyed.

Restocking should be accepted only once, with the exception of medical devices. During the evaluation, returned products should be kept in a segregated area specifically for returns until final disposition.

Each return form should have a unique identification number. The evaluation should take into account at least the following:

- Reasons for return
- Appearance and integrity of the original packaging
- Evidence of conditions in which the cargo was transported and stored throughout the entire time
- Duration of time between the original shipment and its return
- Authenticity of the product
- Representative sampling for quality control analysis
- Expiry date and batch number
- Information from any track-and-trace system in place

The QMS management representative should approve all decisions concerning returns prior to disposition of the returned goods (e.g., restocking or destruction). Records should be kept, and the product should be labeled according to its returned status.

The organization should inform customers if there is a returned product included in their order, prior to shipment.

Recalls

All supply chain partners are responsible for the quality and integrity of products under their control. Any time a deviation is found that affects the

integrity of a marketed material or product, a recall should be promptly initiated.

The organization should have a written procedure establishing the steps for recalling products, including at least:

- Responsibilities for the recall operation
- Instructions for tracking the delivery information on recalled products
- Recall communications, such as customer letters and their approval
- Frequency of recall inventory queries and regulatory updates
- Necessary documentation (e.g., distribution records with names, addresses, phone or fax numbers, contact persons, e-mail addresses, batch or serial numbers, quantities)
- Identification and segregation of recalled products
- Time frames for recall
- Forms for recording the recall progress and the final report
- Any other national or international regulatory requirements

The QMS management representative is responsible for the entire recall process applicable to the organization, including the communication within the organization and with other supply chain partners, regulatory authorities, and certification bodies. Regulatory and legal affairs departments should be aware of the recalling progress. Recalled products should be kept segregated and labeled with their recalled status. Disposition of recalled products should be recorded. Effectiveness assessment of the recall procedure should be done periodically.

Adulterated Materials and Products

The organization should have a written procedure for handling and notifying authorities if an adulterated or suspected adulterated material or product is identified within the supply chain. The marketing authorization holder or the manufacturer, if different, should also be notified.

Adulterated materials and products should be kept segregated and labeled with their adulterated status. Disposition of these products should be recorded and records kept. Counterfeit Products The term "counterfeit drug" means "a drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor" [21 U.S.C. §321(g)(2) (2004)]. This is comparable to the term "falsified medicinal product" used in the EU.

Reprocess and Rework Products

Organizations should have a written procedure for handling reprocess and rework products. A change control should be opened prior to rework and records kept. [NOTE— This item applies to packagers and repackagers.]

Monitoring and Improvements

Product or Service Quality Reviews (PSQR)

Product quality reviews are required of manufacturers. However, service providers are also responsible for product quality while the product is within their control. For this reason, a product or service quality review should be done by distributors, freight providers, importers, and exporters.

PSQRs should be performed at least annually, and summary reports on each material, product, or transportation route should be available for regulatory inspections, audits, and management reviews.

A written SOP should have at least the following, as applicable:

- Period of the review
- Product name and dosage form
- Batch numbers and quantities per batch handled
- Carrier routes
- Deviations or complaints found per product, batch, and carrier route

Audits

Audits are a valuable tool for evaluating QMS effectiveness, along with regulatory inspections. It is necessary to verify if a supply chain partner complies with QMS planning and with GDP requirements.

Internal audits are conducted by or on behalf of the organization itself. External audits are performed by, or on behalf of, organizations that might have an interest in partnering with another organization (e.g., customer for supplier qualification).

The audit criteria, scope, and objective should be clearly defined. Auditors should not be subjected to conflicts of interest that may adversely affect the audit, and for this reason auditors should not audit their own work. The organization should have a written SOP establishing the rationale for audits, which should include at least the following:

- Responsibilities for the audit program
- Description of who can be an auditor
- Competencies of an auditor
- Auditor training

- Frequency of audits
- Instructions for planning an audit (e.g., audit feasibility, criteria, scope, objective, expected duration, auditor team, travel arrangements, translators, necessary clothes and protective equipment, matters related to confidentiality)
- Instructions for conducting on-site audit activities (e.g., opening and closing meetings; collecting and verifying information methods, such as interviews, document reviews, observation activities)
- Audit reports and follow-up
- Audits should be performed at least once a year according to a schedule and discussed during management reviews.

