GUIDE TO GOOD MANUFACTURING

PRACTICE FOR MEDICINAL PRODUCTS

PART I
BASIC REQUIREMENTS

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INTRODUCTION

Licensed pharmaceutical products (complying with the requirements of the marketing authorization) should be manufactured only by licensed manufacturers (holders of a manufacturing license) whose activities are regularly inspected by competent Egyptian authorities. This guide to GMP shall be used as a standard to justify GMP status, which constitutes one of the elements of the GMP Certification Scheme on the Quality of Pharmaceutical Products moving in local and international Commerce, through the assessment of applications for manufacturing authorizations and as a basis for the inspection of manufacturing facilities. It may also be used as training material for government drug inspectors, as well as for production, quality control and quality assurance personnel in the industry.

This guide is applicable to operations for the manufacture of drugs in their finished dosage forms, including large-scale processes in hospitals and the preparation of supplies for use in clinical trials. The good practices outlined below are to be considered general guides, and they may be adapted to meet individual needs. The equivalence of alternative approaches to quality assurance, however, should be validated. The guide as a whole does not cover safety aspects for the personnel engaged in manufacture or environmental protection: these are normally governed by Egyptian legislation. The manufacturer should assure the safety of workers and take the necessary measures to prevent hazard imitation of the external environment governed by the Egyptian legalization.

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CHAPTER 1

Quality Management

PRINCIPLE

The holder of a Manufacturing Authorization must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of 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 by staff in many different departments and at all levels within the company, by the company suppliers and by the distributors. To achieve the quality objective in a reliable manner, there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice and thus Quality Control. It should be fully documented and its effectiveness monitored.

All parts of the Quality Assurance system should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. There are additional legal responsibilities for the holder of the Manufacturing Authorization (Manufacturing License) and for the Persons responsible for Production and Release of products. The basic concepts of Quality Assurance (QA), Good Manufacturing Practice (GMP), Quality Control (QC) and Quality Risk Management are interrelated. They are described here in order to emphasize their relationships and their fundamental importance to the production and control of medicinal products.

QUALITY MANAGEMENT IN THE DRUG INDUSTRY: PHILOSOPHY AND ESSENTIAL ELEMENTS

1.1 In the drug industry at large, quality management is usually defined as the aspect of management function that determines and implements the “quality policy”, i.e. the overall intention and direction of an organization regarding quality, as formally expressed and authorized by top management.

The basic elements of quality management are:

- An appropriate infrastructure or “quality system”, encompassing the organizational structure, procedures, processes and resources
- Systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality. The totality of these actions is termed “quality assurance”.

Within an organization, quality assurance serves as a management tool. In contractual situations, quality assurance also serves to generate confidence in the supplier. The concepts of quality assurance, GMP and quality control are interrelated aspects of quality management. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

QUALITY ASSURANCE (QA)

1.2. 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.

The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that:

(i) medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice ;

(ii) production and control operations are clearly specified and Good Manufacturing Practice adopted;

(iii) managerial responsibilities are clearly specified;

(iv) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials from approved vendor;

(v) all necessary controls on intermediate products, and any other in process controls and validations are carried out;

(vi) the finished product is correctly processed and checked, according to the defined procedures;

(vii) medicinal products are not sold or supplied before the QC/QA operation 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;

(viii) satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;

(ix) There is a procedure for self inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the quality assurance system.

GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS (GMP)

1.3. 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. all necessary facilities for GMP are provided including:
   a. Appropriately qualified and trained personnel.
   b. Adequate premises and space.
   c. Suitable equipment and services.
   d. Correct materials, containers and labels.
   e. Approved procedures and instructions.
   f. Suitable storage and transport.

IV. Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided.

V. Operators are trained to carry out procedures correctly.

VI. Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated.

VII. Records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form.

VIII. The distribution (wholesaling) of the products minimizes any risk to their quality.

IX. A system is available to recall any batch of product, from sale or supply.

X. Complaints about marketed products are recorded and examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence.

QUALITY CONTROL (QC)

1.4. 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.

