QA & QC

GMP

FDA

Quality

Traceability

Safety

Effectiveness

Purity

Compliance

Regulations

Guidelines
Training Outcome of the Module:

The basic concepts of Quality Assurance (QA), GMP and Quality Control (QC) are interrelated. The sum total of all these entities together comprises the pharmaceutical quality system (PQS). The functions or roles of QA, GMP, and QC are collectively critical to the effective and safe production and control of medicinal products.

On completion of this module, you will be able to:

- Recognize how attention to manufacturing a quality product reflects on day-to-day operations.
- Identity the role of Quality Assurance in pharmaceutical manufacturing
- Recognize how companies use GMP rules to minimize errors in manufacturing
- Identify the main roles and responsibilities of Quality Control
- Recognize the key elements of a pharmaceutical quality system
The PQS encompasses the complete supply chain for a pharmaceutical product.

**Part I: Quality Principles**

Pharmaceutical products must be manufactured according to well-established GMP rules. These GMP rules have been developed over the last 50 years and are based on practical experience and accumulated knowledge in the industry.

A quality product refers to much more than one that simply passes its laboratory tests.

**What do the GMP rules say?**

**US FDA CFR 211**

**Sec. 210.1 Status of current good manufacturing practice regulations**
(b) The failure to comply with any regulation set forth in this part and in parts
211 through 226 of this chapter in the manufacture, processing, packing, or
holding of a drug shall render such drug to be adulterated under section
501(a)(2)(B) of the act and such drug, as well as the person who is responsible
for the failure to comply, shall be subject to regulatory action.

**International GMPs**

GMP rules do not specifically define a "quality" product however they do define
under what conditions a batch may be released to the marketplace:

"Medicinal products are not sold or supplied before an authorized person has
certified that each production batch has been produced and controlled in
accordance with the requirements of the marketing authorization and any other
regulations relevant to the production, control and release of medicinal
products."

**Quality principles**

Everybody has a different understanding of the term "quality". However, in the
pharmaceutical industry, quality is very specifically defined. Quality is the sum
total of a product's purity, identity, effectiveness, and of course, its safety.
<table>
<thead>
<tr>
<th>QUALITY ATTRIBUTES</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PURITY</strong></td>
<td>Purity means being free of all foreign matter. Contamination to purity can come from incorrect machine setups, as shown here, or by using dirty equipment. An impure product could easily cause dangerous patient side effects, so there is strict GMP for controlling potential product contamination. Sometimes a contaminant can be present, but cannot be seen. It is very difficult to test for the presence of all possible contaminants.</td>
</tr>
<tr>
<td><strong>IDENTITY</strong></td>
<td>Identity means having the right product in the right container with the right labels. If a product is incorrectly identified, a patient may take the wrong strength of medication, or even the wrong medication entirely. These two situations could then easily cause severe health problems, or in extreme cases, death.</td>
</tr>
<tr>
<td><strong>EFFECTIVENESS</strong></td>
<td>An effective product is one that produces the desired result without any unwanted side effects. Mis-formulating a product or making an error in manufacture could cause a product to lose its effectiveness, leading to patient harm.</td>
</tr>
<tr>
<td><strong>SAFETY</strong></td>
<td>Safety means being free from danger or risks. Consumers have the right to be given drugs that are safe and effective. A safe product does not cause consumers adverse reactions when taken at prescribed doses.</td>
</tr>
</tbody>
</table>
GOOD TO KNOW - CONTAMINANTS

Products are expected to be pure, in that they must not contain any unapproved ingredients or any contaminants. If a product is not pure, it may have an adverse effect on a patient and would therefore become unsafe. An obvious example is bacteria in a sterile product. GMP rules throughout manufacture of the ingredients and the product help us make a pure product.

GOOD TO KNOW - PRODUCT LABELLING

Patients and healthcare professionals rely upon the labelling of a product to ensure that they take the right product and the right strength in the prescribed way.

Product labelling, if wrong, can significantly impact patient health and even cause death. GMP rules, particularly during the packaging steps, help prevent the product from being misidentified.

GOOD TO KNOW - FACTORS AFFECTING EFFICACY

During clinical trials, products are verified that they "work", or are effective. This is confirmed by regulatory agencies when products are approved for commercial manufacture.

Efficacy is largely affected by the amount of active ingredient in the product. For example, 100mg of aspirin is more effective than 50mg in most cases, so it's important to formulate the exact amount only.

The product excipients (non-active chemicals) can also affect efficacy. For example, some drugs release slowly into the bloodstream due to the right excipients being present. If not, they might release too fast (a safety problem).
or too slow (an efficacy/safety problem). GMP rules, particularly around the formulation and manufacturing steps, help to make an effective product.

GOOD TO KNOW – BUILDING SAFETY INTO THE PRODUCT

Product safety is built into the product during its development cycle during non-clinical and clinical studies. In these phases, products are tested and investigated to see if they have unacceptable adverse effects on patients. Manufacturers look for a range of “contra-indications” as well as the benefits of the product. During manufacture, it is possible to adversely impact the safety of a drug or biologic by, for example, mis-formulation, adding ingredients in the wrong order, or not following the exact manufacturing instructions. Changing the processing conditions or allowing product to degrade over the shelf life will impact product safety. Applying the GMP rules helps prevent loss of product safety.

Protecting consumers with GMP rules

To ensure that the product has adequate purity, identity, efficacy, and safety in every manufactured unit every time, GMP rules, internal company procedures, and manufacturing instruction must be strictly followed.

Some fundamental GMP rules include:

- following manufacturing instructions, packaging instruction, and registered formulae exactly
- reporting to management any deviation to instructions
- preventing contamination by:
  - making sure all process equipment is clean before use
  - keeping the facility clean
- preventing product mix-ups by double-checking labels, segregating different products, and conducting line clearances
Responsibility for quality

Traditionally, GMP has emphasized that the responsibility for quality ultimately rested with the QA and QC groups. However, managers, supervisors, process operators, and support staff all have a role in assuring product quality. Every time a product is handled. Inspected, tested, or processed, the potential exists for quality to be affected. Therefore, GMP regulations require:

- the need for suitably qualified personnel in every aspect of manufacture
- production staff having a role in GMP compliance checking
- QC testing being built into manufacturing processes

Despite quality being everyone's responsibility, all codes of GMP insist that a separate department (independent of production pressures) oversee and manage the QA systems, and take final responsibility for the quality of batches released to the consumer.

Companies therefore will usually have some combination of a QA department and QC laboratory.