Management Reviews

The QMS should be reviewed periodically (e.g., in each quarter of the year) in order to assess problems, trends, corrections, preventions, regulatory updates, and concerns. Inputs for the management reviews should include but are not limited to:

- Previous management review reports
- Audit and regulatory inspection reports and actions in place
- Complaints, nonconformance's, returns, and recalls
- Detected or potential counterfeiting
- Status and effectiveness of the CAPA system
- New or updated regulatory requirements
- Quality policy
- Quality objectives metrics as key performance indicators
- Change control reports
- Quality manual

The outputs of the management reviews are:

- Recommendations for improvement of the system, processes, products, or services
- Demand for resources Corrective Action and Preventive Action (CAPA) Organizations should have a written SOP establishing the provisions for corrective and preventive actions as well as instructions for how they should be handled within the organization. Root cause analysis should be performed to identify the cause of a critical deviation in order to implement corrective action. The use of quality tools for this investigation (e.g., Ishikawa diagram) is recommended.

- Confirmed complaints, critical deviations, and audits can trigger an investigation. Trend analyses, frequent non confirmed complaints, and audits can trigger a preventive action. The effectiveness of the corrective or preventive action should be evaluated.

- Continuous Improvement Organizations should implement a systematic approach for performing QMS improvements. Management reviews, audits, regulatory inspections, and QMS planning initiatives are potential triggers for continuous improvement activities and should be followed up by senior management.

Validation

Validation efforts should be established in the validation master plan and should be based on risk assessment. Commissioning and Qualification Commissioning (site acceptance test or factory acceptance test), installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ) should be performed to provide written documentation that equipment, warehouse facilities, and vehicles are installed correctly, operate as expected, and perform as required to ensure product and service quality.

Qualification and validation studies should be performed after instruments are calibrated. As appropriate, commissioning includes, but is not limited to, air-handling units, water systems, boilers, chillers, generators and emergency power systems, access control and alarm systems, safety and security systems, and repackaging equipment.

Commissioning efforts do not differentiate between occupational risk and risk to the product. Commissioning documents and reports can be incorporated into the qualification as part of IQ and OQ efforts.

After commissioning and qualification, periodic tests should be performed in order to ensure that utilities, equipment, and systems are working properly.

Any modification should be done according to change control procedures, and records should be kept. Analytical Methods, Cleaning Validation, and Process Validation Analytical methods used to perform the quality control of products, especially for imported products, should be verified or validated according to approved protocol (see Validation of Compendial Procedures 1225, Verification of Compendial Procedures 1226, and national or international requirements).

Cleaning validation should be performed on equipment and utensils if any packaging or repackaging operation exposes them to the product. Process validation should also be done for all critical operations that have the potential to compromise the quality and integrity of the product or service.

Challenges to the process should simulate regular storage and transportation conditions as well as out-of-specification conditions. Performance qualification

can substitute for process validation. After validation, any modification should be done according to change control procedures, and records should be kept.

Computerized Systems

Computerized systems should be validated according to approved protocols prior to their use. Systems already in place should also be validated. The extent of validation depends on the risk to or impact of the software on product or service quality. Validation is not applied to software that has no impact on quality. An inventory of computerized systems should be done periodically, including at least:

- Software identification (name, version)
- Software supplier
- Processes where software is used
- Process owner
- Risk assessment
- Status (validated, not validated, validation in progress, not applicable)

Amultidisciplinary team with representatives from information technology, quality, and operations should be responsible for protocols and report approvals. Responsibilities for the tests should be assigned in the protocols.

Software validation tests should cover

Security (e.g., access levels, profiles, responsibilities inclusion, exclusion, or changing profiles)

Data validity (e.g., challenge the software with entries above and below specification and with entry value errors).

Documentation (e.g., software design in accordance with user requirements and other documents)

Functionality (e.g., calculations, operations). [NOTE-Most of the functionality tests for embedded software are covered during equipment qualification (installation, operation, and performance qualifications).]

Data integrity (e.g., changes, traceability, backup, recovery, protection) After validation, any modification to the system should be done according to change control procedures. Records should be kept.

Change Control

Improvements, management reviews, complaints and deviation handling, and other monitoring systems can trigger change. The organization should have a written procedure describing the steps for change control.