The basic requirements of Quality Control are that:

I. adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;

II. samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control;

III. test methods are validated;

IV. Records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;

V. the finished products contain active ingredients complying with the qualitative and quantitative composition of the marketing authorization, are of the purity required, and are enclosed within their proper containers and correctly labeled;

VI. Records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;

VII. no batch of product is released for sale or supply prior to certification by an authorized person that it is in accordance with the requirements of the relevant authorizations;

VIII. Sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

PRODUCT QUALITY REVIEW

1.5. Regular periodic or rolling quality reviews of all licensed medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

i. A review of starting materials including packaging materials used in the product, especially those from new sources.

ii. A review of critical in process controls and finished product results.

iii. A review of all batches that failed to meet established specification(s) and their investigation.

iv. A review of all significant deviations or non conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.

v. A review of all changes carried out to the processes or analytical methods.

vi. A review of Marketing Authorization variations submitted/granted/ refused, including those for third country (export only) dossiers.

vii. A review of the results of the stability monitoring program and any adverse trends.

viii. A review of all quality related returns, complaints and recalls and the investigations performed at the time.

ix. A review of adequacy of any other previous product process or equipment corrective actions.

x. For new marketing authorizations and variations to marketing authorizations, a review of post marketing commitments.

xi. The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.

xii. A review of any contractual arrangements as defined in Chapter 7 to ensure that they are up to date.

The manufacturer and marketing authorization holder should evaluate the results of this review and an assessment made of whether corrective and preventative action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventative actions should be completed in a timely and

effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified.

Where the marketing authorization holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The authorized person responsible for final batch certification together with the marketing authorization holder should ensure that the quality review is performed in a timely manner and is accurate.

QUALITY RISK MANAGEMENT

1.6. Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

1.7. The quality risk management system should ensure that:

- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;
- The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

Examples of the processes and applications of quality risk management can be found inter alia in Annex 20.

CHAPTER 2

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

2.1. 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.

2.2. 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.

2.3. 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.

2.4. 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.

KEY PERSONNEL

2.5. Key personnel include the head of production (MANUFACTURING), the head of quality operations (Q.C/Q.A) who is the authorized person for release of finished product. Normally, key posts should be occupied by full-time personnel. The heads of production and quality operations 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.

2.6 Key personnel responsible for supervising the manufacture and quality operations of pharmaceutical products should possess the qualifications of a scientific education and practical experience required by Egyptian 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 judgment, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of pharmaceutical products.

2.7 The heads of the production and quality operations generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on Egyptian 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 control equipment
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.

2.8 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.

2.9 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 with 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 chapter 6

2.10 The authorized person (head of quality operations) 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.

2.11 The authorized person will also be involved in other activities, including the following:

a. implementation (and, when needed, establishment) of the quality system;
b. supervision 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. supervision in external audit (vendor audit);
f. Supervision &approval in validation programs.

2.12 The function of the approval of the release of a finished batch or a product can be delegated to a designated person with appropriate qualifications and experience who will release the product in accordance with an approved procedure. This is normally done by quality assurance manager by means of batch review.

2.13 The person responsible for approving a batch for release should always ensure that the following requirements have been met:

a. the marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned;
b. the principles and guidelines of GMP, as laid down in the guidelines published by Egyptian ministry of health, have been followed;
c. the principal manufacturing and testing processes have been validated, if different;
d. all the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records;
e. Any planned changes or deviations in manufacturing or quality control have been notified in accordance with a well defined reporting system

before any product is released. Such changes may need notification to, and approval by, the drug regulatory authority;

f. any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations;
g. all necessary production and quality control documentation has been completed and endorsed by supervisors trained in appropriate disciplines;
h. appropriate audits, self-inspections and spot-checks are carried out by experienced and trained staff;
i. approval has been given by the head of quality control;
j. All relevant factors have been considered, including any not specifically associated with the output batch directly under review (e.g. subdivision of output batches from a common input, factors associated with continuous production runs).

TRAINING

2.14 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.

2.15 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.

2.16 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.

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

2.18 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.

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

PERSONAL HYGIENE

2.20 All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.

2.21 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.

2.22 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.

2.23 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.

2.24 Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product.

2.25 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.

2.26 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.

2.27 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.

2.28 Any specific requirements for the manufacture of special groups of products, for example sterile preparation, are covered in the supplementary guide lines.

CHAPTER 3

PREMISES AND EQUIPMENT

PRINCIPLE

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

PREMISES

GENERAL

3.1 Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

3.2 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

3.3 Electrical supply Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.

3.4 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

3.5 Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

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

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

3.8 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.

PRODUCTION AREA

3.9 In order to minimize the risk of a serious medical hazard due to cross contamination, dedicated and self contained facilities must be available for the production of particular medicinal products, such as highly sensitizing materials (e.g. penicillin's) or biological preparations (e.g. from live microorganisms).The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non medicinal products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

3.10 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

3.11 The adequacy of the working and in process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different medicinal products or their components, to avoid cross contamination and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

3.12 Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.

3.13 Pipe work, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

3.14 Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

3.15 Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment. These areas should be regularly monitored during both production and non-production periods to ensure compliance with their design specifications.