GOOD TO KNOW – QA SYSTEMS

The QA systems:

- implement checks and balances during operations
- review documentation and master batch records
- organize the systems that prevent errors and product failures
- investigate defects and deviations jointly with production
- organize and review auditing and corrective action programs
- release product for sale

Knowledge and GMP behavior
As quality is everyone’s role, personnel are expected to understand how they are expected to behave in a GMP facility. GMP rules recognize that knowledge of personnel behavior toward GMP and product quality is as important as knowledge in GMP principles. As such, personnel need to know what needs to be done, how to complete tasks, and just as importantly, why they need to follow the rules.

To improve knowledge and GMP behavior, all personnel should:

- communicate with supervision and other experienced staff regarding GMP issues, especially if they think a mistake has been made
- if in doubt, ask before acting
- develop knowledge of how the products are used by customers
<table>
<thead>
<tr>
<th><strong>GMP KNOWLEDGE AND BEHAVIOR</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QUALITY KNOWLEDGE</strong></td>
</tr>
<tr>
<td>Knowing how the product is used by patients and clinicians and what effects it may have if incorrectly manufactured provides important understanding for manufacturing personnel. This knowledge enables people to better recognize why certain rules are required, and hopefully recognize when manufacturing deviations may cause patient concerns.</td>
</tr>
<tr>
<td><strong>GMP KNOWLEDGE</strong></td>
</tr>
<tr>
<td>All international GMP rules require formal training in good manufacturing practices across all levels of management and personnel, the reason for this is that the rule have been developed over 50 years, and contain practical experiential-based requirements to prevent manufacturing errors and defective product.</td>
</tr>
<tr>
<td><strong>PRODUCT / PROCESS KNOWLEDGE</strong></td>
</tr>
<tr>
<td>Manufacturing personnel should be trained and have knowledge of the products that they produce and the processes that they use, this information is often documented in the master batch or master packaging records. Personnel should be familiar with these before they manufacture any product.</td>
</tr>
<tr>
<td><strong>GMP BEHAVIOR</strong></td>
</tr>
<tr>
<td>Minimizing human error in a manufacturing environment is one of the key factors that ensure products are produced in a safe and effective manner. Personnel should always keep in mind that they are making products that are often essential life-saving medicines. The end user relies upon compliant GMP behavior to assure product quality.</td>
</tr>
</tbody>
</table>
**GMP compliance program**

The GMP compliance program assures the quality of products and protects the consumer. A GMP compliance program is made up of four parts: documentation, training, self-inspection, and corrective action for when things go wrong.

---

**GMP COMPLIANCE PROGRAM**

**Documentation**

Documentation provides personnel with essential information about relevant QA and GMP rules through SOPs, and exact ways to manufacture and test products solely through master instructions and test methods. (Companies may have slightly different names for these documents.)

Companies cannot have a quality plan without proper approved documents in place.
It is a GMP requirement that documentation must be followed exactly. Following documentation also helps minimize mistakes.

**Training**

Training is an essential requirement under GMP: personnel must be trained before they are approved to perform a job. Untrained personnel will eventually make errors and mistakes that can cost lives.

It is a GMP rule that staffs are trained to the approved documents applicable to their work areas, and they must sign to the effect that they understand the requirements.

**Self-inspection (internal audit)**

Self-inspections, or internal audits, are requirements under GMP. The purpose of a self-inspection is to independently check that the rules and documents established by QA management are being followed. Self-inspections also provide opportunities to improve procedures and practices in the factory.

**Corrective Actions**

Corrective action is required when an internal audit reveals a problem that might affect the quality of a product. Corrective action may also be required when a problem occurs in production.

Corrective actions must be documented, and incorrect procedures updated, in order to improve the company's quality plan.
Part II: Quality Assurance

One critical requirement of all drug manufacturers is that products can only be released to the marketplace if they meet all QC specifications, and they have been manufactured in accordance with the details approved by the government regulatory agency, and there have been no unresolved manufacturing errors. The batch record provides the evidence and the assurance that the product is safe to release. The QA Department is required to independently oversee and review these activities.

What do the GMP rules say?

US FDA CFR 211

Sec 211.22 Responsibilities of quality control unit.

There shall be a quality control unit** that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

** Note: The term "Quality Control Unit" may be interpreted to mean a suitable combination of Quality Assurance and Quality Control.

FDA Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations

This guidance uses the term quality unit (QU) to reflect modern practice while remaining consistent with the CGMP definition in§ 210.3(b)(15). The concept of a quality unit is also consistent with modern quality systems in ensuring that the various operations associated with all systems are appropriately planned, approved, conducted, and monitored.

International GMPs
Chapter 1 Quality Management

1.1. Quality Assurance is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide.

Overview

QA is a wide-ranging concept that covers all matters affecting product quality. Each company may interpret its QA responsibilities slightly differently.

QA generally includes the oversight and management of:

- compliance with government GMP regulations
- documented procedures and GMP
- control over starting materials
- in-process controls and validation
- QC testing of finished products
- Self-inspections I internal quality audits
- release for sale
- product reviews and trends
- storage and distribution

The need for documentation, records and traceability

GMP regulations require that all stages of manufacture are documented in order to enable traceability. Compliant documentation allows an investigation, if required into the manufacture of the batch. It also allows traceability to where products were sent.
Records that should be retained in a documentation system include records of:

- raw materials
- packaging materials
- manufacturing
- quality control testing
- finished product distribution
- incidents and deviations
- complaints

**Documents and records**

Manufacturing documents should clearly define the manufacturing process, be easy to use, and be easy to check.

There are rules as to how GMP-compliant documents and records are handled:

- Standard Operating Procedures (SOPs) and Work Instructions (WIs) must be kept current and must be readily available at the worksite.
- All SOPs, WIs and batch processing instructions must be followed exactly. Any deviations from procedures should be reported to supervisors.
- Batch documents must be verified and approved before issue to manufacturing.

It is the responsibility of management to provide a documentation system that conforms to the GMP requirements, and then train the users in the requirements of the system.

Records are the documented history of the manufacturing process. They must be complete and accurate, and demonstrate that authorized procedures were followed.
A key GMP principle is: "If it isn't documented, it wasn't done."

**Personnel and training**

The manufacture of quality products relies on people. Therefore, it is important that personnel have the right skills, knowledge, and attitudes to perform their work correctly and diligently. Types of training required by personnel include:

- induction training
- knowledge of GMP rules
- SOP training (understanding of company procedures)
- On-the-job skills training

The company must be able to demonstrate that training has been conducted satisfactorily in the above areas by maintaining training records for each person.

---

**GOOD TO KNOW – HUMAN ERROR AND BEHAVIOUR**

The majority of incidents leading to defective drug products result not from failures in technology, but from human error or simple mistakes. The behavior, attitude, care, and knowledge of employees, therefore, are critical elements in manufacturing safe drug products.

