EAST AFRICAN COMMUNITY

GUIDELINES ON GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS FOR USE IN EAC

APPROVED BY THE EAC COUNCIL OF MINISTERS

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1. ABBREVIATIONS AND ACRONYMS

AHU	-	Air Handling Unit
API	-	Active Pharmaceutical Ingredient
BAS	-	Building Automation System
BCG	-	Bacillus Calmette Guerin
BMGF	-	Bill and Melinda Gates Foundation
BMR	-	Batch Manufacturing Record
BMS	-	Building Management System
BOD	-	Biochemical Oxygen Demand
BP	-	British Pharmacopoeia
CAPA	-	Corrective Action and Preventive Action
COD	-	Chemical Oxygen Demand
CPPs	-	Critical Process Parameters
CQAs	-	Critical Quality Attributes
CTD	-	Common Technical Document
DNA	-	Deoxyribononucleic Acid
DQ	-	Design Qualification
EAC	-	East African Community
EAC-MRH	-	East African Community Medicines Regulatory
eCTD	-	Electronic Common Technical Document
EMA	-	European Pharmaceutical products Agency
EN	-	European Norm
ETP	-	Effluent Treatment Plant
EU	-	European Union
FEAPM	-	Federation of East African Pharmaceutical Manufacturers
FMEA	-	Failure Modes Effects Analysis
FPP	-	Finished Pharmaceutical Product
GCP	-	Good Clinical Practice
GDP	-	Good Distribution Practice
GEP	-	Good Engineering Practice
GLP	-	Good Laboratory Practice
GMP	-	Good Manufacturing Practice
GxP	-	Good (x- variable replaced with manufacturing, clinical, laboratory, storage, distribution and review) Practice
HACCP	-	Hazard Analysis and Critical Control Point
		Harmonization

		Harmonization
HAZOP	-	Hazard Operability Analysis
HEPA	-	High Efficiency Particulate Air
HPW	-	Highly Purified Water
HVAC	-	Heating Ventilation and Air Conditioning
ICH	-	International Conference on Harmonization of Technical
IQ	-	Installation Qualification
ISO	-	International Standard Organization
MA	-	Marketing Authorization
MAL	-	Material Air Lock
MRA	-	Medicines Regulatory Authority
MTC	-	Manufacturing Technology Committee
NEPAD	-	New Partnership for African Development
NMRA	-	National Medicines Regulatory Authority
OQ	-	Operational Qualification
OSD	-	Oral Solid Dosage
PAL	-	Personnel Air Lock
pH	-	Power of Hydrogen
Ph. Eur	-	European Pharmacopoeia
Ph. Int.	-	International Pharmacopoeia
PIC/S	-	Pharmaceutical Inspection Cooperation Scheme
PP	-	Process Parameter
PQ	-	Performance Qualification
PQRI	-	Product Quality Research Institute
PQS	-	Pharmaceutical Quality System
PW	-	Purified Water
QA	-	Quality Assurance
QC	-	Quality Control
QRM	-	Quality Risk Management
QTPP	-	Quality Target Product Profile
		Requirements for Registration of Pharmaceuticals for Human Use
RMP	-	Risk Management Plan
SCADA	-	System Control and Data Acquisition
SOP	-	Standard Operating Procedure
TWG	-	Technical Working Group
UDAF	-	Unidirectional Air Flow
USP	-	United State Pharmacopoeia
VMP	-	Validation Master Plan

WFI	-	Water for Injection
WHO	-	World Health Organization

2. GLOSSARY

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

Active pharmaceutical ingredient: A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient).

Authorized person: A person responsible for the release of batches of finished product for sale or distribution. Such a person is recognized by the national medicines regulatory framework as having the responsibility for ensuring that each of the finished products has been manufactured, tested and approved for release in compliance with the laws and regulations in force in each of the member states.

***Batch (or lot)*:** A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it could be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Batch number (or lot number): A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificates of analysis, etc.

Batch numbering system: standard operating procedure describing the details of the batch numbering.

Batch records: All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bulk product: Any product that has completed all processing stages up to, but not including, final packaging.

Calibration: The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Certification: The final review and formal approval of a validation or revalidation, followed by approval of a process for routine use.

Challenge tests/worst case: A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, that pose the greatest chance of process or product failure when compared with ideal conditions.

Clean area: An area with defined environmental control of particulate and microbial contamination; constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

Consignment (or delivery): The quantity of starting material, or of a drug product, made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

Critical process: A process that may cause variation in the quality of the pharmaceutical product.

Cross-contamination: Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Finished product: A product that has undergone all stages of production, including packaging in its final container and labeling.

Hazardous substance/product: A product or substance that may present a substantial risk of injury, to health or to the environment

In-process control: Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Installation qualification: The performance of tests to ensure that the installations (such as machines, measuring devices, utilities, manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed and operate in accordance with established specifications.