3.16 Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.

3.17 In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross contamination and facilitate cleaning.

3.18 Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix ups or cross contamination.

3.19 Productions areas should be well lit, particularly where visual online controls are carried out.

3.20 In process controls may be carried out within the production area provided they do not carry any risk for the production.

STORAGE AREAS

3.21 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

3.22 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

3.23 Receiving and dispatch bays should protect materials and products from the weather. Receptions areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

3.24 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.

3.25 There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross contamination.

3.26 Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

3.27 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.

3.28 Printed packaging materials are considered critical to the conformity of the medicinal products and special attention should be paid to the safe and secure storage of these materials.

QUALITY CONTROL AREAS

3.29 Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiological and radioisotopes, which should also be separated from each other.

3.30 Quality Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents and records and records.

3.31 Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

3.32 Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples. The design of the laboratories should take into account the suitability of construction materials, prevention of fumes and ventilation. There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, microbiological and radioisotope laboratories.

ANCILLARY AREAS

3.33 Rest and refreshment rooms should be separate from manufacturing &control areas.

3.34 Facilities for changing, storing clothes, and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.

3.35 Maintenance workshops should as far as 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.

3.36 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

EQUIPMENT

3.37 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.

3.38 Repair and maintenance operations should not present any hazard to the quality of the products.

3.39 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.

3.40 Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.

3.41 Equipment should be installed in such a way as to prevent any risk of error or of contamination.

3.42 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 such an extent that it will affect the quality of the product and thus present any hazard.

3.43 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.

3.44 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

3.45 Fixed pipe work should be clearly labeled to indicate the contents and, where applicable, the direction of flow.

3.46 Distilled, deionized and, where appropriate, other water pipes should be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

3.47 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labeled as defective.

3.48 All service piping and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.

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

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

3.51 Current drawings of critical equipment and support systems should be maintained.

CHAPTER 4

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

4.1. Specifications describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Manufacturing Formulae, Processing and Packaging Instructions state all the starting materials used and lay down all processing and packaging operations.

Procedures give directions for performing certain operations e.g. cleaning, clothing, environmental control, sampling, testing, and equipment operations.

Records provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent for the quality of the final product.

4.2. Documents should be designed, prepared, reviewed and distributed with care. They4 should comply with the relevant parts of the manufacturing and marketing authorization dossiers.

4.3. Documents should be approved, signed and dated by appropriate and authorized persons.

4.4. Documents should have unambiguous contents; 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.

4.5. Documents should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.

4.6. Documents should not be handwritten; although, where documents require the entry of data, these entries may be made in clear, legible, indelible handwriting. Sufficient space should be provided for such entries.

4.7. Any alteration made to the entry on 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.

4.8. The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable. They should be retained for at least one year after the expiry date of the finished product.

4.9. Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed 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 authorised 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 result of entry of critical data should be independently checked. Batch records electronically stored should be protected by backup transfer on magnetic tape, microfilm, paper or other means. It is particularly important that the data are readily available throughout the period of retention..

DOCUMENTS REQUIRED

SPECIFICATIONS & TESTING

4.10 Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routine testing.

4.11 There should be appropriately authorized and dated specifications, including tests on identity, content, purity and quality, for starting and packaging materials and for finished products; where appropriate, they should also be available for intermediate or bulk products. Specifications for water, solvents and reagents (e.g. acids and bases) used in production should be included.

4.12 Each specification should be approved, signed and dated, and maintained by quality control, quality assurance unit or documentation centre. Specifications for starting materials, intermediates, and bulk, finished products and packaging materials are referred to in sections (4.15, 4.16,4.17,4.18&4.19).

4.13 Periodic revisions of the specifications may be necessary to comply with new editions of the official compendia.

4.14 Pharmacopoeias, reference standards, reference spectra and other reference materials should be available in the quality control laboratory.

SPECIFICATIONS FOR STARTING AND PACKAGING MATERIALS

4.15 Specifications for starting, primary and printed packaging materials should provide, if applicable, a description of the materials, including:

a) the designated name (if applicable, the INN) and internal code reference;
b) the reference, if any, to a pharmacopoeial monograph;
c) Qualitative and quantitative requirements with acceptance limits.

4.16 Depending on the company's practice other data may be added to the specification, such as:

a) the supplier and the original producer of the materials;
b) a specimen of printed materials;
c) directions for sampling and testing, or a reference to procedures;
d) storage conditions and precautions;
e) The maximum period of storage before re-examination.

4.17 Packaging material should conform to specifications, and should be compatible with the material and/or with the drug product it contains. The material should be examined for compliance with the specification, and for defects as well as for the correctness of identity markings. Documents describing testing procedures should state the required frequency for re-assaying each starting material, as determined by its stability.