The company is required to document procedures and GMP rules, but they have no value unless employees know and follow them in all their work practices.

---

**Internal audits**

Well conducted internal audits, managed by QA, help companies identify any weaknesses in any part of manufacturing or testing processes.

Internal audits:
- are required by government
- involve all manufacturing areas
- must report findings and take corrective action
- present opportunities to improve operations and GMP standards

It is important that audits are conducted in a constructive and professional manner and encourage the active participation of the people that are responsible for corrective actions.

**Effective audits**

The following audits may be conducted:

All audits are designed to ensure the proper procedures and practices are in place and are followed.

During an audit, personnel should:

- Be prepared
- Be positive
- Slick to the facts
- Don't offer personal opinions
- Don't offer irrelevant information
EFFECTIVE AUDITS

Safety in the laboratory, manufacturing, and the warehouse is critical to a good working environment. All employees must abide by the safety rules, and regular safety audits conducted to ensure that the workplace does not present risks to personnel.

GMP rules require that personnel adhere to the requirements of GMP and the company SOPs. One way to verify this is for QA representatives to conduct regular GMP compliance audits and oversee corrective action.
Government regulators will visit the factory at least every 2 years on average to conduct an independent inspection of the facility and manufacturing practices. The outcome of the inspection may determine the issue or retention of a GMP manufacturers license, so these audits are very important.

Sometimes problems arise in the factory that may raise safety or quality concerns with a product or production line. When this happens, senior management may initiate an investigation or audit of the area concerned to see if the real cause of the problem can be identified and fixed.

GMP rules require that products be annually analyzed for trends. The purpose of this is to look for changes in product quality that may be occurring over time. These trend reports must be retained and provided to government auditors if requested.

**GOOD TO KNOW – EXTERNAL AUDITS**

External audits are generally conducted by purchasers, contractors, and accrediting bodies.

Generally, an external audit will include at least the following areas:

- the quality management system
- written procedures
- validation of processes
Corrective action

A documented action plan should be developed if any major problems arise during on internal audit. The action plan should consider the following, as appropriate:

<table>
<thead>
<tr>
<th>ATTRIBUTES OF CORRECTIVE ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activities</strong></td>
</tr>
<tr>
<td>List any activities that must be accomplished to either correct the existing problem or eliminate a potential problem.</td>
</tr>
<tr>
<td>If there are multiple activities, a corrective and preventive action (CAPA) project plan may be valuable. Assign a person to take responsibility for implementing the plan to the agreed timeframe. If the plan is complex, a CAPA team may also be valuable.</td>
</tr>
<tr>
<td>In CAPA activities, it is also important to be realistic about achievable timeframes and milestones.</td>
</tr>
<tr>
<td><strong>Documents</strong></td>
</tr>
<tr>
<td>Implementing a CAPA usually involves a change to existing practices via the change control program, as well as the updating of procedures, instructions and specifications.</td>
</tr>
<tr>
<td>It is important to identify which documents will need to be updated as part of the CAPA plan.</td>
</tr>
<tr>
<td><strong>Processes</strong></td>
</tr>
<tr>
<td>Either quality system procedures or manufacturing processes are usually revised when implementing CAPA.</td>
</tr>
</tbody>
</table>
If manufacturing processes are to be updated, they may require revalidation as part of implementation.

Once manufacturing processes are changed, it's important to continue to monitor the effects of the change on product quality in order to provide quality assurance that the change has not had any adverse effects.

**Training**

Implementing effective CAPAs often requires changes to procedures and现场 practices.

When changes of this nature occur, it is a regulatory expectation that supportive training is conducted so that CAPA permanently fixes the problem.

**Vendor assurance**

Supplier or vendor assurance programs are the first steps in ensuring that quality products are manufactured. If starting materials are sub-standard; the company would have to rely on the laboratory to find any defects through testing. As laboratory testing has some significant limitations, QA is required to implement vendor assurance programs.

QA's role in vendor assurance includes the following activities:

- Auditing critical suppliers
- Approving or rejecting suppliers whose products may affect qualify
- Changing starting material receipt testing plans, depending on the supplier risk
Monitoring the supply chain

**Change management**

Changes to products and processes are some of the hardest areas to manage in a pharmaceutical company. Often, changes have to be approved by government agencies before the changes can take place. The QA Department oversees the change programs.

![Change Management Process Diagram](image)

**Phase 1**

Staffing the process requires a change request to be raised. It is required for the correction of a problem and/or an improvement opportunity. Sources of a change request could be from anyone in manufacturing or QC or even from regulatory agencies. Change requests are formalized and given unique change tracking numbers.
**Phase 2**
This phase, overseen by QA, assesses the potential effects of any proposed change (impact assessment). Of prime concern is the potential impact on product quality, reduction, improvement over process controls, and the impact on product registration.

If the proposed change is not allowed by GMP, results in a reduction of product quality, or results in a loss of process control, the change is not implemented. If the proposed change improves or restores process control, or restores product quality, the change management process progresses to Phase 3.

**Phase 3**
At this change planning phase, there are generally two options for change, minor or major, depending on the change's impact.

Minor changes are effected by updating documents, and conducting retraining, if necessary. For major changes, a documented change plan is necessary that considers regulatory approvals, validation, training, and documentation. The change plan must be approved by QA.

**Phase 4**
In this phase the change plan is implemented. The effectiveness of the implementation is verified, usually by QA, and the documentation is finalized. The change is then closed.

Sometimes, QA may schedule a post implementation review to assess ongoing control or improvement.
**Release for supply or sale**

A formal release for supply or sale is undertaken by QA only after finished product testing has been satisfactorily completed. Release procedures require QA to:

- review all laboratory tests and batch manufacturing records
- ensure that product is correctly formulated and that any process deviations are explained
- verify that yield and reconciliation calculations are accurate
- verify that labelling and packaging is error-free

For a batch to be released to the consumer, simply passing all tests is not enough. Quality must be built in all stages of manufacture.

**GOOD TO KNOW – REVIEWING PRODUCT FOR RELEASE**

What should a good release for sale review process look for?
- a valid batch number and expiry date
the batch was formulated exactly as per the master formula

production is as per the master manufacturing and the finished product meets specifications

yields and reconciliations are within limits

the correct labels and printed matter are applied

there are no unexplained changes, corrections, or alterations in the batch records

environmental tests or controls are satisfactory

in-process checks were within expected tolerances

there were no deviations, or any deviations are fully investigated and explained

The above activities are a combination of checking against specifications (testing in quality) and examination of the process (building in quality). It is not enough to just release product because it passes all tests since only a small proportion of any batch is tested. QA must be assured that all units in the batch would meet requirements if tested and they are safe for the consumer.

