

# Quality assurance essay sample

[Business](#), [Management](#)



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**Abstract :** The purpose of quality assurance in pharmaceutical industry is to help ensure that each medicine reaching a patient is safe, effective, and of acceptable quality. A comprehensive quality assurance program includes both technical and managerial activities, spanning the entire supply process from pharmaceutical selection to patient use. A quality assurance program should include training and supervision of staff members at all levels of the production and supply process and a suitable information system.

### Introduction

“ 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.

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1. 2 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)<sup>1</sup> 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 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. (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.

1. 3 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. Pharmaceutical quality assurance framework

The following five elements are critical to achieving the expected treatment outcome. Using a pharmaceutical product to treat a patient presumes that the—

1. Active pharmaceutical ingredient (API) has been shown to be safe and effective for this treatment
2. Product is of suitable quality to provide an effective outcome
3. Prescriber has accurately identified the need for the Treatment
4. Prescriber or dispenser has properly instructed the patient on how to use the product
5. Patient complies with the prescribed regimen correctly

Data analysis and evaluation

Documentation Review

Decision making and enforcement

Inspection of local/imported product samples, manufacturing sites, and marketplace

Reporting

## Product testing

### Good manufacturing practices for pharmaceutical products (GMP)

2. 1 Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMP are aimed primarily at diminishing the risks inherent in any pharmaceutical production. Such risks are essentially of two types: cross contamination (in particular of unexpected contaminants) and mix-ups

(confusion) caused by, for example, false labels being put on containers.

Under GMP:

(a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;

(b) qualification and validation are performed;

(c) all necessary resources are provided, including:

(i) appropriately qualified and trained personnel;

(ii) adequate premises and space;

(iii) suitable equipment and services;

(iv) appropriate materials, containers and labels;

(v) approved procedures and instructions;

- (vi) suitable storage and transport;
  - (vii) adequate personnel, laboratories and equipment for in-process controls;
- (d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;
- (e) operators are trained to carry out procedures correctly;
- (f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated;
- (g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
- (h) the proper storage and distribution of the products minimizes any risk to their quality;
- (i) a system is available to recall any batch of product from sale or supply; (j) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.

#### 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. 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. Qualification stages

11. 1 There are four stages of qualification:

- design qualification (DQ);
- installation qualification (IQ);
- operational qualification (OQ); and
- performance qualification (PQ).

11. 2 All SOPs for operation, maintenance and calibration should be prepared during qualification.

11. 3. Training should be provided to operators and training records should be maintained.

Design qualification

11. 4 Design qualification should provide documented evidence that the design specifications were met.

Installation qualification

11. 5 Installation qualification should provide documented evidence that the

installation was complete and satisfactory.

11. 6 The purchase specifications, drawings, manuals, spare parts lists and vendor details should be verified during installation qualification. 11. 7

Control and measuring devices should be calibrated.

#### Operational qualification

11. 8 Operational qualification should provide documented evidence that utilities, systems or equipment and all its components operate in accordance with operational specifications.

11. 9 Tests should be designed to demonstrate satisfactory operation over the normal operating range as well as at the limits of its operating conditions (including worst case conditions).

11. 10 Operation controls, alarms, switches, displays and other operational components should be tested.

11. 11 Measurements made in accordance with a statistical approach should be fully described.

#### Performance qualification

11. 12 Performance qualification should provide documented evidence that utilities, systems or equipment and all its components can consistently perform in accordance with the specifications under routine use.

11. 13 Test results should be collected over a suitable period of time to prove consistency.

#### Requalification

11. 14 Requalification should be done in accordance with a defined schedule. The frequency of requalification may be determined on the basis of factors

such as the analysis of results relating to calibration, verification and maintenance. 11. 15 There should be periodic requalification, as well as requalification after changes (such as changes to utilities, systems, equipment; maintenance work; and movement). (See also point 5. 2. 5 above and section 12 below.) 11. 16 Requalification should be considered as part of the change control procedure.

### Revalidation

11. 17 Processes and procedures should be revalidated to ensure that they remain capable of achieving the intended results.

11. 18 There should be periodic revalidation, as well as revalidation after changes. (See also points 5. 2. 5 above, point 11. 21 below and section 12 below.) 11. 19 Revalidation should be done in accordance with a defined schedule. 11. 20 The frequency and extent of revalidation should be determined using a risk-based approach together with a review of historical data.

### 3. Sanitation and hygiene

3. 1 A high level of sanitation and hygiene should be practised in every aspect of the manufacture of drug products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product.

Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene. Product recalls

6. 1 Principle. There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective. 6. 2 The authorized person should be responsible for the execution and coordination of recalls. He/she should have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.

6. 3 There should be established written procedures, which are regularly reviewed and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly down to the required level in the distribution chain.