Intermediate product: Partly processed material that must undergo further manufacturing steps before it becomes a bulk product.

Large-volume parenterals: Sterile solutions intended for parenteral application with a volume of 100 ml or more in one container of the finished dosage form.

Manufacture: All operations of purchase of materials and products, production, packaging, quality control, release, storage, shipment of finished products, and the related controls.

Manufacturer: A company that carries out at least one step of manufacture.

Manufacturing process: The transformation of starting materials into finished products (drug substances or pharmaceutical dosage forms) through a single operation or a sequence of operations involving installations, personnel, documentation and environment.

Marketing authorization (product license, registration certificate): A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other

recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling and shelf-life.

Master formula: A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master record: A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Medicinal product: Any medicine or similar product intended for human use, which is subject to control under national legislation in the manufacturing or importing State. *(see also Pharmaceutical product)*

Operational qualification: Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

Packaging: All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not the finally packaged, primary container.

Packaging material: Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical product: Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

Production: All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging, to completion of the finished product.

Qualification of equipment: The act of planning, carrying out and recording the results of tests on equipment to demonstrate that it will perform as intended. Measuring instruments and systems must be calibrated.

Quality assurance: See Chapter 1

Quality control: See Chapter 1

Quality unit (s): An organizational unit independent of production which fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in form of a separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine: The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing.

Reconciliation: A comparison, making due allowance for normal variation, between the amount of product or materials theoretically produced or used and the amount actually produced or used.

Recovery (or blending): The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture.

Reprocessing: The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

Returned product: Finished product sent back to the manufacturer.

Revalidation**:** Repeated validation of an approved process (or a part thereof) to ensure continued compliance with established requirements.

Specification: A document describing in detail the requirements with which the products or materials used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation.

Standard operating procedure (SOP): An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g., equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting material: Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

System: A regulated pattern of interacting activities and techniques that are united to form an organized whole.

Validation: The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

Validation protocol (or plan): A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process—or a part thereof—for routine use.

Validation report: A document in which the records, results and evaluation of a completed validation program are assembled. It may also contain proposals for the improvement of processes and/or equipment.

3. INTRODUCTION

The quality of medicinal products in the EAC region has always been a concern of National Medicine Regulatory Authorities. EAC NMRAs strive to ensure quality, safety and efficacy of human and veterinary medicines and other health care products through regulation and control of their production, importation, distribution and use.

Through the medicine regulation harmonization initiative in the EAC region, the GMP guidelines have been developed to ensure that medicinal products marketed in the Partner States meet uniform and acceptable quality, safety and efficacy.

The EAC Guide on Good Manufacturing Practices (GMP) is based on the World Health Organization (WHO) Good Manufacturing Practices guidelines in the WHO Technical Report Series No. 961, 2011. This guide also refers to the Pharmaceutical Inspection Convention Scheme (PIC/S) guide PE 009-9.

The national drug laws across all Partner States require medicinal products to be manufactured only by manufacturers whose activities are regularly inspected and authorized by the EAC NMRAs or competent inspectorates recognized by EAC NMRAs.

All manufacturers of medicinal products shall demonstrate, during a factory inspection, compliance with manufacturing principles specified in these guidelines. Local and foreign manufacturers of pharmaceutical products to be marketed in the EAC region shall be subjected to GMP conformity assessment following these guidelines and are required to meet an acceptable standard of GMP.

4. SCOPE

This guideline and its annexes shall be used as a basis for the inspection of medicinal products manufacturing facilities and as a standard to justify GMP status during the assessment of applications for manufacturing authorizations. The annexes provide details on specific areas which include; sterile preparations, biological medicinal products and vaccines for human use, computerized systems, water for pharmaceutical use, heating ventilation and air conditioning systems, qualification & validation, GMP for manufacture of active pharmaceutical ingredients, waste management for medicinal product manufacturers, quality risk management and authorized persons.

This guideline is applicable to all manufacturers (local and foreign) of finished pharmaceutical product formulations and active pharmaceutical ingredients manufactured and marketed in the EAC region for human use.

5. CHAPTERS

CHAPTER 1: QUALITY MANAGEMENT

Principle

The manufacturer's responsibility is to ensure the quality of medicinal products manufactured is fit for their intended use, comply with the requirements of market authorization and do not place patients at risk due inadequate safety, quality or efficacy. The achievement of this objective is the responsibility of management and requires the participation and commitment by staff in different departments and at all levels within the company, by the company's suppliers and distributors.

To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality assurance incorporating GMP and thus Quality control. It should be fully documented and its effectiveness monitored. All parts of the Quality Assurance systems should be adequately resourced with competent personnel and suitable and sufficient premises, equipment and facilities.

1.1 The basic concepts of Quality assurance, GMP, and Quality control are inter-related 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.

1.2 Quality management is defined as the aspect of management function that determines and implements the "quality policy" that is, the overall intention and direction of an organization 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; and systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality.

