



NAFDAC GOOD MANUFACTURING PRACTICE
GUIDELINES FOR PHARMACEUTICAL PRODUCTS
2016

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For all enquiries or comments, write to:

The Director General,
Attention: The Director, Drug Evaluation and Research
National Agency for Food and Drug Administration and Control,
Plot 2032, Olusegun Obasanjo Way
Wuse Zone 7, Abuja, Nigeria

der.headquarter@nafdac.gov.ng

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ACRONYMNS

API	Active Pharmaceutical Ingredients
CAPA	Corrective And Preventive Action
DFID	UK Department for International Development
DQ	Design Qualification
FAT	Factory Acceptance Test
FEFO	First -Expired, First-Out
FRS	Functional Requirement Specification
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HVAC	Heating, Ventilation and Air-Conditioning
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Products
INN	International Non-proprietary Name
IQ	Installation Qualification
ISO	International Standards Organization
NAFDAC	National Agency for Food and Drug Administration and Control
NIS	Nigerian Industrial Standard
OOS	Out-Of-Specification
OOT	Out-Of-Trend
OQ	Operational Qualification
PAT	Process Analytical Technology
PATHS 2	Partnership for Transforming Health Systems
PLC	Programmable Logic Controllers
PPQ	Process Performance Qualification
PQS	Pharmaceutical Quality System
QA	Quality Assurance
QC	Quality Control
QRM	Quality Risk Management
SAT	Site Acceptance Test
SMT	Site Master File
SOP	Standard Operating Procedure
TSE	Transmissible Spongiform Encephalopathy
URS	User Requirement Specification
VMP	Validation Master Plan
WHO	World Health Organization

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Mrs. Titilope O. Owolabi

Director, Drug Evaluation & Research
NAFDAC

INTRODUCTION

Good Manufacturing Practice (GMP) is that part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by their marketing authorisations. It ensures that pharmaceutical products are manufactured so that they are fit for their intended use, comply with the requirements of the marketing authorisations and do not place the populace at risk.

The National Agency for Food and Drug Administration and Control (NAFDAC) ACT Cap N1, LFN 2004 empowers the Agency to control and regulate the manufacture, importation, exportation, distribution, advertisement, sale and use of its regulated products. This mandate requires that the Agency ensures the quality, safety and efficacy of all regulated products. The Agency, therefore has developed NAFDAC Good Manufacturing Practice Regulations which stipulate the minimum standards that manufacturers are required to adhere to ensure the quality of pharmaceutical products.

These guidelines are intended to help all stakeholders comply with the provisions of the NAFDAC Good Manufacturing Practice Regulations for pharmaceutical products. The regulations contain good manufacturing practice requirements for methods, facilities and controls for the manufacture, processing, packaging, or holding of a pharmaceutical product for human or animal use. The regulations are meant to ensure that pharmaceutical products meet the requirements of safety, quality and efficacy they purport or are represented to possess.

These guidelines apply to pharmaceutical, biological, and veterinary products as required by their marketing authorisations. They are also relevant for pharmaceutical manufacturing processes, such as those undertaken in hospitals. These guidelines are not applicable to the compounding of a pharmaceutical product by a registered pharmacist in a government or private health institution in order to fill a prescription.

The attainment of this quality objective is the responsibility of top management and requires the participation and commitment of all staff members in the different departments and at all levels within the

organisation as well as their suppliers.

This document is to be used in conjunction with other existing relevant pharmaceutical product statutes in the country. The good practices outlined below are to be considered general guides, and they may be adapted to meet individual needs as long as the industry achieves compliance with regulatory objectives. As new technology becomes available, operational procedures and equipment standards in the industry may vary from those described in this document. Materials and/or methods other than those specified in the guidelines may be used by manufacturers, if they can provide sound and scientific evidence that clearly demonstrates compliance with the regulatory objectives.

All stakeholders are encouraged to send their comments to the Agency during the use of these guidelines in order to improve future editions.