After the product is released for sale, the next product review is by the customer or patient. Any problems here will result in customer complaints, or even worse, a product recall.
GMP rules have been developed over the last 50 years based on incidents, errors and disasters in drug manufacture. They represent an accumulated body of past experiences written down as rules, so that companies do not repeat past mistakes and put patients at risk.

The GMP rules are there so companies do not learn by trial-and-error. Patients' lives depend on pharmaceutical manufacturers not making mistakes.

**What do the GMP rules say?**

**US FDA CFR 211**

**FDA Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations**

Other CGMP assigned responsibilities of the QU are consistent with modern quality system approaches (§ 211.22):

- Ensuring that controls are implemented and completed satisfactorily during manufacturing operations
- Ensuring that developed procedures and specifications are appropriate and followed, including those used by a firm under contract to the manufacturer
- Approving or rejecting incoming materials, in-process materials, and drug products
- Reviewing production records and Investigating any unexplained discrepancies
International GMPs

Chapter 1 Quality Management - Clause 1.2

1.2 Good Manufacturing Practice is that part of Quality Assurance which ensures that Medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization or product specification.

Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

i. all manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;

ii. critical steps of manufacturing processes and significant changes to the process are validated;

iii. instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;

iv. operators are trained to carry out procedures correctly;

v. records ... demonstrate that all the steps required by the defined procedures and instructions were in fact taken. Any significant deviations are fully recorded and investigated ...

Overview

GMP refers to a set or licensing requirements to which companies must adhere in order to obtain and retain a manufacturer’s license. GMP rules have been agreed upon by government and industry, and the rules have been gradually refined during over 50 years or experience in practice.

Internationally, GMP rules are referred to as codes, rules, or guidance to GMP. In the USA, GMP rules (also called current GMP or cGMP) are legally enforceable regulations. While the USA and international GMP are written differently, there
is little difference in practice. The codes are written in a practical way to help manufacturers consistently make quality products.

Applying GMP correctly helps companies minimize errors during manufacture and packaging. GMP, then, always involves people, and the effects or their behavior during manufacture.

GMP requires personnel to document what they intend to do, to do what they intended, record what was actually done, and check the results against agreed specifications.

**Scope of GMP rule**

Topics covered by the GMP rules include:

- Quality management
- Personnel and training
- Equipment
- Premises and grounds
- Factory sanitation and personal hygiene
- Documentation
- Production control

**GMP and documentation**

Manufacturing documents and records provide proof of product quality, so it's very important that a complete set of documentation is maintained.

This means documenting policies and procedures such as:

- manufacturing formulae and instructions
- Specifications
- test methods

All records have to be accurately documented as well, including:
- batch records
- test records
- distribution records
- equipment log books
- training records

**Essential GMP requirements**

GMP compliance encompasses many activities that are documented in the GMP regulations, codes and rules.

<table>
<thead>
<tr>
<th>ESSENTIAL GMP REQUIREMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Validation:</strong></td>
</tr>
<tr>
<td>According to the international GMP definition, validation is “the action of proving (in accordance with GMP) that any procedure, process, equipment, material, activity, or systematically leads to expected results.”</td>
</tr>
<tr>
<td>The FDA's definition of validation is &quot;establishing documented evidence which provides a high degree of assurance that a specific process will consistently product a product a meeting its predetermined specifications and quality attributes.&quot;</td>
</tr>
<tr>
<td><strong>Process Control:</strong></td>
</tr>
<tr>
<td>GMP regulations require that all processes operate &quot;in control&quot;. In practice, this means that</td>
</tr>
</tbody>
</table>
production conditions are documented in the master production and master packaging instructions, the instructions are followed by operators, and the process is monitored to ensure that it stays in control.

Batch records provide evidence whether or not the process remained in control.

Managing Deviation:
A deviation occurs when the batch processing is not performed exactly as per the master instructions or SOPs. When a deviation does occur, GMP requires it to be formally documented and reported to QA for review.

All deviations must be resolved before a batch can be released to market.

Contamination Control:
A medicinal product is consumed by patients that are unwell or otherwise vulnerable. If the product is contaminated, this may be a health hazard for the patient. GMP rules are largely written to prevent the possibility of contamination of products either by other products, the environment, the facility, personnel, equipment or microbiologically.

GMP rules also place particular emphasis on proper and validated cleaning and sanitation procedures.
**Why does GMP require us to validate processes?**

One of the essential GMP requirements is to prevent cross-contamination of products by using effective cleaning procedures and processes.

There are a few ways to check that products being processed in this tank are not cross-contaminated:

1. **Sample and test the tank after each cleaning.**

   The tank can be sampled and tested every time, but this is expensive, time-consuming, and subject to sampling errors.

   Additionally, there is a problem of what to test for: should the tank be tested for detergent residues? Unremoved product? Bacterial contamination?

2. **Test the finished product for contaminants.**

   This approach is not a reasonable or economic approach. Again, what possible contaminants should be tested for? What will be the cost of rejecting the batch if a contaminant is found? What would be the health risk to the patient if the contaminant wasn’t detected?
3. **Validate the cleaning process.**

Validating the cleaning process would involve demonstrating under a set of specific conditions (the approved cleaning procedure) that all contaminants can consistently be removed. If the conditions can be reproduced usually three times, the cleaning process can be validated.

When the process is validated, then the company no longer has to rely on intensive and expensive testing to prove cleanliness each time.

**What needs to be validated?**

There are many things that require validation under GMP. These include:

- the suitability of the manufacturing facility
- the suitability of critical utilities such as gases and water
- GMP-related computer systems
- production equipment
- equipment and facility cleaning procedures
- laboratory test methods
- manufacturing and packaging processes

---

**GOOD TO KNOW – TEST METHOD VALIDATION**

The laboratory is required to demonstrate that all test methods are reliable. This means they must be validated by verifying the following attributes:

- precision (amount of variation in the assay)
- accuracy (difference between the average results and the "true" value)
- selectivity (ability of the method to measure the analyte in the presence of Interfering compounds)
sensitivity (limit of quantitation or limit of detection of the method)

linearity and range (over what range the method measures the analyte in direct proportion)

ruggedness (how the test method is affected by reasonable changes)

GMP regulations require that all critical steps of manufacture are reliable or validated. If a method is not validated, it is difficult to be assured results are reliable.

GOOD TO KNOW – PROCESS VALIDATION

Over the last years, the industry has learned by experience that:

"Quality cannot be tested into product, but must be built in at each stage of manufacture.”