6. 4 An instruction should be included in the written procedures to store recalled products in a secure segregated area while their fate is decided. 6. 5 All competent authorities of all countries to which a given product has been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.

6. 6 The distribution records should be readily available to the authorized person, and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.

6. 7 The progress of the recall process should be monitored and recorded. Records should include the disposition of the product. A final report should be issued, including a reconciliation between the delivered and recovered quantities of the products.

6. 8 The effectiveness of the arrangements for recalls should be tested and evaluated from time to time.

#### Self-inspection and quality audits

Principle. The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The selfinspection 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. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

#### 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:

- (a) personnel;
- (b) premises including personnel facilities;
- (c) maintenance of buildings and equipment;
- (d) storage of starting materials and finished products;
- (e) equipment;

- (f ) production and in-process controls;
- (g) quality control;
- (h) documentation;
- (i) sanitation and hygiene;
- (j) validation and revalidation programmes;
- (k) calibration of instruments or measurement systems;
- (l) recall procedures;
- (m) complaints management;
- (n) labels control;
- (o) results of previous self-inspections and any corrective steps taken.

#### Self-inspection team

Management should appoint a self-inspection team consisting of experts in their respective fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

#### Frequency of self-inspection

The frequency at which self-inspections are conducted may depend on company requirements but should preferably be at least once a year. The frequency should be stated in the procedure.

#### Self-inspection report

A report should be made at the completion of a self-inspection. The report should include:

- (a) self-inspection results;
- (b) evaluation and conclusions;
- (c) recommended corrective actions.

### Follow-up action

There should be an effective follow-up programme. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

### Quality audit

It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors.

### Suppliers' audits and approval

The person responsible for quality control should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

Before suppliers are approved and included in the approved suppliers' list or specifications, they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier's ability to conform with GMP standards.

### Personnel

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

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.

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.

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.

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.



### Key personnel

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.

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.

### Training

The manufacturer should provide training in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required.

Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness periodically assessed. Approved training programmes should be available. Training records should be kept.

Personnel working in areas where contamination is a hazard, e. g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.

The concept of quality assurance and all the measures which aid its understanding and implementation should be fully discussed during the training sessions.

Visitors or untrained personnel should preferably not be taken into the production and quality control areas. If this is unavoidable, they should be given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing. They should be closely supervised.

Consultant and contract staff should be qualified for the services they provide. Evidence of this should be included in the training records. Premises

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

#### General

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.

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.

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.

Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.

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.

Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.

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.

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.

Premises should be designed to ensure the logical flow of materials and personnel.

#### Storage areas

12. 3 Storage areas should be well organized and tidy. Special attention should be paid to cleanliness and good maintenance. Any accidental spillage should be cleaned up immediately using methods that minimize the risk of cross-contamination of other materials, and should be reported. 12. 4 The set-up of storage areas depends on the type of materials stored. The areas should be well labelled and materials stored in a such a way as to avoid any risk of cross-contamination. An area should be identified for the quarantine of all incoming herbal materials.

12. 5 Storage areas should be laid out to permit effective and orderly segregation of the various categories of materials stored, and to allow

rotation of stock. Different herbal materials should be stored in separate areas. 12. 6 To protect the stored material, and reduce the risk of pest attacks, the duration of storage of any herbal material in unpacked form should be kept to

a minimum.

12. 7 Incoming fresh herbal materials should be processed, unless specified otherwise, as soon as possible. If appropriate, they should be stored between 2 °C and 8 °C, whereas frozen materials should be stored below –18 °C. 12.

8 Where materials are stored in bulk, to reduce the risk of mould formation or fermentation it is advisable to store them in aerated rooms or containers using natural or mechanical aeration and ventilation. These areas should also be equipped in such a way as to protect against the entry of insects or animals, especially rodents. Effective measures should be taken to limit the spread of animals and microorganisms brought in with the plant material and to prevent cross-contamination.

12. 9 Herbal materials, even when stored in fibre drums, bags or boxes, should be stored off the floor and suitably spaced to permit cleaning and inspection. 12. 10 The storage of plants, extracts, tinctures and other preparations may require special conditions of humidity and temperature or protection from light; appropriate steps should be taken to ensure that these conditions are provided, maintained, monitored and recorded.

12. 11 Herbal materials, including raw herbal materials, should be kept in a dry area protected from moisture and processed following the principle of “first in, first out” (FIFO).

## Production areas

12. 12 Production areas should comply with the general requirements of GMP

(1). As a rule, campaign work in their processing is necessary. However, if feasible, the use of dedicated premises is encouraged. Moreover, the special nature of the production of herbal medicines requires that particular attention be given to processing products that generate dust. When heating or boiling of the materials is necessary, a suitable air exhaust mechanism should be employed to prevent accumulation of fumes and vapours.