Quality assurance

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

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

(a) Medicinal products are designed and developed in a way that takes account of the requirements of GMP, GLP and GCP;
(b) Production and control operations are clearly specified in a written form and GMP requirements are adopted;

(c) Managerial responsibilities are clearly specified in job descriptions;
(d) Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
(e) All necessary controls on starting materials, intermediate products, and bulk products and any other in-process controls, calibrations, and validations are carried out;
(f) The finished product is correctly processed and checked, according to the defined procedures;
(g) Medicinal products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of medicinal products;
(h) 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;
(i) There is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system;

(j) Deviations are reported, investigated and recorded;

(k) There is a system for approving changes that may have an impact on product quality;

(l) Regular evaluation of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement;

(m) And there is a system for quality risk management (QRM);

Good manufacturing practices (GMP)

1.4 Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization and product specifications. GMP rules are directed primarily to diminishing the risks, inherent in any pharmaceutical production that cannot be prevented completely through the testing of final products. Such risks are essentially of two types: cross-contamination (in particular by unexpected contaminants) and mix-ups (confusion) caused by false labels being put on containers. The basic requirements of GMP are that:

(a) 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 that comply with their specifications;
(b) critical steps of manufacturing processes and any significant changes made to the processes are validated;
(c) all necessary facilities are provided, including:

(i) appropriately qualified and trained personnel;
(ii) adequate premises and space;
(iii) suitable equipment and services;

(iv) correct materials, containers, and labels;
(v) approved procedures and instructions;
(vi) suitable storage and transport, and;
(vii) adequate personnel, laboratories, and equipment for in-process controls under the responsibility of the production management.

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

Quality control

1.5 Quality control is the part of GMP 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 neither released for use, nor for sale or supply, until their quality has been judged to be satisfactory. Quality control should not be confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

Each manufacturer should have a quality control department. The independence of quality control from production is considered fundamental. The quality control department should be independent of other departments and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his or her 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:

(a) Adequate facilities, trained personnel and approved procedures must be 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.
(b) 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.
(c) Test methods must be well documented and validated.
(d) 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.

(e) 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.

(f) Records must be made of the results of inspecting and testing starting materials, 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.

(g) 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. In certain countries, by law, the batch release is a task of the authorized person from the production department together with the authorized person from the quality control department.

(h) Sufficient reference 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.

1.6 The quality control department as a whole will also have other duties, such as to establish, validate, and implement all quality control procedures, to evaluate, maintain, and store the reference standards for substances, to ensure the correct labeling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

1.7 Assessment of finished products should embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack.

1.8 Quality control personnel must have access to production areas for sampling and investigation as appropriate.

Product Quality Review

1.9 Regular, periodic or rolling quality reviews of all 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:

(a) review of starting materials and packaging materials used for the product, especially those from new sources;

(b) a review of critical in-process controls and finished product results;

(c) a review of all batches that failed to meet established specification(s) and their investigation;

(d) a review of all significant deviations or non-conformances, the related investigations and the effectiveness of resultant corrective and preventive actions taken;

(e) a review of all changes made to the processes or analytical methods;

(f) a review of dossier variations submitted, granted or refused;

(g) a review of the results of the stability monitoring programme and any adverse trends;

(h) a review of all quality-related returns, complaints and recalls and the investigations performed at the time;

(i) a review of adequacy of any other previous corrective actions on product process or equipment;

(j) for new dossiers and variations to the dossiers, a review of post-marketing commitments;

(k) the qualification status of relevant equipment and utilities, e.g. heating, ventilation and air-conditioning (HVAC), water, or compressed gases; and

(l) a review of technical agreements to ensure that they are up to date.

The manufacturer and marketing authorization holder, where different, should evaluate the results of this review and an assessment should be made whether corrective and preventive action or any revalidation should be undertaken. Reasons for such corrective actions should be documented.

Agreed corrective and preventive 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 should be verified during self-inspection.

Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, or sterile products, 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

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

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

Sanitation and hygiene

A high level of sanitation and hygiene should be practiced in every aspect of the manufacture of drug products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene. (For *hygiene,* please refer to chapter 2, “Personnel”, and for *sanitation* to chapter 3, “Premises”.)

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 understood by the individuals concerned and recorded.

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 as to present any risk to quality.

2.2 The manufacturer must have an organization chart. 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.

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, the head of the quality unit; the head of Quality Assurance, the head of quality control, and the authorized person(s). Normally, key posts should be occupied by full-time personnel. The heads of production and quality control should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.