This statement is the basis of process validation. Process validation assures that under specific and documented operating conditions, a process step will perform reliably, be in control, and will deliver a quality product every time. Limited laboratory testing is conducted to confirm that the process is still operating satisfactorily. To conduct process validation, the following must be defined:

(a) Process inputs: The critical process parameters, or CPPs, that may affect process reliability. Often, CPPs could be time, temperature, speed, order of addition, etc.

(b) Process outputs: The product critical quality attributes, or CQAs, that the process delivers. Examples of CQAs include strength or potency, particle size, moisture, purity, weight, appearance, and dissolution. CQAs will vary with the type of product manufactured.
**GMP and process control**

Under GMP, all manufacturing process steps must be "under control". After processes are initially validated, to maintain control:

- Inputs (CPPs or critical processing parameters) should be monitored throughout the process.
- Outputs (CQAs or critical quality attributes) should also be monitored against tolerances.

Adjustment to process steps are also part of maintaining control. Most manufacturing processes have documented tolerances or control limits, which if exceeded, require adjustment of the process, and sometimes raising a deviation report. Processes require adjustment if they drill into the upper and lower action zones as shown in the diagram.

![Diagram](image)

**Process deviations**

Rejects and recalls are often associated with significant deviations from standard processing conditions, so deviations should be assessed before batch release. GMP requires that deviations should be properly documented when they occur in order for QA to investigate them.
Some of the QA/GMP requirements for managing deviations include:

- QA should review process deviations.
- Planned batch deviations must be approved by QA.
- Deviations during production must be recorded.
- Batches must not be released until investigations are complete.
- Reprocessing or reworking must be approved by QA.

**Contamination control**

One of the fundamental aims of GMP is to provide rules to prevent product contamination from occurring, as contamination is almost impossible to detect once it happens. Since many patients are already unwell, contamination may make them more unwell.

Not all contaminants can be seen (e.g. bacterial contaminants), and so strict controls are needed to prevent contamination. Personnel should record on the batch records if they suspect contamination has occurred, as well as report it to supervision.

These two ampoules are actually contaminated. However, you cannot see this with the naked eye. It's important to know that not all contamination in medicinal products can be seen, and in many cases, cannot be detected in laboratory testing.
## GMP rules and cleaning

The GMP rules are very explicit regarding the requirement to clean and sanitize equipment and the manufacturing facility.

Since most residues cannot be seen nor reliably tested for, the company's standard procedures and cleaning records are relied upon as evidence of cleaning.

<table>
<thead>
<tr>
<th><strong>GMP CLEANING</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLEANING PROCEDURES</strong></td>
</tr>
<tr>
<td>GMP requires the cleaning procedures to be fully documented in written procedures. These procedures are initially validated (shown to be effective) specifically for an item of equipment or on an area.</td>
</tr>
<tr>
<td>Once validated, the procedures are then published and used.</td>
</tr>
<tr>
<td><strong>CLEANING VALIDATION</strong></td>
</tr>
<tr>
<td>All cleaning procedures should be validated (shown to be effective) under specific conditions of use. These conditions of use are specified in the written procedure.</td>
</tr>
<tr>
<td>If employees alter the conditions of use, the cleaning methods may be &quot;invalidated&quot; and may not be effective, for example, it would seem logical that adding more sanitizer than the procedure requires would make cleaning faster or better. This is not always the case. Adding additional sanitizer may alter the pH of the cleaning agent and make it less effective.</td>
</tr>
<tr>
<td>The relevant GMP rules are to only clean under validated conditions, and to follow procedures exactly.</td>
</tr>
</tbody>
</table>
### CLEANING CONDITIONS

The written procedures describe the required conditions under which cleaning is optimal. These conditions may include a range of the following:

- strength of the cleaning or sanitizing agent (e.g. 2.0% v/v)
- the type of water or solvent to be used
- the pH of the cleaning agent
- the temperature of the water to be used
- how much to dismantle equipment before cleaning commences
- the contact or residence time for the sanitizing agent on the surface
- what agents to use to clean off the sanitizing agent
- what standard of water to use in the final rinse (GMP, for example, requires purified or water for injection as the final rinse)

### CLEANING RECORDS

One essential GMP rule is the keeping of detailed cleaning records. Cleaning records provide not only proof that cleaning took place, but also provide evidence of the cleaning outcomes, for example, that the surfaces are visually clean, or the results of rinse water tests. The records must also identify who did the cleaning and when, and must be signed.

For automatic cleaning procedures such as clean in place (CIP), the cycle conditions are usually automatically monitored and the conditions recorded. Cycle conditions may include the temperature, flow rate, time, concentration of...
solvent, and solvent agitation time. Often CIP systems have alarms when something goes wrong.

The completed and signed records should be attached to the records, since they provide the only real evidence that cleaning has occurred.

---

**Part IV: Quality Control**

QC testing is only designed to test for product attributes that are well-known and understood. These attributes are part of the product specification. However, laboratory testing cannot pick up all defects because the test may not exist, the test may not be sensitive enough, or the test may not be required for that product.

Companies therefore have to rely upon GMP rules and QA systems to prevent these problems from occurring in the first place.

**What do the GMP rules say?**

**US FDA CFR 211**

**Sec. 211.160 General requirements.**

(a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit.

(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures
designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity.

**International GMPs**

**Chapter 1
QUALITY CONTROL**

1.3. Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

**Overview**

QC is the part of QA that checks the quality of a batch after it has been manufactured. QC verifies that ingredients and products meet written and approved standards, often called "specifications".

The QC laboratory tests samples of raw materials and finished products. It is critical to get accurate results from QC tests. Otherwise, defective batches may be released and good batches may be rejected.

The role of the QC laboratory then, is to detect any possible defects once they have occurred, rather than prevent them from occurring in the first GMP Rules place. The QC laboratory’s specific responsibilities include: -

- sampling, inspecting, and testing of starting materials and finished product
- calculating and checking results against specifications
- reporting all results and releasing on~ passed batches
**Typical sample flow in a QC laboratory**

![Diagram of sample flow](image)

**DOCUMENTED STEPS TO TEST A SAMPLE**

<table>
<thead>
<tr>
<th>Received labelled sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>The laboratory maintains a Sample Receiving Register. This register logs the batch and sample number, number of samples provided and the time and date the sample first entered the laboratory. This is the commencement of sample tracking.</td>
</tr>
</tbody>
</table>
Many test methods require sample preparation before the test is run. The test method should describe exactly how the sample is prepared. This may involve simple dilution or more complex extraction and manipulation. Always refer to the current test method before setting up the sample.