12. 13 To facilitate cleaning and to avoid cross-contamination, adequate precautions should be taken during the sampling, weighing, mixing and processing of medicinal plants, e. g. by use of dust extraction and air-handling systems to achieve the desired differential pressure and net airflow.

## Equipment

13. 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, 13. 2 Equipment should be installed in such a way as to minimize any risk of error or of contamination.

13. 3 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

13. 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.

13. 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.

13. 6 Production equipment should be thoroughly cleaned on a scheduled basis.

13. 7 Laboratory equipment and instruments should be suited to the testing procedures undertaken.

13. 8 Washing, cleaning and drying equipment should be chosen and used so as not to be a source of contamination.

13. 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.

13. 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.

13. 11 Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is opened, precautions should be taken to minimize contamination.

13. 12 Non-dedicated equipment should be cleaned according to validated cleaning procedures between production of different pharmaceutical products to prevent cross-contamination.

13. 13 Current drawings of critical equipment and support systems should be maintained. and, in general, any adverse effect on the quality of products.

## Documentation

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

Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.

Documents should be approved, signed and dated by the appropriate responsible persons. No document should be changed without authorization and approval.

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.

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.

Where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.

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.

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.

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

## Documents required

- \* Labels
- \* Specifications and testing procedures
- \* Specifications for starting and packaging materials
- \* Specifications for intermediate and bulk products
- \* Specifications for finished products
- \* Master formulae
- \* Packaging instructions
- \* Batch processing records
- \* Batch packaging records
- \* Standard operating procedures (SOPs) and records

## Standard operating procedures (SOPs) and records

15. 31 Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for:
- (a) equipment assembly and validation;
  - (b) analytical apparatus and calibration;
  - (c) maintenance, cleaning and sanitization;
  - (d) personnel matters including qualification, training, clothing and hygiene;
  - (e) environmental monitoring;
  - (f) pest control;
  - (g) complaints;
  - (h) recalls;
  - (i) returns.

15. 32 There should be standard operating procedures and records for the receipt of each delivery of starting material and primary and printed packaging material.

15. 33 The records of the receipts should include:

- (a) the name of the material on the delivery note and the containers; (b) the “ in-house” name and/or code of the material if different from (a); (c) the date of receipt;
- (d) the supplier’s name and, if possible, manufacturer’s name; (e) the manufacturer’s batch or reference number;
- (f ) the total quantity, and number of containers received;
- (g) the batch number assigned after receipt;
- (h) any relevant comment (e. g. state of the containers).

15. 34 There should be standard operating procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

15. 35 Standard operating procedures should be available for each instrument and piece of equipment (e. g. use, calibration, cleaning, maintenance) and placed in close proximity to the equipment.

15. 36 There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples.

15. 37 The sampling instructions should include:

- (a) the method of sampling and the sampling plan;
- (b) the equipment to be used;
- (c) any precautions to be observed to avoid contamination of the material or

any deterioration in its quality;

(d) the amount(s) of sample(s) to be taken;

(e) instructions for any required subdivision of the sample; (f ) the type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling, and labelling;

(g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

15. 38 There should be a standard operating procedure describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.

15. 39 The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

15. 40 The standard operating procedure for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.

15. 41 Batch-number allocation should be immediately recorded, e. g. in a logbook. The record should include at least the date of allocation, product identity and size of batch.

15. 42 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

15. 43 Analysis records should include at least the following data: (a) the name of the material or product and, where applicable, dosage form; (b) the batch number and, where appropriate, the manufacturer and/or supplier; (c) references to the relevant specifications and testing procedures; (d) test results, including observations and calculations, and reference to any specifications (limits); (e) date(s) and reference number(s) of testing; (f) the initials of the persons who performed the testing; (g) the date and initials of the persons who verified the testing and the calculations, where appropriate; (h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

15. 44 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.

15. 45 Records should be maintained of the distribution of each batch of a product in order, e. g. to facilitate the recall of the batch if necessary. 15. 46 Records should be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out. 15. 47 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.

15. 48 There should be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned. Such written procedures should be followed.

#### Master formulae

15. 22 A formally authorized master formula should exist for each product and batch size to be manufactured.

15. 23 The master formula should include:

- (a) the name of the product, with a product reference code relating to its specification;
- (b) a description of the dosage form, strength of the product and batch size;
- (c) a list of all starting materials to be used (if applicable, with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);
- (d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
- (e) a statement of the processing location and the principal equipment to be used;
- (f) the methods, or reference to the methods, to be used for preparing and operating the critical equipment, e. g. cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;
- (g) detailed step-wise processing instructions (e. g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);

(h) the instructions for any in-process controls with their limits; (i) where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions; (j) any special precautions to be observed.