2.6 Key personnel responsible for supervising the manufacture and quality unit including quality assurance and quality control for the manufacture of pharmaceutical products should possess the qualifications of a scientific education and practical experience required by the partner states drug legislations. Their education should include the study of an appropriate combination of at least bachelors in:

(a) Pharmacy
(b) pharmaceutical sciences and technology

(c) chemistry (analytical or organic) or biochemistry,
(d) chemical engineering,
(e) microbiology

The education for head of production should include at least bachelor in any of the following:

(a) Pharmacy
(b) pharmaceutical sciences and technology,
(c) chemistry (analytical or organic) or biochemistry,
(d) chemical engineering,

The education for head of quality unit should include at least bachelor in any of the following:

(a) Pharmacy
(b) pharmaceutical sciences and technology,
(c) chemistry (analytical or organic) or biochemistry,

The education for head of quality control should include at least bachelor in any of the following:

(a) Pharmacy
(b) pharmaceutical sciences and technology,
(c) chemistry (analytical or organic) or biochemistry,
(d) microbiology

2.7 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.

2.8 The heads of the production and quality control departments generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on national regulations:

(a) the authorization of written procedures and other documents, including amendments;
(b) the monitoring and control of the manufacturing environment;
(c) plant hygiene;
(d) process validation and calibration of analytical apparatus;
(e) training, including the application and principles of quality assurance;
(f) the approval and monitoring of suppliers of materials;
(g) the approval and monitoring of contract manufacturers;
(h) the designation and monitoring of storage conditions for materials and products;
(i) the performance and evaluation of in process controls
(j) the retention of records;
(k) the monitoring of compliance with GMP requirements;

(l) the inspection, investigation, and taking of samples, in order to monitor factors that may affect product quality.

2.9 The head of the production department 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 before they are made available to the quality control department;
(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.

2.10 The head of the quality unit including quality assurance and quality control department generally has the following responsibilities:

(a) to approve or reject starting materials, packaging materials, and intermediate, bulk, and finished products;
(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 done;
(h) to ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need;
(i) establishment, implementation and maintenance of the quality system;
(j) supervision of regular internal audits or self-inspections;
(k) participation in external audits (vendor audits);
(l) participation in validation programmes.

Training

2.11 The manufacturer should provide training in accordance with a written programme for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance, and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

2.12 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 should be

periodically assessed. Training programs should be available, approved by the head of either production or quality control, as appropriate. Training records should be kept.

2.13 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.

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

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

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

Personal hygiene

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

2.18 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.

2.19 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.

2.20 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.

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

2.22 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.

2.23 Eating, drinking, smoking, chewing, and storage of plants, food, drinks, 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.

2.24 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.

2.25 Any specific requirements for the manufacture of special groups of products, for example sterile preparations, are covered in the guidelines under annexes.

CHAPTER 3: PREMISES

Principle

Premises 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.

General

3.1 Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

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

3.3 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.

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

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

3.6 Premises should be designed and equipped so as to provide maximum protection against the entry of insects, birds or other animals. There should be a procedure for rodent and pest control.

Production Area

3.7 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated, separate and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g., penicillins, cephalosporins) or biological preparations (e.g., live microorganisms). The production of certain additional products, such as certain antibiotics, hormones, cytotoxic substances, highly active medicinal products, and non-medicinal products, should not be conducted in the same facilities. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products.

3.8 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, materials flow, personnel movement and to the requisite cleanliness levels.

3.9 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 pharmaceutical 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.

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

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

3.12 Drains should be of adequate size and equipped to prevent back-flow. Open channels should be avoided where possible, but if they are necessary they should be shallow to facilitate cleaning and disinfection.

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

3.14 Where dust is generated (e.g. during sampling, weighing, mixing, processing operations and packaging of powders) measures should be taken to avoid cross contamination and facilitate cleaning.

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

3.16 Production areas should be well lit, particularly where visual on-line controls are carried out.

Storage areas

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

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

3.19 Receiving and dispatch bays should be separate and protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

3.20 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.

3.21 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.

3.22 Segregation should be provided for the storage of rejected, recalled, or returned materials or products.

3.23 Highly active materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire, or explosion should be stored in safe and secure areas.

3.24 Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labeling, and special attention should be paid to sampling, the safe and secure storage of these materials.

Weighing Areas

3.25 The weighing of starting materials and the estimation of yield by weighing should usually be carried out in separate weighing areas designed for that use, for example with provisions for dust control.

Quality control Areas

3.26 Quality control laboratories should be separated from production areas. Areas where biological, microbiological, or radioisotope test methods are employed should be separated from each other.

3.27 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), and records.

3.28 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.

3.29 A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture, and other external factors, or where it is necessary to isolate the instruments.

Ancillary areas

3.30 Rest and refreshment rooms should be separate from other areas.

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

3.32 Maintenance workshops should if possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

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

CHAPTER 4: EQUIPMENT

Principle

The layout, design and location 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.

General

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

4.2 Repairs and maintenance operations should not present any hazard to the quality of the products.

4.3 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 clean and dry condition.

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

4.5 Cleaning and drying equipment should be chosen and used so as not to be a source of contamination.

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

4.7 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.