SPECIFICATIONS FOR INTERMEDIATE AND BULK PRODUCTS

4.18 Specifications for intermediate and bulk products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used for the evaluation of the finished product. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

SPECIFICATIONS FOR FINISHED PRODUCTS

4.19 Specifications for finished products should include:

a. the designated name of the product and the code reference where applicable;
b. the formula or a reference to;
c. a description of the pharmaceutical form and package details;
d. directions for sampling and testing or a reference to procedures;
e. the qualitative and quantitative requirements, with the acceptance limits;

f. the storage conditions and any special handling precautions, where applicable;
g. the shelf life
h. the designated name(s) of the active ingredient(s) (if applicable, with the INN(s)

MANUFACTURING FORMULA AND PROCESSING INSTRUCTIONS

4.20 Formally authorized Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured. They are often combined in one document.

4.21 The Manufacturing Formula should include:

a. the name of the product, with a product reference code relating to its specification;
b. a description of the pharmaceutical form, strength of the product and batch size;
c. a list of all starting materials to be used, with the amount of each, described using the designated name and a reference which 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.

4.22 The Processing Instructions should include:

a. a statement of the processing location and the principal equipment to be used;
b. the methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilizing);
c. detailed stepwise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
d. the instructions for any in process controls with their limits;
e. where necessary, the requirements for bulk storage of the products; including the container, labeling and special storage conditions where applicable;
f. Any special precautions to be observed.

PACKAGING INSTRUCTIONS

4.23. There should be formally authorized Packaging Instructions for each product for pack size and type. These should normally include, or have a reference to, the following:

a. name of the product;
b. description of its pharmaceutical form, and strength where applicable;
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 of each packaging material;
e. where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;
f. special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
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

4.24 A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions. The method of preparation of such records should be designed to avoid transcription errors. The record should carry the number of the batch being manufactured.

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

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 in agreement by the person responsible for the processing operations:

a. the name of the product;
b. dates and times of commencement, of significant intermediate stages and of completion of production;
c. name of the person responsible for each stage of production;
d. initials of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing);
e. the batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
f. any relevant processing operation or event and major equipment used;
g. a record of the in process controls and the initials of the person(s) carrying them out, and the results obtained;
h. the amount of product yield obtained at different and pertinent stages of manufacture;

i. Notes on special problems including details, with signed authorization for any deviation from the Manufacturing Formula and Processing Instructions.

BATCH PACKAGING RECORDS

4.25 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions and the method of preparation of such records should be designed to avoid transcription errors. The record should carry 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.

Before any packaging operation begins, there should be recorded checks 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.

The following information should be entered at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:

a. the name of the product;
b. the date(s) and times 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. records of checks 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;
g. whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;
h. notes on any special problems or unusual events including details with signed authorization for any deviation from the Manufacturing Formula and Processing Instructions;
i. the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation

CHAPTER 5

PRODUCTION

PRINCIPLE

Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorizations.

GENERAL

5.1 Production should be performed and supervised by competent people.

5.2 All handling of materials and products, such as receipt and quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

5.3 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labeled with the prescribed data.

5.4 Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.

5.6 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

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

5.8 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.

5.9 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

5.10 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross contamination ex using closed systems.

5.11 At every stage of processing, products and materials should be protected from microbial and other contamination.

5.12 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials(Provision should be made for proper air control)

5.13 At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labeled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production (In some cases it may be useful to record also the name of the previous product that has been processed).

5.14 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colors to indicate status (for example, quarantined, accepted, rejected, cleans, ...).

5.15 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

5.16 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.

5.17 Access to production premises should be restricted to authorized personnel.

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5.18 Normally, the production of non medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.

5.19 In-process controls are usually performed within the production area. The performance of such in-process controls should not have any negative effect on the quality of the product or another product (e.g. cross-contamination or mix-up)

PREVENTION OF CROSSCONTAMINATION & BACTERIAL CONTAMINATION DURING PRODUCTION

5.20 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross contamination arises from the uncontrolled release of dust, gases, vapors, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly sensitizing materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.

5.21 Cross contamination should be avoided by appropriate technical or organizational measures, for example:

a. production in segregated areas ,dedicated & self contained (required for products such as penicillin's, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;

b providing appropriate airlocks and air extraction;(pressure differentials, and air supply and extraction systems)

c. minimizing the risk of contamination caused by recirculation or reentry of untreated or insufficiently treated air;

d. keeping protective clothing inside areas where products with special risk of cross contamination is processed;

e. using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross contamination;

f. using "closed systems" of production;

g. testing for residues and use of cleaning status labels on equipment.