1 PHARMACEUTICAL QUALITY SYSTEM

Quality management in the pharmaceutical industry: philosophy and essential elements

- 1.1. In the pharmaceutical industry at large, quality management is usually defined as the aspect of the management function that determines and implements the “quality policy”, i.e. the overall intention and direction of an organization regarding quality, as formally expressed and authorized by top management. The basic elements of quality management are:
 - a. An appropriate infrastructure or “quality system”, encompassing the organizational structure, procedures, processes and resources;
 - b. Systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality.
- 1.2. The totality of these actions is termed quality assurance (QA). Within an organization, QA serves as a management tool. In contractual situations, QA also serves to generate confidence in the supplier. The concepts of QA, GMP, QC and quality risk management (QRM) are interrelated aspects of quality management and should be the responsibility of all personnel. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

Pharmaceutical quality system

Principle

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

incorporating GMP and QRM

- 1.5. Top management has the ultimate responsibility to ensure an effective PQS is in place, is adequately resourced, and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organization. Top management's leadership and active participation in the PQS is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organization to the PQS.
- 1.6. Quality management is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality management, therefore, incorporates GMP and other factors, including those outside the scope of this guide, such as product design and development. GMP applies to the life-cycle stages from the manufacture of investigational medicinal products, technology transfer, and commercial manufacturing, through to product discontinuation. The PQS can extend to the pharmaceutical development life-cycle stage and should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities. All parts of the PQS should be adequately resourced and maintained, including being provided with sufficient competent personnel, suitable premises, equipment and facilities.
- 1.7. The PQS appropriate to the manufacture of pharmaceutical products should ensure that:
 - a. Product realization is achieved by designing, qualifying, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;
 - b. Product and process knowledge is managed throughout all lifecycle stages;
 - c. Pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of Good Laboratory Practice (GLP) and Good Clinical Practice (GCP);
 - d. Production and control operations are clearly specified in a written form and GMP requirements are adopted;

- e. Managerial responsibilities are clearly specified in job descriptions;
- f. Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is the correct material from the approved supply chain;
- g. All necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations and validations are carried out;
- h. The finished product is correctly processed and checked according to defined procedures;
- i. Pharmaceutical products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products(*see 2.13 to 2.16*);
- j. Processes are in place to assure the management of outsourced activities;
- k. Satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored, distributed and subsequently handled such that quality is maintained throughout their shelf-life;
- l. There is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the PQS;
- m. Product and processes are monitored and the results taken into account in batch release, in the investigation of deviations and with a view to taking preventive action to avoid potential deviations occurring in future;
- n. Arrangements are in place for the prospective evaluation and approval of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required. After implementation of any change, an evaluation is undertaken to confirm that the quality objectives were achieved and that there was no

- unintended adverse impact on product quality;
- o. Regular reviews of the quality of pharmaceutical products are conducted with the objective of verifying the consistency of the process and identifying where there is a need for improvement;
 - p. A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality;
 - q. Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge;
 - r. There is a system for QRM;
 - s. Deviations, suspected product defects and other problems are reported, investigated and recorded. An appropriate level of root cause analysis is applied during such investigations. The most likely root cause(s) should be identified and appropriate corrective actions and/or preventive actions (CAPAs) should be identified and taken. The effectiveness of CAPAs should be monitored.
- 1.8. There should be periodic management reviews of the operation of the PQS, with the involvement of top management, to identify opportunities for continual improvement of products, processes and the system itself. Unless otherwise justified, such reviews should be conducted at least annually.
- 1.9. The PQS should be defined and documented. A quality manual should be established and should contain a description of the quality management system including management responsibilities.

Good Manufacturing Practice (GMP) for Pharmaceutical Products

- 1.10. Good manufacturing practice is that part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the clinical trial authorisation, marketing authorisation, or product specification. Good manufacturing practice is concerned with both production and quality control.
- 1.11. GMP applies to the life-cycle stages from the manufacture of investigational pharmaceutical products, technology transfer, and commercial manufacturing, through to product discontinuation. GMP

is aimed primarily at managing and minimizing the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products.