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

4.9 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated and checked at defined intervals using appropriate methods. Adequate records of such tests should be maintained.

4.10 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 on the equipment.

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

4.12 Fixed pipework should be clearly labeled to indicate the contents and, where applicable, the direction of flow.

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

4.14 Water for pharmaceutical use (PW, WFI) and other water pipes should be sanitized, according to written procedures that detail the action limits for microbial contamination and the measures to be taken.

4.15 Control-laboratory equipment and instruments should be suited to the testing procedures undertaken.

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

CHAPTER 5: DOCUMENTATION

Principle

Good documentation constitutes an essential part of the quality assurance system and, as such, should be related to all aspects of GMP. Its aims are to define the specifications 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, and to provide an audit trail that will permit investigation of the history of any suspected defective batch. It ensures the availability of data needed for validation, review and statistical analysis. Documents must be free from errors and available in writing. 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

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

5.2 Documents should be approved, signed, and dated by appropriate authorized persons. No document should be changed without authorization.

5.3 Documents should have unambiguous contents: the title, nature, and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

5.4 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specified period of time

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

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

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

5.8 Data may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of

the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs, or other means. It is particularly important that, during the period of retention, the data are readily available.

Labels

5.9 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 colours to indicate status (for example: quarantined, accepted, rejected, or clean).

5.10 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 International Non-proprietary Names), showing the amount of each present, and a statement of the net contents, e.g., number of dosage units, weight, or 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; and
(g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

5.11 For reference standards, the label or accompanying document should indicate concentration, date of manufacture, expiry date, date the closure is first opened, and storage conditions, where appropriate.

Documents required

Specifications and testing procedures

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

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

5.14 Each specification and test procedure should be approved and maintained by the quality control unit.

5.15 Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.

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

Specifications for starting and packaging materials

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

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

Depending on the company's practices other data may be added to the specifications such as

a) the approved supplier;
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.

Packaging material should conform to specifications, with emphasis placed on the compatibility of the material with the drug product it contains. The material should be examined for defects as well as for the correctness of identity markings.

5.18 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

5.19 Specifications for intermediate and bulk products should be available. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

5.20 Specifications for finished products should include:

(a) the designated name of the product and the code reference where applicable;
(b) the designated name(s) of the active ingredient(s) (if applicable, the International Nonproprietary Name(s));
(c) the formula or a reference to the formula;
(d) a description of the dosage form and package details;
(e) directions for sampling and testing or a reference to procedures;
(f) the qualitative and quantitative requirements, with acceptance limits;
(g) the storage conditions and precautions, where applicable; and
(h) the shelf-life.

Master formulae and Processing instructions

5.21 A formally approved master formula should exist for each product and batch size to be manufactured.

5.22 The master formula should include:

(a) the name of the product, with a product reference code relating to its specification;
(b) a description of the dosage form, strength of the product, and batch size;
(c) a list of all starting materials to be used (if applicable, with the International Nonproprietary Names), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);
(d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

5.23 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 (especially after a change in product), 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 storage of the products, including the container, the labelling, and any special storage conditions;
(f) any special precautions to be observed.

Packaging instructions

5.24 There should be formally approved packaging instructions for each product pack size and type. These should normally include, or make reference to the following:

(a) the name of the product;
(b) a description of its pharmaceutical form, strength, and method of application 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 for each packaging material;
(e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
(f) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after operations ;
(g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;

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

Batch processing records

5.25 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved master formula. 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.

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

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

(a) the name of the product;
(b) the number of the batch being manufactured;
(c) dates and times of commencement, of significant intermediate stages, and of completion of production;
(d) the name of the person responsible for each stage of production;
(e) the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g., weighing);
(f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
(g) any relevant processing operation or event and the major equipment used;
(h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
(i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;
(j) notes on special problems including details, with signed authorization for any deviation from the master formula.

Batch packaging records

5.28 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the packaging instructions, and the method of preparing such records should be designed to avoid transcription errors.

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

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

(a) the name of the product, the batch number, and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained, and the reconciliation;
(b) the date(s) and time(s) of the packaging operations;
(c) the name of the responsible person carrying out the packaging operation;
(d) the initials of the operators of the different significant steps;
(e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
(f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;
(g) whenever possible, samples of the printed packaging materials used, including specimens bearing approval of the printing, the batch number, expiry date, and any additional overprinting;
(h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
(i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed, or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

Procedures (SOPs) and records

Receipts

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

5.32 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) the date of receipt;
(d) the supplier’s name and, if possible, manufacturer’s name;
(e) the manufacturer’s batch or reference number;
(f) the total quantity, and number of containers received;
(g) the batch number assigned after receipt;
(h) any relevant comment (e.g., state of the containers).