5.22 Measures to prevent cross contamination and their effectiveness should be checked periodically according to set procedures.

5.23 Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological monitoring and particulate matter where appropriate).

VALIDATION

5.24 Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

5.25 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.26 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.

5.27 Processes and procedures should undergo periodic critical revalidation to ensure that they remain capable of achieving the intended results.

MATERIALS

PRINCIPLE

5.28 The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging). Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labeling materials.

GENERAL

5.29 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.

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

5.31 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 & first in first out (FIFO) rule.

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

STARTING MATERIALS

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

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

5.35 For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.

5.36 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labeled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.

5.37 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.

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

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

- the designated name of the product and the internal code reference where applicable;
- a batch number OR a control number given at receipt ,the batch number given by the supplier documented to insure traceability
- where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected ,returned ,recalled)
- where appropriate, an expiry date or a date beyond which retesting is necessary.

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

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

5.41 Only starting materials which have been released by the Quality Control Department and which are within their shelf life should be used.

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

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

5.44 Materials dispensed for each batch should be kept together and conspicuously labeled as such.

PROCESSING OPERATIONS: INTERMEDIATE AND BULK PRODUCTS

5.45 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation, product residues, labels or documents not required for the current operation.

5.46 Intermediate and bulk products should be kept under appropriate conditions.

5.47 Critical processes should be validated.

5.48 Any necessary in process controls and environmental controls should be carried out and recorded.

5.49 Any significant deviation from the expected yield should be recorded and investigated.

5.50 Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

5.51 Time limits for storage of equipment after cleaning and before use should be stated and based on data.

5.52 Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at pre-specified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated, preferably on a label attached to the instrument.

5.53 Repair and maintenance operations should not present any hazard to the quality of the products.

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

PACKAGING MATERIALS

5.55 The purchase, handling and control of primary and printed packaging materials should be accorded attention similar to that given to starting materials.

5.56 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorized access. 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 authorized personnel following an approved and documented procedure.

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

5.58 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

5.59 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.

PACKAGING OPERATIONS

5.60 When setting up a programme for the packaging operations, particular attention should be given to minimizing the risk of cross contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

5.61 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line clearance should be performed according to an appropriate checklist recorded .

5.62 The name and batch number of the product being handled should be displayed at each packaging station or line.

5.63 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.

5.64 Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

5.65 Normally, filling and sealing should be followed as quickly as possible by labeling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabeling can occur.

5.66 The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded.

5.67 Special care should be taken when cut labels are used and when overprinting is carried out off-line, and in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix-ups. On-line verification of all labels by automated electronic means can be helpful in preventing mix-ups, but checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly. When labels are attached manually, in-process control checks should be performed more frequently.

5.68 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

5.69 Online control of the product during packaging should include at least checking the following:

a. general appearance of the packages;
b. whether the packages are complete;
c. whether the correct products and packaging materials are used;
d. whether any overprinting is correct;
e. correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

5.70 Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorized personnel. Detailed record should be kept of this operation.

5.71 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

5.72 Upon completion of a packaging operation, any unused batch coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

FINISHED PRODUCTS

5.73 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

5.74 The evaluation of finished products and documentation which is necessary before release of product for sale is described in (Quality Control).

5.75 After release, finished products should be stored as usable stock under conditions established by the manufacturer.

5.76 All finished drug products should be identified by labeling, as required by the national legislation, bearing at least the following information:

a. the name of the drug product;
b. a list of the active ingredients (if applicable, with the INNs), showing the amount of each present and a statement of the net contents (e.g. number of dosage units, weight, volume);
c. the batch number assigned by the manufacturer;
d. the expiry date in an uncoded form;
e. any special storage conditions or handling precautions that may be necessary;
f. directions for use, and warnings and precautions that may be necessary;
g. the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

REJECTED, RECOVERED, REPROCESSED AND RETURNED MATERIALS

5.77 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. Whatever action is taken should be approved and recorded by authorized personnel.

5.78 The reprocessing of rejected products should be exceptional. It is only permitted 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. Record should be kept of the reprocessing.

5.79 The recovery of all or part of earlier batches, which conform to the required quality by incorporation 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 ,a reprocess or recovered batch should be given a new batch number.

5.80 The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.

5.81 Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for resale, relabeling or recovery with a subsequent batch only after they have been critically assessed by the Quality Control Department 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, although basic chemical reprocessing to recover active ingredients may be possible. Any action taken should be appropriately recorded.