- 1.12. The basic requirements of GMP are that:
 - a. All manufacturing processes are clearly defined, systematically reviewed for associated risks in the light of scientific knowledge and experience and shown to be capable of consistently manufacturing pharmaceutical products of the required quality and complying with their specifications;
 - b. Critical steps of manufacturing processes and significant changes to the process are validated;
 - c. All necessary facilities for GMP are provided including:
 - i. Appropriately qualified and trained personnel;
 - ii. Adequate premises and space;
 - iii. Suitable equipment and services;
 - iv. Appropriate materials, containers and labels;
 - v. Approved procedures and instructions;
 - vi. Suitable storage and transport;
 - vii. Adequate personnel, laboratories and equipment for in-process controls;
- 1.13. Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
- 1.14. Operators are trained to carry out procedures correctly;
- 1.15. Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated; with the objective of determining the root cause and ensuring appropriate corrective and preventive actions are implemented;
- 1.16. Records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

- 1.17. The proper storage and distribution of the products minimizes any risk to their quality and takes account of Good Distribution Practice (GDP);
- 1.18. A system is available to recall any batch of product from sale or supply;
- 1.19. 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 re-occurrence.

Quality Control (QC)

- 1.20. Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been adjudged to be satisfactory.
- 1.21. The basic requirements of Quality Control are that:
 - a. Adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
 - b. Samples of starting materials, packaging materials, intermediate, bulk and finished products are taken by personnel and by methods approved by quality control;
 - c. Test methods are validated;
 - d. Records are made manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;
 - e. The finished products contain active ingredients complying with the qualitative and quantitative composition of the marketing authorisation, are of the purity required, and are enclosed within their proper containers and correctly labelled;
 - f. Records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is

formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;

- g. No batch of product is released for sale or supply prior to certification by an authorised person that it is in accordance with the requirements of the relevant authorisations;
- h. Sufficient retention samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

Quality Risk Management (QRM)

- 1.22. QRM is the overall and continuing process of appropriately managing risks to product quality throughout the product's life-cycle in order to optimize its benefit–risk balance. It is a systematic process for the assessment, control, communication and review of risks to the quality of the pharmaceutical product. It can be applied both proactively and retrospectively.
- 1.23. QRM principles can be applied by pharmaceutical manufacturers in the design, development, manufacture and distribution, i.e. the life-cycle of a pharmaceutical product. QRM should be an integral element of the pharmaceutical quality system.
- 1.24. QRM should ensure that:
 - a. The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient; and
 - b. The level of effort, formality and documentation of the QRM process is commensurate with the level of risk.
- 1.25. In addition to the two principles above, the following principles are also part of the QRM methodology:
 - a. When applied, processes using QRM methodologies should be dynamic, iterative and responsive to change.
 - b. The capability for continual improvement should be embedded in the QRM process.

Quality risk management process

- 1.26. QRM activities should be performed using systematic processes designed to coordinate, facilitate and improve science-based decision-making with respect to risk. The possible steps to be taken in initiating and planning a QRM process might include the following:
- a. Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;
 - b. Assemble background information and/or data on the potential hazard, harm or human health impact relevant to the risk assessment;
 - c. Identify a leader and the necessary resources;
 - d. Specify a timeline, the deliverables, and an appropriate level of decision-making for the risk management process. Internal SOPs should define steps, stakeholders, roles and responsibilities.

Personnel involved in QRM

- 1.27. The manufacturer should ensure that personnel with appropriate product-specific knowledge and expertise are available to ensure effective planning and completion of QRM activities. This may be best accomplished by assembling a multidisciplinary team. The personnel appointed should be able to:
- a. Conduct a risk analysis;
 - b. Identify and analyse potential risks;
 - c. Evaluate risks and determine which ones should be controlled and which ones can be accepted;
 - d. Recommend and implement adequate risk control measures;
 - e. Devise procedures for risk review, monitoring and verification;
 - f. Consider the impact of risk findings on related or similar products and/or processes.
 - g. Define and document QRM activities.

Knowledge of the product and process

- 1.28. QRM should be based on knowledge of the product or processes concerned according to the stage of the product life-cycle. A flow diagram may be helpful, covering all operations and controls in the process under evaluation. When applying QRM to a given operation, the steps preceding and following that operation should also be considered. A block-type diagram may be sufficiently descriptive.

Amendments to the flow diagram may be made where appropriate, and should be documented.

Product Quality Review

- 1.29. Regular periodic or rolling quality reviews of all licensed pharmaceutical 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 products 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. A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances.
 - 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, their related investigations, and the effectiveness of resultant corrective and preventive actions (CAPA) taken.
 - e. A review of all changes made to the processes or analytical methods;
 - f. A review of Marketing Authorisation variations submitted/granted/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 marketing authorisations and variations to marketing authorisations, a review of post-marketing commitments.