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

Sampling

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

5.35 The sampling instructions should include:

(a) the method of sampling and the sampling plan;

(b) the equipment to be used;
(c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
(d) the amount(s) of sample(s) to be taken;
(e) instructions for any required subdivision of the sample;
(f) the type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling;
(g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

Testing

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

5.37 Analysis records should include at least the following data:

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

Others

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

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.

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

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

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

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

5.43 Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for:

- Validation
- equipment assembly and qualification
- analytical apparatus and calibration;
- maintenance, cleaning, and sanitization;
- personnel matters including qualification, training, clothing, and hygiene;
- environmental monitoring;
- pest control;
- complaints;
- recalls;
- returns.

5.44 Logbooks should be kept with major and critical equipment and should record, as appropriate, any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.

5.45 Clear standard operating procedures should be available for major items of manufacturing and test equipment and placed in close proximity to the equipment.

5.46 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.

5.47 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 to be cleaned. Such written procedures should be followed.

CHAPTER 6: GOOD PRACTICES IN PRODUCTION

Principle

Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

General

6.1 Production should be performed and supervised by competent people.

6.2 All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labeling, dispensing, processing, packaging, and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded. Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labeling materials.

6.3 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be done in accordance with an approved procedure; the authorization of the deviation should be approved in writing by a designated person, with the involvement of the quality control department, when appropriate.

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

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

6.6 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate the rooms and packaging lines used should be labeled or otherwise identified with an indication of the product or material being processed, its strength (where applicable), and the batch number. Where applicable, this indication should also mention the stage of production.

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

6.8 Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.

6.9 In-process controls are mostly performed within the production area. They should not carry any risk for the quality of the product.

Prevention of cross-contamination and bacterial contamination in production

6.10 When dry materials and products are used in production, special pre-cautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g supply and extraction of air of suitable quality)

6.11 Contamination of a starting material or of a product by another material or product has to be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays, or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.

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

(a) production in dedicated and self -contained areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations and certain other biologicals),

(b) conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;
(c) providing appropriate airlocks, pressure differentials, and air extraction;
(d) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
(e) wearing protective clothing in areas where products with special risk of cross-contamination are processed;
(f) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
(g) using a "closed system" of production;
(h) testing for residues;
(i) using cleanliness status labels on equipment.

6.13 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to standard operating procedures.

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

6.15 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.

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

Validation

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

6.18 Whenever a 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 consistently yield a product of the required quality.

6.19 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.

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

Starting materials

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

6.22 Starting materials should be purchased only from suppliers named in the relevant specification and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed and agreed upon 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 and agreed upon between the manufacturer and the supplier.

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

6.24 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 data. Where additional labels are attached to containers, the original information should not be lost.

6.25 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.

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

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

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

(b) the batch number(s) given by the supplier and on receipt by the manufacturer, if any;
(c) where appropriate, the status of the contents (e.g., on quarantine, on test, released, rejected, returned, recalled);
(d) where appropriate, an expiry date or a date beyond which retesting is necessary.

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

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

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

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

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

6.32 Materials dispensed for each batch of the final product should be kept together and conspicuously labeled as such.

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

6.34 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-expiry, first-out rule.

Processing operations: intermediate and bulk products

6.35 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, labels, or documents not required for the current operation.

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

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

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

6.39 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.

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

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

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

6.43 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.

Packaging materials

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

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

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

6.47 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and its disposal recorded.

Packaging operations

6.48 When the program for packaging operations is being set up, 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 or the use of electronic surveillance.

6.49 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 and not required for the current operation. The line clearance should be performed according to an appropriate procedure, checklist and recorded.

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

6.51 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.

6.52 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.

6.53 Normally, filling and sealing should be followed as quickly as possible by labeling. If labeling is delayed, appropriate procedures should be applied to ensure that no mix-ups or mislabeling can occur.

6.54 The correct performance of any printing (for example of code numbers or expiry dates) done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand, which should be rechecked at regular intervals.

6.55 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. Online 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.

6.56 Checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly.

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

6.58 On-line control of the product during packaging should include at least checks on:

(a) the 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) the correct functioning of line monitors.

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

6.59 Products that have been involved in an unusual event during packaging should be reintroduced into the process only after special inspection, investigation, and approval by authorized personnel. A detailed record should be kept of this operation.

6.60 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.

6.61 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure requiring checks to be performed before returning unused materials should be followed if uncoded printed materials are returned to stock

Finished products

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

6.63 The evaluation of finished products and the documentation necessary for release of a product for sale are described in Chapter 7, "Good practices in quality control".

Rejected, Recovered Reprocessed and Returned materials

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

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

6.66 The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery should be recorded.

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

6.68 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; they may be considered for resale, re-labelling, or bulking 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 the active ingredient may be possible. Any action taken should be appropriately recorded.

Waste materials

6.69 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.

6.70 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

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

CHAPTER 7: GOOD PRACTICES IN QUALITY CONTROL

Principle

Quality control is concerned with sampling, specifications, and testing as well as with the organization, documentation, and release procedures that 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 that may concern the quality of the product. The independence of quality control from production is considered fundamental to the satisfactory operation of Quality control.