Once the sample is prepared, it is included in the test run. Care must be taken to ensure that the sample is not degraded, e.g. by spillage, exposure to atmosphere, or temperature degradation on the bench. Always refer to the current test method for instructions and how to protect the sample during testing. Concurrent with testing the sample, analysts should ensure that the instrument or a logbook records the sample number, and it traced exactly to the test result.

For instrumental runs such as HPLC/GC, the test method usually includes a verification that the entire instrumental system is performing satisfactorily on the day of the run. This is called "system suitability testing" (SST). Non-instrumental methods may also include control or equivalent verification systems. The test methods should describe how the integrity of particular test runs is verified.

Once the sample has been run, either the instrument or the analyst will perform a calculation to arrive of a result. It is essential to double check all calculations before finalizing sample results.
All QC laboratories have written procedures for handling and investigating only result that appears to be OOS. The analyst should ensure that as soon as an OOS event occurs, supervision is notified, the sample is retained, and a documented investigation is commenced.

Once the sample has been run, either the instrument or the analyst will perform a calculation to arrive of a result. It is essential to double check all calculations before finalizing sample results.

Before commencing any assay, the analyst should refer to the current version of the test method. The test method should be available at the worksite.

Samples must be processed through qualified and calibrated instruments. The analyst should be aware of the status of the instrument before conducting the test. In particular, the analyst should pay attention to the instrument calibration status. If an instrument is out of calibration, do not proceed with the test. All laboratory instruments, upon introduction to the laboratory, should undergo formal qualification.

Many tests require comparison of the sample to an official reference standard. The same core should be taken in preparing the reference standard as is taken when preparing the sample for test. The analyst should ensure that only the current approved reference standard should be used. The
reference standard number must be recorded in the test record.

In all QC testing laboratories, there will be a set of published and approved specifications for each starting material and finished product. When calculating and checking results, the analyst should refer to the current specification to decide the status of the sample. These specifications are often registered with the regulatory agency and cannot be changed.

Role of the laboratory

QC compliance encompasses many activities that are documented in the GMP rules.
## LABORATORY QC COMPLIANCE

<table>
<thead>
<tr>
<th>Sampling</th>
<th>Testing</th>
<th>Laboratory Documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampling of starting materials and finished products is completely governed by GMP regulations. All sampling procedures and plans must be documented. If wrong or insufficient samples are taken or a poor sampling technique is used, any subsequent testing may then give misleading results. As a result, good product may be rejected, or much worse, defective product may be released.</td>
<td>Testing of samples in the laboratory is a mandatory requirement under GMP regulations. Its effectiveness, though, is limited because the entire batch cannot be tested nor can the batch be tested for all types of potential contamination. In fact, QC testing is limited to looking for defects after they have occurred, so it is not a QA prevention system but rather a defect detection system.</td>
<td>Each product has a specific set of specifications registered with the government authorities. Starting materials and finished products are required to be tested to these specifications, and the results reported to QA management if there is a problem. Batches may not be released to the market if results do not conform to the approved specifications.</td>
</tr>
</tbody>
</table>
Laboratory documentation and records must follow the same rules as manufacturing GMP documents. The QC lab is required to have SOPs, test methods, specifications, registers, logs and testing records in place.

These documents must be current approved, accurate, provide traceability and be archived for later review. Government auditors are particularly interested in the QC testing records when they conduct GMP audits.

**G(Control)LP**

GMP rules is they are applied to the QC laboratory are sometimes called G(Control)LP rules, or G(C)LP. These G(C)LP rules are also checked during laboratory audits:

- Conduct test to approved, written test methods.
- Calibrate and quality instruments.
- All samples and standards are traceable and accounted for.
- Complete test records accurately and in real time.
- All tests are supported by validated methods.
- Record or capture all generated raw data directly, promptly and legibly.
- Use traceable data sheets or sequentially numbered notebooks.
- Date and sign or initial data entries on the day of entry.
- Archive records so that they are protected secure, and easily retrievable.

**Laboratory documentation**
The laboratory documents are designed to ensure there is linkage between the standard procedures and test methods (what is required to do) and the laboratory records (what was actually done). This forms the laboratory records quality system.

LABORATORY DOCUMENTATION OVERVIEW

**LABORATORY QUALITY MANUALS**

The laboratory quality manual and laboratory policies are top level documents describing the overall management and organization of the laboratory. These documents should reflect the requirements under GMP rules.

**STANDARD OPERATING PROCEDURES**

Standard operating procedures provide more detailed and specific requirements for each of the laboratory quality elements. For example, SOPs describe how to
| **TEST METHODS AND SPECIFICATIONS** | handle a sample, how to conduct an audit, how to release a result from the laboratory and how to manage a complaint. SOPs are generally not specific to test methods. |
| **SAMPLE AND REAGENT PREPARATION SHEETS** | Test methods provide specific step-wise direction on how to properly execute a test procedure in a standardized manner. A test method is specific to an analysis and for on instrumental technique such as HPLC. Specifications generally accompany test methods and provide pass/fail criteria and acceptance criteria for a test method, such as system suitability or control limits. |
| **LABORATORY DOCUMENTS** | Sample and reagent preparation sheets are used to document the instructions for preparing laboratory solutions, standards, and working reagents. It is important in a laboratory to provide accurate instructions and records of these preparations. Usually these sheets are linked to specific test methods. Equally important are the instructions for calibrating standard solutions. |
| | Records of testing include laboratory analyst note books, specific testing sheets, and analytical printouts, electronic records such as chromatographs, and ancillary records that support the compliance of the laboratory. Ancillary records would include calibration reports, training records, and monitoring of the environment. |
**Specifications**

Specifications are documented for starting materials, in-process product, and finished products. These specifications are submitted to the regulatory authorities when products are first registered. If specifications need to be altered for whatever reason, approval must be sought from the government regulators.

The finished product is required to meet the specifications throughout the full shelf life under the approved storage condition.

Each batch must conform to each specification when tested. All out-of-specification (OOS) conditions must be investigated.

Pharmacopoeias are legal standards for the quality of products and materials. They specify the quality attributes of products and materials in “monographs”, and provide information on how tests should be conducted.

---

<table>
<thead>
<tr>
<th>SPECIFICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting materials</strong></td>
</tr>
<tr>
<td>In the pharmaceutical industry, the requirements for starting materials must be well-defined and documented to ensure that you get the material specified or ordered, and that there are no mix ups.</td>
</tr>
<tr>
<td>Starting materials are defined by a standard name, the supplier's/manufacturer's code, and a unique item code.</td>
</tr>
<tr>
<td>Specifications for starting materials should include:</td>
</tr>
<tr>
<td>- inspections and/or tests required</td>
</tr>
<tr>
<td>- reference to test methods and acceptance criteria</td>
</tr>
<tr>
<td>- material storage conditions</td>
</tr>
</tbody>
</table>
Intermediate products

In the pharmaceutical industry, specifications for intermediate and bulk products should be available if these are received or dispatched, or if data obtained from tests on intermediate or bulk products are used for the evaluation of the finished product or further processing.