2 PERSONNEL

Principle

- 2.1. 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.
- 2.2. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

General

- 2.3. The manufacturer should have an organisational chart. Personnel in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of satisfactory qualification. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of good manufacturing practice.
- 2.4. The manufacturer should have 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.
- 2.5. 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.
- 2.6. All personnel should be motivated to support the establishment and maintenance of high quality standards.
- 2.7. Steps should be taken to prevent unauthorized people from entering production, storage and QC areas. Personnel who do not work in these areas should not use them as a passageway.

Key personnel

- 2.8. In implementing GMP, key personnel are the head of Production, the head of Quality Assurance, and/or the head of Quality Control. The quality unit typically comprises the quality assurance and quality control functions. In some cases, these could be combined in one department. These key posts should be occupied by full-time personnel. The heads of production and quality unit 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.
- a. The head of the production unit for pharmaceutical products must be a registered pharmacist in Nigeria.
 - b. Key personnel responsible for supervising the quality unit for pharmaceutical products should possess the qualifications of a scientific education and practical experience. Their educational qualifications should be in any of the following disciplines:
 - i. Chemistry (analytical or organic) or biochemistry;
 - ii. Chemical engineering;
 - iii. Microbiology;
 - iv. Pharmaceutical sciences and technology;
 - v. Pharmacology and toxicology;
 - vi. Physiology; or
 - vii. Other related sciences.
- 2.9. They should also have adequate practical experience in the manufacture and quality assurance of pharmaceutical products. The scientific education and practical experience of such persons should be such as to enable them exercise independent professional judgment, based on the application of scientific principles and understanding of the practical problems encountered in the manufacture and QA of pharmaceutical products.
- 2.10. The heads of the production and the quality unit generally have some shared, or jointly exercised, responsibilities relating to quality. These may include:
- a. Authorization of written procedures and other documents, including amendments;

- b. Monitoring and control of the manufacturing environment;
 - c. Plant hygiene;
 - d. Process validation and calibration of analytical apparatus;
 - e. Training, including the application and principles of QA;
 - f. Approval and monitoring of suppliers of materials;
 - g. Approval and monitoring of contract manufacturers;
 - h. Designation and monitoring of storage conditions for materials and products;
 - i. Performance and evaluation of in-process controls;
 - j. Retention of records;
 - k. Monitoring of compliance with GMP requirements; and
 - l. Inspection, investigation and taking of samples in order to monitor factors that may affect product quality.
- 2.11. The head of production generally has the following responsibilities:
- a. Ensure that products are manufactured and stored according to the appropriate documentation in order to obtain the required quality;
 - b. Approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation;
 - c. Ensure that the production records are evaluated and signed by a designated person before they are sent to the quality unit;
 - d. Check the maintenance of the department, facilities, premises and equipment;
 - e. Ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available;
 - f. Ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

- 2.12. The head of the quality unit generally has the following responsibilities:
- a. Approves or rejects starting materials, packaging materials, and intermediate, bulk and finished products in relation with their specifications;
 - b. Evaluates batch records;
 - c. Ensures that all necessary testing is carried out;
 - d. Approves sampling instructions, specifications, test methods and other QC procedures;
 - e. Approves and monitors analyses carried out under contract;
 - f. Checks the maintenance of the department, facilities, premises and equipment;
 - g. Ensures that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are carried out;
 - h. Ensures that the required initial and continuing training of quality unit personnel is carried out and adapted according to need.
 - i. Establishes, implements and maintains the quality system;
 - j. Supervises the regular internal audits or self-inspections;
 - k. Participates in external audit (supplier audit);
 - l. Participates in validation programmes
- 2.13. The authorized person is responsible for compliance with technical or regulatory requirements related to the quality of finished products and the approval of the release of the finished product for sale or supply.
- 2.14. 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.
- 2.15. No batch of product is to be released for sale or supply prior to certification by the authorized person.
- 2.16. The authorized person responsible for approving a batch for release

should always ensure that the following requirements have been met:

- a. The marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned;
- b. The principles and guidelines of GMP have been followed;
- c. The principal manufacturing and testing processes have been validated, if different;
- d. All the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records;
- e. Any planned changes or deviations in manufacturing or quality control have been notified in accordance with a well-defined reporting system before any product is released. Such changes may need notification to, and approval by the Agency;
- f. Any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations;
- g. All necessary production and QC documentation have been completed and endorsed by supervisors trained in appropriate disciplines;
- h. Appropriate audits, self-inspections and spot-checks are carried out by experienced and trained staff;
- i. Approval has been given by the head of the quality unit;
- j. All relevant factors have been considered, including any not specifically associated with the output batch directly under review (e.g. subdivision of output batches from a common input, factors associated with continuous production runs)
- k. The function of the approval of the release of a finished batch or a product can be delegated to a designated person with appropriate qualifications and experience who will release the product in accordance with an approved procedure. This is normally done by the quality unit by means of batch review
- l. Ensuring that the stability of the active pharmaceutical ingredients and products is monitored;
- m. Participating in the investigation of complaints related to the

- quality of the product;
- n. Participation in QRM programmes.
- 2.17. Other duties of QC are summarized in **Chapter 8 “Quality Control”**.

Training

- 2.18. The manufacturer should provide training in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required.
- 2.19. Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness periodically assessed. Approved training programmes should be available. Training records should be kept.
- 2.20. 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.
- 2.21. The concept of QA and all the measures which aid its understanding and implementation should be fully discussed during the training sessions.
- 2.22. Visitors or untrained personnel should preferably not be taken into the production and QC areas. If this is unavoidable, they should be given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing. They should be closely supervised.
- 2.23. Consultants and contract staff should be qualified for the services they provide. Evidence of this should be included in the training records.

Records should be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

Personal hygiene

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

3 PREMISES AND EQUIPMENT

Principle

- 3.1. Premises and equipment should be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design should aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.

Premises

General

- 3.2. Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.
- 3.3. Premises should be designed to ensure the logical flow of materials and personnel.
- 3.4. Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals. There should be procedures for rodent and pest control.
- 3.5. Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.
- 3.6. Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix-ups, contamination or cross-contamination.
- 3.7. Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products.
- 3.8. Premises should be cleaned and, where applicable, disinfected according to detailed written procedures and cleaning records should be maintained.
- 3.9. Where dust is generated (e.g. during sampling, weighing, mixing and

- processing operations, packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning.
- 3.10. 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.
 - 3.11. Steps should be taken in order to prevent the entry of unauthorized persons. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.
 - 3.12. Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the cleanliness levels required.
 - 3.13. 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.
 - 3.14. 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.
 - 3.15. Pipework, 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.
 - 3.16. Drains should be of adequate size, designed 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.
 - 3.17. There should be defined areas of adequate size or other controlled systems to prevent contamination or mix-ups for the following:
 - a. Receipt, identification, sampling, storage, and quarantine of materials, pharmaceutical product containers, closures, and labelling, pending the appropriate sampling, testing, or

examination by quality control before release for manufacturing or packaging;

- b. Holding rejected materials, pharmaceutical product containers, closures, and labelling before disposition (e.g. return, reprocessing or destruction);
- c. Storage of released materials, pharmaceutical product containers, closures, and labelling;
- d. Storage of in-process materials;
- e. Manufacturing and processing operations;
- f. Packaging and labelling operations;
- g. Quarantine storage before release or rejection of pharmaceutical products;
- h. Storage of pharmaceutical products after release;
- i. Control and laboratory operations;
- j. Aseptic processing, which includes as appropriate:
 - i. Floors, walls, and ceilings of smooth, hard surfaces that can be easily cleaned and disinfected or sterilized routinely;
 - ii. Temperature and humidity controls
 - iii. An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or non-laminar;
 - iv. A system for monitoring environmental conditions
 - v. A system for cleaning and disinfecting the room and equipment to produce aseptic conditions;
 - vi. A system for preventive and breakdown maintenance of all equipment used to control and monitor the aseptic conditions.

Dedicated facilities

- 3.18. In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g. β -lactams) or biological preparations (e.g. live microorganisms). The production of certain other highly active products such as some antibiotics, hormones, cytotoxic substances and certain non-pharmaceutical products should

not be conducted in the same facility. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products.