WASTE MATERIALS

5.82 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

5.83 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

MISCELLANEOUS

5.84 Rodenticides, insecticides, fumigating agents and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products.

PROCEDURES AND RECORDS

STANDARD OPEREATING PROCEDURES

5.85 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.

5.86 There should be written procedures and records for the receipt of each delivery of each starting and primary and printed packaging material.

5.87 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 material (if different from a);
c. date of receipt;
d. supplier's name and, if possible, manufacturer's name;
e. manufacturer's batch or reference number;
f. total quantity, and number of containers received;
g. the batch number assigned after receipt;
h. any relevant comment (e.g. state of the containers).

5.88 There should be written procedures for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

OTHER

5.89 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 the authorised person(s) designated for the purpose.

5.90 Records should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.

5.91 There should be written procedures and the associated records of actions taken or conclusions reached, where appropriate, for:

a. validation;
b. equipment assembly and calibration;
c. maintenance, cleaning and sanitization;
d. personnel matters including training, clothing, hygiene;
e. environmental monitoring;
f. pest control;
g. complaints;
h. recalls;
i. returns.

5.92 Clear operating procedures should be available for major items of manufacturing and test equipment(e.g. use, calibration, cleaning ,maintenance)& place in a closed proximity to the equipment.

5.93 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.

5.94 Log books should be kept for major or critical equipment recording, as appropriate, any validations, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.

5.95 Log books should also record in chronological order the use of major or critical equipment and the areas where the products have been processed.

5.96 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.

5.97 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.

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

5.99 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.

CHAPTER 6

QUALITY CONTROL

PRINCIPLE

Quality Control is concerned with sampling, specifications and testing as well as the organization, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control (see also chapter 1).

GENERAL

6.1 Each holder of a manufacturing authorization should have a Quality Control Department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out. The basic requirements for quality control are as follows:

i. adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;

ii. samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department;

iii. qualification and validation must be performed;

iv. records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated;

v. the finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container and correctly labeled;

vi. records must be made of the results of inspecting and testing the materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;

vii. no batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of the marketing authorization.

viii. sufficient samples of starting materials and products must be retained to permit future examination of the product if necessary; the retained product must be kept in its final pack unless the pack is exceptionally large.

6.2 The principal duties of the head of Quality Control are summarized in Chapter 2. The Quality Control Department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, keep the reference samples of materials and products, ensure the correct labeling of containers of materials and products, ensure the monitoring of the stability of the products, participate in the investigation of complaints related to the quality of the product, etc. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

6.3 Finished product assessment should embrace all relevant factors, including production conditions, results of in process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.

6.4 Quality Control personnel should have access to production areas for sampling and investigation as appropriate.

GOOD QUALITY CONTROL LABORATORY PRACTICE

6.5 Control Laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3.

6.6 The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed in Chapter 7, Contract Analysis, can be accepted for particular reasons, but this should be stated in the Quality Control records.

DOCUMENTATION

6.7 Laboratory documentation should follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department:

- specifications;

- sampling procedures;
- testing procedures and records (including analytical worksheets and/or laboratory notebooks);
- analytical reports and/or certificates;
- data from environmental monitoring, where required;
- validation records of test methods, where applicable;
- procedures for and records of the calibration of instruments and maintenance of equipment.

6.8 Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch.

6.9 For some kinds of data (e.g. analytical tests results, yields, environmental controls, ...) it is recommended that records in a manner permitting trend evaluation be kept.

6.10 In addition to the information which is part of the batch record, other original data such as laboratory notebooks and/or records should be retained and readily available.

SAMPLING

6.11 The sample taking should be done in accordance with approved written procedures that describe:

- the method of sampling;
- the equipment to be used;
- the amount of the sample to be taken;
- instructions for any required subdivision of the sample;
- the type and condition of the sample container to be used;
- the identification of containers sampled;
- any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
- the storage conditions;
- instructions for the cleaning ,sterilization(if necessary) and storage of sampling equipment.

6.12 Sampling should be carried out so as to avoid contamination or mix-up or other adverse effects on quality. The containers that have been sampled should be marked accordingly and carefully resealed after sampling.

6.13 Reference samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process).

6.14 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling, signature of the sampler and the containers from which samples have been drawn.

6.15 Reference samples from each batch of finished products should be retained till one year after the expiry date. Finished products should usually be kept in their final packaging

and stored under the recommended conditions. Samples of starting materials (other than solvents, gases and water) should be retained for at least two years after the release of the product if their stability allows. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter. Reference samples of materials and products should be of a size sufficient to permit at least a full reexamination.