General

7.1 Each holder of 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.

7.2 The principle duties of the head of Quality Control and the Quality Control department as a whole are summarized in Chapter 1. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

Documentation

7.3 Laboratory documentation should follow the principles given in chapter 5. 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 record for calibration of instruments and maintenance of equipment.

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

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

7.6 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

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

- the method of sampling;
- the equipment to be used;
- the quantity of sample to be taken;
- instructions for any required sub-division 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 and storage of sampling equipment.

7.8 Reference samples should be representative of the batch of materials or products from which they are taken.

7.9 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. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of starting materials (other than solvents, gases and water) should be retained for at least one year beyond the expiry date 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 two full examination.

Control of starting materials and intermediate, bulk products

7.10 All tests should follow the instructions given in the relevant written test procedure for each material or product. The result should be checked by the supervisor before the material or product is released or rejected.

7.11 Samples should be representative of the batches of material 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).

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

7.13 Care should be taken during sampling to guard against contamination or mix-up of, or by, the material being sampled. All sampling equipment that comes into contact with the material should be clean. Some particularly hazardous or potent materials may require special precautions.

7.14 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.

7.15 Each sample container should bear a label indicating:

(a) the name of the sampled material;
(b) the batch or lot number;
(c) the number of the container from which the sample has been taken;
(d) the number of the sample
(e) the signature of the person who has taken the sample; and
(f) the date of sampling.

Test requirements

Starting and packaging materials

7.16 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.

7.17 An identity test should be conducted on a sample from each container of starting material.

7.18 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 (see sections 10.7 and 10.8) and through on-site audits of the supplier's capabilities. (This does not affect section 7.18). Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain the following information:

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

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

In-process control

7.19 In-process control records should be maintained and form a part of the batch records (see section 6.24).

Finished products

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

7.21 Products failing to meet the established specifications or any other relevant quality criteria should be rejected. Reprocessing may be performed, if feasible, but the

reprocessed product should meet all specifications and other quality criteria prior to its acceptance and release.

Batch record review

7.22 Production and control records should be reviewed and 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.

7.23 Out-of-specification results obtained during testing of materials or products should be investigated in accordance with an approved procedure. Records should be maintained.

Stability studies

7.24 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.

7.25 The purpose of the on-going 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.

7.26 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 on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.

7.27 The on-going stability programme should be described in a written protocol following the general rules of Chapter 5 and results formalised as a report. The equipment used for the on-going stability programme (stability chambers among others) should be qualified and maintained.

7.28 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 on-going 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.

7.29 In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going 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.

7.30 Results of on-going stability studies should be made available to key personnel and, in particular, to the Authorised Person(s). Where on-going 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. Results of on-going stability studies should be available at the site of manufacture for review by the competent authority.

7.31 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 9 of the GMP Guide and in consultation with the NMRA in the member state.

7.32 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.

7.33 The quality control department should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.

7.34 The quality control department should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

7.35 A written programme for ongoing stability determination should be developed and implemented to include elements such as:

(a) a complete description of the drug involved in the study;
(b) the complete testing parameters and methods describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
(c) provision for the inclusion of a sufficient number of batches;
(d) the testing schedule for each drug;
(e) provision for special storage conditions;
(f) provision for adequate sample retention; and
(g) a summary of all the data generated, including the evaluation and the conclusions of the study.

7.36 Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.

Reagents and culture media

7.37 All reagents and culture media should be recorded upon receipt or preparation.

7.38 Reagents made up in the laboratory should be prepared according to written procedures and appropriately labeled. The label should indicate the concentration, standardization factor, shelf-life, the date when re-standardization is due, and the storage conditions. The label should be signed and dated by the person preparing the reagent.

7.39 Both positive and negative controls should be applied to verify the suitability of culture media. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

Reference standards

7.40 Reference standards may be available in the form of official reference standards. Official reference standards are those obtained from official recognized pharmacopeia source for example B.P, Ph. Eur, Ph. Int., USP

7.41 Reference standards prepared by the producer should be tested, released, and then stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.

7.42 Reference standards should be properly labelled with at least the following information:

(a) name of the material;

(b) batch or lot number and control number;

(c) date of preparation;

(d) shelf-life;

(e) potency;

(f) storage conditions.

7.43 Official reference standards should be used only for the purpose described in the appropriate monograph.

7.44 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization.

7.45 All in-house reference standards should be standardized against an official reference standard, when available, initially and at regular intervals thereafter.

7.46 All reference standards should be stored and used in a manner that will not adversely affect their quality.

CHAPTER 8: CONTRACT PRODUCTION AND ANALYSIS

Principle

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

General

8.1 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.