#### Packaging instructions

15. 24 Formally authorized packaging instructions should exist for each product, pack size and type. These should normally include, or make reference to:

- (a) the name of the product;
- (b) a description of its pharmaceutical form, strength and, where applicable, method of application;
- (c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
- (d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging material; (e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
- (f) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;
- (g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;

(h) details of in-process controls with instructions for sampling and acceptance limits.

#### Batch processing records

15. 25 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)

15. 26 Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.

15. 27 During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations:

(a) the name of the product;

(b) the number of the batch being manufactured;

(c) dates and times of commencement, of significant intermediate stages, and of completion of production;

(d) the name of the person responsible for each stage of production; (e) the initials of the operator(s) of different significant steps of production and,



where appropriate, of the person(s) who checked each of these operations (e. g. weighing)

(f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);

(g) any relevant processing operation or event and the major equipment used; (h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;

(i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;

(j) notes on special problems including details, with signed authorization for any deviation from the master formula.

#### Batch packaging records

15. 28 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)

15. 29 Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.

15. 30 The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:

(a) the name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;

(b) the date(s) and time(s) of the packaging operations;

(c) the name of the responsible person carrying out the packaging operation;

(d) the initials of the operators of the different significant steps; (e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;

(f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;

(g) whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;

(h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;

(i) the quantities and reference number or identification of all printed pack

aging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

#### 14. Materials

14. 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).

14. 2 Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labelling materials.

#### General

14. 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.

14. 4 All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.

14. 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.

14. 6 Water used in the manufacture of pharmaceutical products should be suitable for its intended use.

## Starting materials

14. 7 The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.

14. 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. 14. 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.

14. 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. 14. 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.

14. 12 If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release. 14. 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.

14. 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.

14. 15 Only starting materials released by the quality control department and within their shelf-life should be used.

14. 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.

14. 17 Each dispensed material and its weight or volume should be independently checked and the check recorded.

14. 18 Materials dispensed for each batch of the final product should be kept together and conspicuously labelled as such.

#### Packaging materials

The purchase, handling and control of primary and printed packaging materials should be as for starting materials.

Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized access. Roll-feed labels should be used wherever possible. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.

Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

Outdated or obsolete primary packaging material or printed packaging material

should be destroyed and its disposal recorded.

All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

#### Intermediate and bulk products

Intermediate and bulk products should be kept under appropriate conditions.

Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

#### Finished products

Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.

The evaluation of finished products and the documentation necessary for release of a product for sale are described in section 17, " Good practices in quality control".

#### Rejected, recovered, reprocessed and reworked materials

Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a timely manner. Whatever action is taken should be approved by authorized personnel and recorded.

The reworking or recovery of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept of the reworking or recovery. A reworked batch should be given a new batch number.

The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture

should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery should be recorded.

The need for additional testing of any finished product that has been reprocessed, reworked or into which a recovered product has been incorporated, should be considered by the quality control department.

#### Recalled products

Recalled products should be identified and stored separately in a secure area until a decision is taken on their fate. The decision should be made as soon as possible.

#### Returned goods

Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabelling, or alternative action taken only after they have been critically assessed by the quality control function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.

#### Practical approaches to quality assurance

The procedures to establish a comprehensive quality assurance program can be divided into three categories— 1. Procedures to ensure that only medicine



products that meet current standards for quality are bought. These include—

- Careful product selection
- Careful supplier selection
- Certificate of analysis for each batch of product
- Certification of good manufacturing practices
- Batch certification (WHO-type certificate of a pharmaceutical product)
- Inclusion of detailed product-quality specifications

in the contract

2. Procedures to verify that shipped goods meet the specifications. These include—

- Pre- and postshipment inspection
- Analytical pharmaceutical testing

3. Procedures to monitor and maintain the quality of pharmaceuticals from the moment they are received until the medicine is finally consumed by the patient.

These involve—

- Proper storage and distribution procedures
- Appropriate dispensing
- Instructions to the patient on proper use of medications
- Product defect and pharmacovigilance reporting programs

Conclusion

Recommendations and guidelines provide an essential foundation for the development and maintenance of quality assurance of pharmaceutical

products. But it is personnel who are crucial to quality assurance at all levels of pharmaceutical manufacture, regulation and distribution. While quality assurance is founded on regulations and standards, it is the people who enforce the regulations or work to comply with the standards who make the difference between quality assurance and lack of it. The assurance of quality, safety and efficacy of medicines is a continuing concern of WHO. This compilation of material is intended to assist all involved in the manufacture, regulation and distribution of pharmaceuticals to achieve these aims more effectively. The manufacturer Hetero Drugs Ltd, Unit III, located in Hyderabad, India was considered to be operating at an acceptable level of GMP compliance but has not yet been certified by the WHO and US FDA.

#### References

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