It should include: responsibilities, an impact assessment of the change based on risk, necessary validation, documentation review, regulatory impact, and the necessity to have planned activities for the change.

The organization should have a team of experts to evaluate the change, including representatives from operations, quality, regulatory and legal affairs, and logistics and maintenance.

The QMS management representative should approve all changes prior to implementation. An effectiveness assessment should be carried out to confirm that QMS integrity after implementation has not changed.

Customers and regulatory bodies should be notified of any MSDS changes in packaging, handling, storage, transportation, or documentation (e.g., MSDS or labels).

Regulatory Affairs

Supply chain partners should apply for all required licenses and authorizations for their activities. These documents should be readily available for regulatory inspections and supplier and customer audits upon request.

This also applies to subcontractors. Only drug products holding marketing authorizations can be distributed within the commercial supply chain, except for investigational drug products.

A written procedure for this kind of product should be established by the organization, determining all precautions needed to ensure integrity through the supply chain. A written procedure for controlled drug substances, drug products, and radiopharmaceuticals inventory should be in place, and records should be available for audit by competent authorities. Senior management should assign a person to be in charge of all regulatory updates, applications, and issues regarding storage and distribution of materials and products handled within the organization. This person should also work to increase the regulatory awareness within the organization.

Quality Management System in Testing Laboratories

Professionals of testing laboratories have shown increasing interest in understanding the QMS and attaining accreditation status for their services since the introduction of international standards for the quality management system (QMS).

Thus Quality assurance therefore is defined as the process or the end of the process which confirms for the integrity of a product to meet the standard for the intended use. Quality assurance is an obligation automatically imposed on the manufacturer of any product to ensure that it meets the needs of the end-user in the measures intended for use. For the end-user, the benchmark of quality is perfection they cannot allow less than 100%.

Elements of the Quality Management System

The laboratory is a complex system, involving many steps of activity and many people. The complexity of the system requires that many processes and procedures be performed properly. Therefore, the QMS model, which looks at the entire system, is very important for achieving good laboratory performance. The QMS is defined as a 'management system to direct and control an organization with regard to quality. The QMS covers the laboratory activities, including drug sampling, analysis and reporting. The QMS consists of documentation of the laboratory policy and objectives, system procedures and instructions for assuring the quality of its results to meet safety and regulatory requirements and to satisfy the needs of the customers.

Pharmaceutical Quality Management System

It is applicable to drug products, including biotechnology and biological products, throughout the product lifecycle the systems supporting the development and manufacture of pharmaceutical drug substances. It includes,

- Pharmaceutical Development
- Manufacturing and development of APIs.
- Manufacture of medical kits and devices for investigation.
- Development of medical delivery systems.
- Pilot plant scale-up activities
- Manufacturing process of formulation
- Development of medical devices for accurate dosing Analytical Method Development
- During Manufacturing Process
- Acquisition and control of materials
- Provision of facilities, utilities, and equipment Production (including packaging and labelling)Quality control and assurance.
- Release
- Storage During Product Technology Transfer During product discontinuation
- Retention of sample and related documentation
- Continued product assessment and reporting

The term quality cannot be confined to one definition. It is tensile in nature and people define it in their own ways but one thing is common in all and that is satisfaction. Manufacturer is satisfied if the product meets it specification and consumer is happy when the particular product fulfils his need. But in anyways Quality is unavoidable thing today and one cannot ignore it. When it

comes in context of Pharma then Quality is a legal issue and must be maintained in pharmaceutical products. The present chapter focuses on some aspects and need of maintaining Quality in Pharma through Quality Management System pharmaceutical products.

Important Questions

1. What are the goals of a quality management system?

2. What value does a quality management system add?

3. What are the Benefits of QMS?

4. What are the prerequisites for implementing and certifying a QMS?

5. How return and recalls an important part of quality management system?

6. Change control is defined with target closure dates? Explain.

7. What are the different elements of Pharmaceutical Quality management system?

8. How important is CAPA once deviation is reported? Explain Briefly.

9. What is the difference between deviation and change control?

10. What is the difference between CAPA and QMS?

11. Define and explain in brief advantages of Audit.

12. Define SOP and advantage of SOP.