

REVIEW ARTICLE

“Quality Audit of Finished Products”

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ABSTRACT

The purpose of self-inspection is to evaluate the manufacturer’s compliance with GMP in all aspects of production and quality control. The self inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommendations for corrective action should be implemented [5].

Key words: Self inspection, GMP, Product recalls

INTRODUCTION

Finished Product:

The medical product which has undergone all stages of production including packaging in its final container. (WHO guidelines)

Specifications:

1. Generic name of product
2. Trade name
3. Dosage form & strength
4. Description including colour, shape, taste & etc.
5. Physical properties such as weight, volume, pH, viscosity, density, hardness, friability, disintegration and dissolution time.
6. Date of expiry
7. Date of issue of specification [18]

Quality audit is the process of systematic examination of a quality system carried out by an internal or external quality auditor or an audit team. It is an important part of organization's quality management system and is a key element in the ISO quality system standard, ISO 9001 [19].

Audits are an essential management tool to be used for verifying objective evidence of processes, to assess how successfully processes have been implemented, for judging the effectiveness of achieving any defined target levels, to provide

evidence concerning reduction and elimination of problem areas. For the benefit of the organisation, quality auditing should not only report non-conformances and corrective actions, but also highlight areas of good practice. In this way other departments may share information and amend their working practices as a result, also contributing to continual improvement [21].

Type of Audits:

1. Routine Audits
2. For cause Audit
3. Pre-inspection audit
4. System audit
5. Investigator site Audit(The pharma review)

Items for self-inspection:

Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:

- (1) Personnel
- (2) Premises including personnel facilities
- (3) Equipment
- (4) Qualification and validation
- (5) Quality contro;
- (6) Quality assurance
- (7) Documentation [21]

(1) Personnel

Principle: The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

General

- 1.1. The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive so as to present any risk to quality.
- 1.2. All responsible staff should have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP. The manufacturer should have an organization chart.
- 1.3. All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high-quality standards.
- 1.4. Steps should be taken to prevent unauthorized people from entering production, storage and quality control areas. Personnel who do not work in these areas should not use them as a passageway^[8].
- 1.5. Key personnel include the head of production, the head of quality control and the authorized person. Normally, key posts should be occupied by full-time personnel. The heads of production and quality control should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.
- 1.6. Key personnel responsible for supervising the manufacture and quality control of pharmaceutical products should possess the qualifications of a scientific education and practical experience required by national legislation. Their education should include the study of an appropriate combination of:

- (a) Chemistry (analytical or organic) or biochemistry;
- (b) Chemical engineering;
- (c) Microbiology
- (d) Pharmaceutical sciences and technology;
- (e) Pharmacology and toxicology;
- (f) Physiology;
- (g) Other related sciences.

They should also have adequate practical experience in the manufacture and quality assurance of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such as to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of pharmaceutical products.

- 1.7. The heads of the production and quality control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on national regulations:
 - (a) Authorization of written procedures and other documents, including amendments
 - (b) Monitoring and control of the manufacturing environment
 - (c) Plant hygiene
 - (d) Process validation and calibration of analytical apparatus
 - (e) Training, including the application and principles of quality assurance
 - (f) Approval and monitoring of suppliers of materials
 - (g) Approval and monitoring of contract manufacturers
 - (h) Designation and monitoring of storage conditions for materials and products
 - (i) Performance and evaluation of in-process controls
 - (j) Retention of records
 - (k) Monitoring of compliance with GMP requirements
 - (l) Inspection, investigation and taking of samples in order to monitor factors that may affect product quality^[14,16].
- 1.8. The head of the production generally has the following responsibilities:
 - (a) To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality

- (b) To approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation
 - (c) To ensure that the production records are evaluated and signed by a designated person
 - (d) To check the maintenance of the department, premises, and equipment
 - (e) To ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available
 - (f) To ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.
- 1.9. The head of the quality control generally has the following responsibilities:
- (a) To approve or reject starting materials, packaging materials, and intermediate, bulk and finished products in relation to their specifications;
 - (b) To evaluate batch records
 - (c) To ensure that all necessary testing is carried out
 - (d) To approve sampling instructions, specifications, test methods and other quality control procedures
 - (e) To approve and monitor analyses carried out under contract
 - (f) To check the maintenance of the department, premises and equipment
 - (g) To ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are carried out
 - (h) To ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need. Other duties of the quality control are summarized in sections 17.3 and 17.4.
- 1.10. The authorized person is responsible for compliance with technical or regulatory requirements related to the quality of finished products and the approval of the release of the finished product for sale.
- 1.11. The authorized person will also be involved in other activities, including the following:
- (a) Implementation (and, when needed, establishment) of the quality system
 - (b) Participation in the development of the company's quality manual
 - (c) Supervision of the regular internal audits or self-inspections
 - (d) Oversight of the quality control department
 - (e) Participation in external audit (vendor audit)
 - (f) Participation in validation programmes^[13].
- Personal hygiene**
- a) All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.
 - b) All personnel should be trained in the practices of personal hygiene. A high level of personal hygiene should be observed by all those concerned with manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions observed.
 - c) Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials or drug products until the condition is no longer judged to be a risk.
 - d) All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment or personnel) that they consider may adversely affect the products.
 - e) Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product.
 - f) To ensure protection of the product from contamination, personnel should wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, should be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.
 - g) Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines should not be permitted in production, laboratory and storage areas, or in any other areas where they might adversely influence product quality.

h) Personal hygiene procedures including the use of protective clothing should apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees, e.g. contractors' employees, visitors, senior managers, and inspectors.¹¹

(2) Premises

Principle:- Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out.

General

- 2.1 The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.
- 2.2 Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning.
- 2.3 Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.
- 2.4 Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.
- 2.5 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.
- 2.6 Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.
- 2.7 Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.
- 2.8 Premises should be designed and equipped so as to afford maximum protection against the entry of insects, birds or animals. There should be a procedure for rodent and pest control.
- 2.9 Premises should be designed to ensure the logical flow of materials and personnel.

- 2.10 Rest and refreshment rooms should be separate from manufacturing and control areas.
- 2.11 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not communicate directly with production or storage areas^[30].
- 2.12 Maintenance workshops should if possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.
- 2.13 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities. Storage areas
- 2.14 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.
- 2.15 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, controlled, monitored and recorded where appropriate.
- 2.16 Receiving and dispatch bays should be separated and protect materials and products from the weather. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.
- 2.17 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.
- 2.18 Segregation should be provided for the storage of rejected, recalled, or returned materials or products.
- 2.19 Highly active and radioactive materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas^[21,27].

(3) Equipment

- 3.1 Equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.
- 3.2 Equipment should be installed in such a way as to minimize any risk of error or of contamination.
- 3.3 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.
- 3.4 All service pipings and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.
- 3.5 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated on a scheduled basis.
- 3.6 Production equipment should be thoroughly cleaned on a scheduled basis.
- 3.7 Laboratory equipment and instruments should be suited to the testing procedures undertaken.
- 3.8 Washing, cleaning and drying equipment should be chosen and used so as not to be a source of contamination.
- 3.9 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.
- 3.10. Defective equipment should be removed from production and quality control areas. If this is not possible, it should be clearly labelled as defective to prevent use.
- 3.11. Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is opened, precautions should be taken to minimize contamination.
- 3.12. Non-dedicated equipment should be cleaned according to validated cleaning procedures between production of different pharmaceutical products to prevent cross-contamination.
- 3.13 Current drawings of critical equipment and support systems should be maintained ^[14].

4. Qualification and validation

- 4.1 In accordance with GMP, each pharmaceutical company should identify what qualification and validation work is required to prove that the critical aspects of their particular operation are controlled.
- 4.2 The key elements of a qualification and validation programme of a company should be clearly defined and documented in a validation master plan.
- 4.3 Qualification and validation should establish and provide documentary evidence that:
 - (a) The premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP (design qualification, or DQ)
 - (b) The premises, supporting utilities and equipment have been built and installed in compliance with their design specifications (installation qualification, or IQ)
 - (c) The premises, supporting utilities and equipment operate in accordance with their design specifications (operational qualification, or OQ)
 - (d) A specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process validation, or PV, also called performance qualification, or PQ).
- 4.4 Any aspect of operation, including significant changes to the premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, should be qualified and validated.
- 4.5 Qualification and validation should not be considered as one-off exercises. An ongoing programme should follow their first implementation and should be based on an annual review.
- 4.6 The commitment to maintain continued validation status should be stated in the relevant company documentation, such as the quality manual or validation master plan.
- 4.7 The responsibility of performing validation should be clearly defined.
- 4.8 Validation studies are an essential part of GMP and should be conducted in accordance with predefined and approved protocols.
- 4.9 A written report summarizing the results recorded and the conclusions reached should be prepared and stored.
- 4.10. Processes and procedures should be established on the basis of the results of the validation performed.