TESTING

6.16 Analytical methods should be validated. All testing operations described in the marketing authorization should be carried out according to the approved methods.

6.17 The results obtained should be recorded and checked to make sure that they are consistent with each other. Any calculations should be critically examined.

6.18 The tests performed should be recorded and the records should include at least the following data:

- name of the material or product and, where applicable, dosage form;
- batch number and, where appropriate, the manufacturer and/or supplier;
- references to the relevant specifications and testing procedures;
- test results, including observations and calculations, and reference to any certificates of analysis;
- dates of testing;
- initials of the persons who performed the testing;
- initials of the persons who verified the testing and the calculations, where appropriate;
- a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

6.19 All the in process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.

6.20 Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media. They should be prepared in accordance with written procedures.

6.21 Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardization and the last current factor should be indicated.

6.22 Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

6.23 For reference standards, the label and/or accompanying document should indicate potency or concentration, date of manufacture, expiry date, date the closure is first opened, storage conditions and control number, as appropriate.

6.24 Animals used for testing components, materials or products, should, where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use

STARTING AND PACKAGING MATERIALS

6.25 Before releasing a starting or packaging material for use, the quality control manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters.

6.26 An identity test should be conducted on a sample from each container of starting material (see also section 5.40).

6.27 Each batch (lot) of printed packaging materials must be examined following receipt.

6.28 In lieu of testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results and through on-site audits of the supplier's capabilities. Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain at least the following information:

- identification (name and address) of the issuing supplier;
- signature of the competent official, and statement of his or her qualifications;
- the name of the material tested;
- the batch number of the material tested;
- the specifications and methods used;
- the test results obtained;
- the date of testing.

IN-PROCESS CONTROL

6.29 In-process control records should be maintained and form a part of the batch records.

FINISHED PRODUCTS

6.30 For each batch of drug product, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

6.31 Products failing to meet the established specifications or any other relevant quality criteria should be rejected.

BATCH RECORD REVIEW

6.32 Production and quality control records should be reviewed as part of the approval process of batch release. Any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

6.33 Retention samples from each batch of finished product should be kept for at least one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials should be retained for at least one year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases, and water) should be retained for a minimum of two years if their stability allows. Retention samples of materials and products should be of a size sufficient to permit at least two full re-examinations.

ONGOING STABILITY PROGRAMME

6.34 After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities, or dissolution profile) associated with the formulation in the marketed package.

6.35 The purpose of the ongoing stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labeled storage conditions.

6.36 This mainly applies to the medicinal product in the package in which it is sold, but consideration should also be given to the inclusion in the programme of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an ongoing basis. However, when relevant, the stability of reconstituted product can also be monitored.

6.37 The ongoing stability programme should be described in a written protocol following the general rules of Chapter 4 and results formalized as a report. The equipment used for the ongoing stability programme (stability chambers among others) should be qualified and maintained following the general rules of Chapter 3 and annex 15.

6.38 The protocol for an ongoing stability programme should extend to the end of the shelf life period and should include, but not be limited to, the following parameters:

- number of batch(es) per strength and different batch sizes, if applicable
- relevant physical, chemical, microbiological and biological test methods
- acceptance criteria
- reference to test methods
- description of the container closure system(s)
- testing intervals (time points)
- description of the conditions of storage (standardized ICH conditions for long term testing, consistent with the product labeling, should be used)
- other applicable parameters specific to the medicinal product.

6.39 The protocol for the ongoing stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorization dossier provided that this is justified and documented in the protocol (for example the frequency of testing, or when updating to ICH recommendations).

6.40 The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year). For products where ongoing stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.

6.41 In certain situations, additional batches should be included in the ongoing stability programme. For example, an ongoing stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.

6.42 Results of ongoing stability studies should be made available to key personnel and, in particular, to the Authorised Person(s). Where ongoing stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned.

6.43 Results of ongoing stability studies should be available at the site of manufacture for review by the competent authority.

6.44 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with chapter 8 of the GMP Guide and in consultation with the relevant competent authorities.

6.45 A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

CHAPTER 7

CONTRACT MANUFACTURE AND ANALYSIS

PRINCIPLE

Contract manufacture and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or work of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The contract must clearly state the way in which the authorized person releasing each batch of product for sale exercises his full responsibility.

Note: This Chapter deals with the responsibilities of manufacturers towards the Health Authorities with respect to the granting of marketing and manufacturing authorizations. It is not intended in any way to affect the respective liability of contract acceptors and contract givers to consumers.

GENERAL

7.1 There should be a written contract covering the manufacturing and or analysis contract and any technical arrangements made in connection with it

7.2 All arrangements for contract manufacture and analysis including any proposed changes in technical or other arrangements should be in accordance with the marketing authorization for the product concerned.