8.2 There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.

8.3 The contract should permit the contract giver to audit the facilities of the contract accepter.

8.4 In the case of contract analysis, the final approval for release must be given by the authorized person(s) of the contract giver.

The contract giver

8.5 The contract giver is responsible for assessing the competence of the contract accepter in successfully carrying out the work or tests required and for ensuring by means of the contract that the principles of GMP described in this guide are followed.

8.6 The contract giver should provide the contract accepter 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 accepter is fully aware of any problems associated with the product, work, or tests that might pose a hazard to premises, equipment, personnel, other materials, or other products.

8.7 The contract giver should ensure that all processed products and materials delivered by the contract accepter comply with their specifications or that the product has been released by the authorized person(s).

The contract accepter

8.8 The contract accepter must have adequate premises, 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 holds a manufacturing authorization.

8.9 The contract accepter should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract accepter 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 accepter.

8.10 The contract accepter should refrain from any activity that may adversely affect the quality of the product manufactured and/or analyzed for the contract giver.

The contract

8.11 A contract should be drawn up between the contract giver and the contract accepter that 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 GMP. All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

8.12 The contract should specify the way in which the authorized person releasing the batch for sale ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.

8.13 The contract should describe clearly who is responsible for purchasing, testing, and releasing materials and for 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 accepter should take samples at the premises of the manufacturer.

8.14 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.

8.15 The contract should describe the handling of starting materials, intermediate and bulk products, and finished products if they are rejected. It should also describe the processing of information if the contract analysis shows that the tested product must be rejected.

8.16 Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and GMP.

8.17 All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

CHAPTER 9: COMPLAINTS HANDLING 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.

9.1 A person responsible for handling the complaints and deciding the measures to be taken should be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter should be made aware of any complaint, investigation, or recall.

9.2 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.

9.3 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.

9.4 If product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular, other batches that may contain reprocessed product from the defective batch should be investigated.

9.5 Immediate corrective actions should be taken to address the root cause of the problem, and actions should be taken to prevent it from recurring. There should be active follow-up of the implementation of corrective actions.

9.6 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.

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

9.8 Complaints records should be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.

9.9 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, or any other serious quality problems with a product.

Product recall:

9.10 A person responsible for the execution and coordination of recalls should be designated, as well as sufficient staff to handle all aspects of the recalls with the

appropriate degree of urgency. This person should normally be independent of sales and marketing department. If this person is different from the authorized person, the latter should be made aware of any recall operation.

9.11 There should be established written procedures, regularly checked and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly at least down to the level of an hospital or pharmacy or any authorized drug outlet.

9.12 All competent authorities of all countries to which a given product may have been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.

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

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

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

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

CHAPTER 10: SELF-INSPECTION, QUALITY AUDITS, SUPPLIER AUDITS AND APPROVALS

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

Items for self-inspection

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

(a) personnel;

(b) premises including personnel facilities;

(c) maintenance of buildings and equipment;

(d) storage of starting materials and finished products;

(e) equipment;

(f) production and in-process controls;

(g) QC;

(h) documentation;

(i) sanitation and hygiene;

(j) validation and revalidation programmes;

(k) calibration of instruments or measurement systems;

(l) recall procedures;

(m) complaints management;

(n) labels control;

(o) results of previous self-inspections and any corrective steps taken.

Self-inspection team

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

Frequency of self-inspection

10.4 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

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

(a) self-inspection findings;

(b) evaluation and conclusions; and

(c) recommended corrective actions.

Follow-up action

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

Quality audit

10.7 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 8, “Contract production and analysis”).

Vendors’/Suppliers’ audits and approval

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

10.9 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 vendor’s/supplier’s history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier’s ability to conform with GMP standards.

6. REFERENCES

a) WHO TRS GMP Guide: Basic requirements 2011
b) Guide to Good Manufacturing Practices Part 1: PEE-009-9 September 2009, Pharmaceutical Inspection Cooperation Scheme (PIC/S)

7. REVISION HISTORY

Revision No:	Date	Author(s)	Section(s) revised	Description of change	Approvals
00	17th April 2014	EAC TWG GMP Members	All	Approval by the Sectoral Council on Health	REF: EAC/SC/DECISION-----/17TH APRIL 2014
00	November 2014	EAC TWG Members	All	Final approved version	EAC/CM/DECISION…/26 September 2014

8. LIST OF ANNEXES

Annex 1: Manufacture of Sterile Medicinal Products

Annex 2: Manufacture of Biological Medicinal Products for Human Use

Annex 3: Qualification and Validation

Annex 4: Computerized Systems

Annex 5: Water for Pharmaceutical Use

Annex 6: Heating, Ventilation and Air Conditioning Systems for Non-sterile Pharmaceutical Dosage Forms

Annex 7: Authorized Persons

Annex 8: Quality Risk Management

Annex 9: GMP for Manufacture of Active Pharmaceutical Ingredients

Annex 10: Waste Management for medicinal product manufacture

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