4.11. It is of critical importance that particular attention is paid to the validation of analytical test methods, automated systems and cleaning procedures^[3,12].

(5) Materials

5.1 **Principle:** The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging).

5.2 Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labelling materials.

5.3 No materials used for operations such as cleaning, lubrication of equipment and pest control, should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks.

5.4 All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.

5.5 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation by a first-expire, first-out rule.

5.6 Water used in the manufacture of pharmaceutical products should be suitable for its intended use.

Starting materials

5.7 The purchase of starting materials is an important operation that should involve staff who has a particular and thorough knowledge of the products and suppliers.

5.8 Starting materials should be purchased only from approved suppliers and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all critical aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements as well as complaints and rejection procedures, are contractually agreed between the manufacturer and the supplier.

5.9 For each consignment, the containers should be checked for at least integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.

5.10 All incoming materials should be checked to ensure that the consignment corresponds to

the order. Containers should be cleaned where necessary and labelled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.

5.11 Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the quality control department and investigated.

5.12 If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release.

5.13 Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

(a) The designated name of the product and the internal code reference where applicable;

(b) The batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;

(c) The status of the contents (e.g. on quarantine, on test, released, rejected, returned, recalled)

(d) Where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully validated computerized storage systems are used, not all of the above information need be in a legible form on the label.

5.14 There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.

5.15 Only starting materials released by the quality control department and within their shelf-life should be used.

5.16 Starting materials should be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

5.17 Each dispensed material and its weight or volume should be independently checked and the check recorded.

5.18 Materials dispensed for each batch of the final product should be kept together and conspicuously labelled as such^[2,4,16].

(6) Quality control

- (a) Adequate space is required for working area.
- (b) Adequate space for working facility.
- (c) Well trained staff
- (d) The procedure for disposal of the waste
- (e) The availability of personnel protective equipment
- (f) Separate SOP's for all equipment
- (g) Calibration procedure & records are available
- (h) Properly reagents are labelled
- (i) Culture media stored separate area
- (j) Reference & Standards are store in separate area
- (k) Samples are store in separate area
- (l) All test procedure are documented^[2,18].

(7) Quality assurance

Principle: "Quality assurance" is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

7.1 The system of quality assurance appropriate to the manufacture of pharmaceutical products should ensure that

- (a) Pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice (GLP)¹ and good clinical practice (GCP)
- (b) Production and control operations are clearly specified in a written form and GMP requirements are adopted
- (c) Managerial responsibilities are clearly specified in job descriptions;
- (d) Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials
- (e) All necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out
- (f) The finished product is correctly processed and checked, according to the defined procedures
- (g) Pharmaceutical products are not sold or supplied before the authorized persons (see also sections 9.11 and 9.12) have

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 pharmaceutical products

- (h) Satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf-life; this is a code governing the testing of chemicals to obtain data on their properties and ensuring safety with respect to human health and the environment. It is different from that described in "Good laboratory practices in governmental drug control laboratories" in the Thirtieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 748, 1987, Annex 1).
- (i) There is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system
- (j) Deviations are reported, investigated and recorded
- (k) There is a system for approving changes that may have an impact on product quality
- (l) Regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.

7.2 The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in many different departments and at all levels within the company, the company's suppliers, and the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of quality assurance

incorporating GMP and quality control. It should be fully documented and its effectiveness monitored. All parts of the quality assurance system should be adequately staffed with competent personnel, and should have suitable and sufficient premises, equipment, and facilities^[3,21].

(8) Documentation

Principle: Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases some or all of the documents described below may be brought together, but they will usually be separate.

General

- 8.1 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.
- 8.2 Documents should be approved, signed and dated by the appropriate responsible persons. No document should be changed without authorization and approval.
- 8.3 Documents should have unambiguous contents: the title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.
- 8.4 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.
- 8.5 Where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.

8.6 Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

8.7 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records should be retained for at least one year after the expiry date of the finished product.

8.8 Data (and records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked. Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs or other means. It is particularly important that, during the period of retention, the data are readily available^[3,22].

CONCLUSION

Quality audits are typically performed at predefined time intervals and ensure that the institution has clearly-defined internal quality monitoring procedures linked to effective action. This can help determine if the organization complies with the defined quality system processes and can involve procedural or results-based assessment criteria.

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