The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Packaging materials

In the pharmaceutical industry, the requirements for pre-printed packaging materials must be well-defined and documented to ensure that you get the items you specified or ordered and that there are no mix-ups.

Packaging materials are defined by a standard name, and a unique item code.

Specifications for packaging materials should include:
- a detailed description of the item
- inspections and/or tests required
- acceptance criteria
<table>
<thead>
<tr>
<th>Finished products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specifications for products typically include:</td>
</tr>
<tr>
<td>an exact statement of the active material</td>
</tr>
<tr>
<td>the product code (if any)</td>
</tr>
<tr>
<td>the dosage form and/or strength</td>
</tr>
<tr>
<td>physical appearance and identity</td>
</tr>
<tr>
<td>all tests and their limits</td>
</tr>
<tr>
<td>details of, or reference to, the test methods</td>
</tr>
<tr>
<td>sampling instructions</td>
</tr>
<tr>
<td>the shelf life and storage conditions</td>
</tr>
<tr>
<td>designated name</td>
</tr>
<tr>
<td>package details</td>
</tr>
<tr>
<td>formula (or reference to a formula)</td>
</tr>
<tr>
<td>any precautions</td>
</tr>
</tbody>
</table>
GOOD TO KNOW – OUT-OF-SPECIFICATIONS (OOS) CONDITIONS

If a single assay result does not meet the agreed specification, a laboratory investigation is required before any repeat assays are conducted.

The laboratory must determine, if possible, whether a laboratory error or a sample or batch failure is the cause of the out-of-specification result.

The Investigation should be documented according to a written procedure.

GOOD TO KNOW – TEST METHOD VALIDATION

The laboratory is required to demonstrate that all test methods are reliable, this means they must be validated by verifying the following attributes:

- precision (amount of variation in the assay)
- accuracy (difference between the average results and the "true" value)
- selectivity (ability of the method to measure the analyte in the presence of interfering compounds)
- sensitivity (limit of quantitation or limit of detection of the method)
- linearity and range (over what range the method measures the analyte in direct proportion)
- ruggedness (how the test method is affected by reasonable changes)

If a method is not validated, it is difficult to be assured that the results are reliable. GMP requires that all critical steps of manufacture are reliable or validated. This naturally includes laboratory test methods.
**Sampling**

Sampling is the removal of a representative portion of a lot to access the lot’s composition and characteristics. The purpose of testing samples is to make some inference about the lot from which the sample is drawn:

- to determine the quality level
- to detect a certain level of defects
- to assess the level of heterogeneity
- to identify mix-ups, mislabeling, or contamination

It is assumed or accepted when sampling that:

- There is an agreed or implied inherent risk in any conclusions.
- Defects are randomly distributed in the batch.
- The production process is stable and continuous.

**Sampling limitations**

No matter how well or how often QC testing is conducted, there is always some risk that defects were not detected in the lot.

This means that defective product could be released even though it passed all the tests. If one wanted to be 100% sure that a batch does not contain any defects, every unit would have to be tested. Since this is not practical, some risks would have to be accepted.

Despite these limitations, GMP regulations require companies to routinely conduct QC test. However, properly following GMP regulations and QA rules during manufacture and packaging will help prevent defects from occurring in the first place, which reduces the company's reliance on QC testing.
GOOD TO KNOW – SAMPLING PLANS AND RISKS

Sampling plans decide which lots of product to accept and release, and which lots to reject and either rework or discard. Ideally, a sampling plan should reject all "bad" lots while accepting all "good" lots. However, because the sampling plan bases its decision on a sample of the lot and not the entire lot, there is always a chance of making an incorrect decision. This is termed the **sampling risk**. If a good lot is rejected incorrectly, this is called the **suppliers risk**. Conversely, if a poor lot is accepted incorrectly, this is called the **consumers risk**. Sampling plans generally try and set these risks between 5% and 10%.

Naturally, the way the sample is selected has a big impact on the level of risk.

**Altering records**

A critical part of QC is ensuring the reliability of results.

One way to ensure that the results are error-free is to conduct a second check of calculations and raw data. This check should be independent that is, done by a different analyst or supervisor.

The following should be checked:

- The record has been completed to quality control standards.
- Current approved test method and specifications were used.
- There was an accurate recording or summary of results from the chromatographs.
- All calculations are accurate.
- Replicate results are internally consistent.
- There were no deviations from the approved test method.
- Results reported are within specification.
GOOD TO KNOW – ALTERING RECORDS

Observations, data and calculations shall be recorded at the time they are made and shall be identifiable to the specific task.

When mistakes occur in records, each mistake shall be crossed out, not erased, made illegible or deleted and the correct value entered alongside. All such alterations to records shall be signed or Initialed by the person making the correction. In the case of records stored electronically, equivalent measures shall be taken to avoid loss or change of original data.

(extract from ISO 17025)

Part V: Pharmaceutical Quality System (PQS)

PQS key elements

The PQS guidance combines critical management principles and key processes that support product quality throughout the lifecycle of the product.
### PQS KEY ELEMENTS

<table>
<thead>
<tr>
<th>2.1 MANAGEMENT COMMITMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Senior management has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the quality objectives, end that role, responsibilities, and authorities are defined. Communicated and implemented throughout the company.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3.2.1 PROCESS PERFORMANCE AND PRODUCT QUALITY MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical companies should plan and execute a system for the monitoring of process performance and product quality to ensure a state or control is maintained.</td>
</tr>
</tbody>
</table>

(b)(5) (Management should conduct) management reviews of process performance and product quality and of the pharmaceutical quality system ...
An effective monitoring system provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement.

The pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring...

The change management system ensures continual improvement is undertaken in a timely and effective manner. It should provide a high degree of assurance there are no unintended consequences of the change...

(q) Quality risk management should be utilized to evaluate proposed changes...