THE CONTRACT GIVER

7.3 The Contract Giver is responsible for assessing the competence of the Contract Acceptor to carry out successfully the work required and for ensuring by means of the contract that the principles and Guidelines of GMP as interpreted in this Guide are followed.

7.4 The Contract Giver should provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.

7.5 The Contract Giver should ensure that all processed products and materials delivered to him by the Contract Acceptor comply with their specifications or that the products have been released by an authorised person

THE CONTRACT ACCEPTOR

7.6 The Contract Acceptor must have adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the Contract Giver. Contract manufacture may be undertaken only by a manufacturer who is the holder of a manufacturing authorization.

7.7 The Contract Acceptor should ensure that all products or materials delivered to him are suitable for their intended purpose.

7.8 The Contract Acceptor should not pass to a third party any of the work entrusted to him under the contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original Contract Giver and Contract Acceptor.

7.9 The Contract Acceptor should refrain from any activity which may adversely affect the quality of the product manufactured and/or analyzed for the Contract Giver

THE CONTRACT

7.10 A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and Good Manufacturing Practice. All arrangements for manufacture and analysis must be in accordance with the marketing authorization and agreed by both parties.

7.11 The contract should specify the way in which the authorised person releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of Marketing Authorization.

7.12 The contract should describe clearly who is responsible for purchasing materials, testing and releasing materials, undertaking production and quality controls, including in process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the Contract Acceptor should take samples at the premises of the manufacturer.

7.13 Manufacturing, analytical and distribution records, and reference samples should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a

suspected defect must be accessible and specified in the defect/recall procedures of the Contract Giver.

7.14 The contract should permit the Contract Giver to visit the facilities of the Contract Acceptor.

7.15 In case of contract analysis, the Contract Acceptor should understand that he is subject to inspection by the Health Authorities.

CHAPTER 8

COMPLAINTS AND PRODUCT RECALL

PRINCIPLE

All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures. In order to provide for all contingencies, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

COMPLAINTS

8.1 A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him. If this person is not the authorized person, the latter should be made aware of any complaint, investigation or recall.

8.2 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

8.3 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control should normally be involved in the study of such problems.

8.4 If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch should be investigated.

8.5 All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

8.6 Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.

8.7 The Health Authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, and detection of counterfeiting or any other serious quality problems with a product.

RECALLS

8.8 A person should be designated as responsible for execution and coordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organization. If this person is not the authorized person, the latter should be made aware of any recall operation.

8.9 There should be established written procedures, regularly checked and updated when necessary, in order to organize any recall activity.

8.10 Recall operations should be capable of being initiated promptly and at any time.

8.11 All Competent Authorities of all countries to which products may have been distributed should be informed promptly if products are intended to be recalled because they are, or are suspected of, being defective.

8.12 The distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.

8.13 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.

8.14 The progress of the recall process should be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of the products.

8.15 The effectiveness of the arrangements for recalls should be evaluated r

CHAPTER 9

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 self-inspection program 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 program.

ITEMS FOR SELF INSPECTION

9.1 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:

- personnel;
- premises including personnel facilities;
- maintenance of buildings and equipment;
- storage of starting materials and finished products;
- equipment;
- production and in-process controls;
- quality control;
- documentation;
- sanitation and hygiene;
- validation and revalidation programs;
- calibration of instruments or measurement systems;
- recall procedures;
- complaints management;
- labels control;
- Results of previous self-inspections and any corrective steps taken.

SELF INSPECTION BY ORGANIZATION

9.2 Management should appoint a self-inspection organization consisting of expert(s) in their respective fields and familiar with GMP. The inspector expert(s) may be appointed from inside or outside the company.

FREQUENCY OF SELF INSPECTION

9.3 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

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

- self-inspection results;
- evaluation and conclusions;
- Recommended corrective actions.

FOLLOW-UP ACTION

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

QUALITY AUDIT

9.6 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 (see section 7, “Contract production and analysis”).

SUPPLIERS AUDITS AND APPROVAL

9.7 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.

9.8 Before suppliers are approved and included in the approved supplier’s 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 comply with GMP standards.

REFERNCES

1. WHO Technical report series no. 909, 302 – Annex 4 – Good Manufacturing Practice for Pharmaceutical Products: Main Principals.
2. MHRA, Rules and Guidance for Pharmaceutical Manufacturers and Distributors – 2008
3. PIC/S Guide to Good Manufacturing Practices for Medicinal Products – Part I , 15 Jan. 2009