**Management responsibility**

The PQS places additional emphasis on the critical role management plays in ensuring product quality, compliance and effective process controls. Management provides leadership, and approves processes, systems and resources. They also take ultimate responsibility for the effectiveness of the QA. GMP and QC processes and procedures.
<table>
<thead>
<tr>
<th>MANAGEMENT RESPONSIBILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHANGE OF OWNERSHIP</strong></td>
</tr>
<tr>
<td>When product ownership changes, management should consider the complexity of this and ensure that the ongoing responsibilities are defined for each company involved and that the necessary information is transferred.</td>
</tr>
<tr>
<td><strong>RESOURCE MANAGEMENT</strong></td>
</tr>
<tr>
<td>Management should ensure that resources are appropriately applied to a specific product process or site.</td>
</tr>
<tr>
<td><strong>QUALITY PLANNING</strong></td>
</tr>
<tr>
<td>Senior management should ensure the quality objectives needed to implement the quality policy are defined and communicated. Performance indicators that measure progress against quality objectives should be established, monitored, communicated regularly and acted upon.</td>
</tr>
<tr>
<td><strong>PRODUCT QUALITY REVIEWS</strong></td>
</tr>
<tr>
<td>Pharmaceutical companies should plan and execute a system for the monitoring of process performance and product quality to ensure a state of control is maintained.</td>
</tr>
<tr>
<td><strong>QUALITY POLICY</strong></td>
</tr>
<tr>
<td>Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality.</td>
</tr>
<tr>
<td><strong>MANAGEMENT REVIEW OF THE QUALITY SYSTEM</strong></td>
</tr>
<tr>
<td>Management should assess the conclusions of periodic reviews of process performance and product quality and of the PQS.</td>
</tr>
</tbody>
</table>
Senior management has the ultimate responsibility to ensure an effective PQS is in place to achieve the quality objectives, and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the company.

Communication processes should ensure the appropriate and timely escalation of certain product quality and PQS issues.

The pharmaceutical quality system extends to the control and review of any outsourced activities and quality of purchased materials.

### Corrective and preventive action (CAPA) systems

Neither the FDA CFR 211 regulations nor international GMP standards specifically mandate CAPA systems as part of the quality assurance system, however, they are implied and expected. ICH Q10 makes this requirement more explicit. A compliant CAPA system consists of the following:

While not essential, it is helpful to describe the CAPA system as a policy, since it is such a critical quality system element. This ensures everyone knows actions to fix problems essential to compliance and improvement.
### CAPA SOP

The CAPA SOP describes the processes required actions and responsibilities for identifying, processing and resolving CAPA issues.

### CAPA REPORT

The CAPA report describes the actual CAPA event and provides a GMP record of how it was resolved. The CAPA records will also be of interest to government auditors.

### CAPA REGISTER

The register provides a list of CAPA events and their current status. From the register, managers can tell which CAPA events are the most common, and what stage they are at in being resolved. The register will also be of interest to government auditors.

In addition to this documentation, best-practice CAPA systems also have the following features:

- In-built risk assessment
- A means to trend CAPA to identify related issues
- Assigned responsibilities for CAPA actions
- A system for identifying when a CAPA closeout has not been met
- Integration with management review meetings
GOOD TO KNOW – CORRECTIVE ACTION

The organization shall take action to eliminate the cause of nonconformities in order to prevent recurrence. Corrective actions shall be appropriate to the effects of the nonconformities encountered.

A documented procedure shall be established to define requirements for
a) reviewing nonconformities (including customer complaints),
b) determining the causes of nonconformities,
c) evaluating the need for action to ensure that nonconformities do not recur,
d) determining and implementing action needed,
e) records of the results of any investigation and of the action taken, and
f) reviewing corrective action taken and its effectiveness.

Source: ISO 13485 extract

GOOD TO KNOW – PREVENTIVE ACTION

The organization shall determine action to eliminate the causes of potential nonconformities in order to prevent their occurrence. Preventive actions shall be appropriate to the effects of the potential problems.

A documented procedure shall be established to define requirements for
a) determining potential nonconformities and their causes,
b) evaluating the need for action to prevent occurrence of nonconformities,
c) determining and implementing action needed,
d) records of the results of any investigations and of action taken, and
e) reviewing preventive action taken and its effectiveness.

Source: ISO 13485 extract
CAPA phases

The CAPA system can be broken down into four distinct phases, each of which requires different actions, different outcomes, and probably different responsibilities.

Initiating event

A potential CAPA can be initialed from multiple different sources or events:

- External events or marketplace feedback such as complaints, adverse events, or service reports.
- Manufacturing nonconformities such as errors, process deviations, laboratory out-of-specifications, or starting material failures.
- Quality management system noncompliance originating from, for example, documented procedures, internal audits, regulatory audits, or product or process trend reviews.
- Poor product design

CAPAs can also originate from opportunities to improve any of the above.
Raising the CAPA
Not all problems or issues necessarily warrant a CAPA report. Companies should put in place business rules that qualify on issue as a CAPA.

One of the key tools for qualifying a CAPA is risk assessment. Generally applying risk assessment to an issue will answer the question: "Does this incident merit a further investigation and a CAPA?"

If a CAPA is raised, it should be formally documented using a CAPA form and assigned a unique tracking number. Responsibility is then assigned for conducting an investigation and root cause analysis. There are no particular rules regarding who should assume responsibility, but often it is the group or person that knows most about the problem or will derive benefit by its resolution.

The CAPA plan
This phase is about ensuring that there is a clear CAPA action plan based on the investigation and root cause analysis in the previous phase. The plan should be approved, actions to be taken should be set out, responsibilities assigned, and target completion or progress review dates nominated for particularly large CAPAs, a formal project plan would be useful.

The CAPA plan should be approved by the quality representative and the area management before implementation. The plan should also be linked to change controls where they apply.

Implement, monitor and close
The last phase of a CAPA is to implement the approved plan and track is progress against agreed dates.

Once a CAPA plan is implemented, it is necessary to verify that it has been effective by monitoring the Impact of the actions. The verification could be immediate or delayed until the CAPA impact becomes evident. It is usual to keep the CAPA in "open" status during the monitoring phase until it is formally closed.
Summary

Quality is everyone's job, and it should pervade every aspect of pharmaceutical manufacture and packaging. Quality should not be tested into products, rather, it must be built in at each step or manufacture.

Quality manifests itself in not only obvious ways, such as during actual processing steps, but also in diverse areas such as in vendor assurance, personnel training, internal audits, change management, release for supply, and QC sampling.

Pharmaceutical manufacturers must integrate the key functions of quality control (which checks for defects after they have occurred) and regulations or GMP under the banner of quality assurance. QA is charged with preventing defects and errors from occurring by overseeing all aspects of producing a quality product.
TAKE THE TEST NOW

- Number of questions: 10
- No time limit
- Allow you save and finish at a later date
- Allow you to go back and change your answer
- Attempting each question is mandatory
- Pass mark at and above 70%
- Print results and certificates