Production area

- 3.19. Production areas should be well lit, particularly where visual on-line controls are carried out.
- 3.20. Production areas should be effectively ventilated, with air control facilities (including filtration of air to a sufficient level to prevent contamination and cross contamination as well as control of temperature and where necessary humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas should be regularly monitored during both production and non-production periods to ensure compliance with their design specifications.
- 3.21. In-process controls may be carried out within the production area provided they do not pose any risk to - production.

Weighing areas

- 3.22. The weighing of starting materials and the estimation of yield by weighing should be carried out in separate weighing areas designed for that use, for example, with provisions for dust control. Such areas may be part of either storage or production areas.

Quality Control Areas

- 3.23. 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.
- 3.24. Quality Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix ups and cross-contamination. There should be adequate and suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents and records.
- 3.25. 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.
- 3.26. 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.

Storage Areas

- 3.27. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.
- 3.28. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, controlled, monitored and recorded where appropriate.
- 3.29. Receiving and dispatch bays should be separated and should protect materials and products from the weather. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned, if necessary, before storage.
- 3.30. Where quarantine status is ensured by storage in separate areas, these areas should be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.
- 3.31. Segregated and secure areas should be provided for the storage of rejected, recalled, or returned materials or products.
- 3.32. There should be a separate sampling area for starting materials to prevent contamination or cross contamination.
- 3.33. Printed packaging materials are considered critical to the conformity of the pharmaceutical product and special attention should be paid to sampling and the safe and secure storage of these materials.
- 3.34. Highly active and radioactive materials, narcotics, other dangerous medicines, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.

Ancillary areas

- 3.35. Rest and refreshment rooms should be separate from manufacturing and control areas.
- 3.36. Adequate, clean washing and toilet facilities should be provided for

personnel.

- 3.37. Washing facilities provided should be equipped with hot and cold water, soap or detergent, air driers or single-service towels, and disinfectants. Clean toilet facilities should be easily accessible to working areas and should be adequately separated from production areas.
- 3.38. 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.
- 3.39. Maintenance workshops should 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.
- 3.40. Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

Lighting

- 3.41. Adequate lighting should be provided in all areas and should be appropriate to facilitate cleaning, maintenance, dispensing and other operations that may impact product quality.

Heating, Ventilation and Air-Conditioning (HVAC)

- 3.42. Adequate ventilation, air filtration, air heating, cooling and exhaust systems should be provided where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross contamination as well as protect the integrity of starting materials, packaging materials, intermediates and finished products.
- 3.43. Equipment for adequate control of air pressure, micro-organisms, dust, humidity, and temperature should be provided when appropriate for the manufacture, processing, packaging, or holding of a pharmaceutical product.
- 3.44. Air filtration systems, including pre-filters and particulate matter air filters, should be used when appropriate on air supplies to production and sampling areas.
- 3.45. Where air is re-circulated to production areas, appropriate measures should be taken to control re-circulation of dust from production. In areas where air contamination occurs during production, there should be adequate exhaust systems or other systems adequate to

control contaminants.

- 3.46. The manufacture, processing and packaging of highly sensitizing materials such as β -lactams or biological preparations such as live microorganisms, highly active products such as some antibiotics, hormones, cytotoxic substances and technical poisons such as pesticides and herbicides should be carried out in dedicated facilities to prevent cross contamination.

Water supply and plumbing

- 3.47. Water used in the manufacture of pharmaceutical products should be suitable for its intended use.
- 3.48. Unless otherwise justified, process water should at a minimum meet Nigerian Industrial Standard (NIS) for drinking (potable) water quality. Water not meeting such standards should not be permitted in the potable water system.
- 3.49. Where drinking (potable) water is insufficient to ensure pharmaceutical product quality, stricter chemical and/or microbiological water quality specifications are required. Appropriate specification for physical/chemical attributes, total microbial counts, objectionable organisms and endotoxins should be established.
- 3.50. Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.
- 3.51. Potable water should be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any pharmaceutical product.
- 3.52. Drains should be of adequate size and, where connected directly to a sewer, should be provided with an air break or any other mechanical device to prevent back-siphonage.
- 3.53. Open drains should be avoided; where unavoidable, should be easily accessible and shallow for easy cleaning and disinfection.
- 3.54. Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination.

Sewage and refuse

- 3.55. Sewage, refuse, and other wastes in and from the building and immediate premises should be disposed of in a safe and sanitary manner.
- 3.56. Containers and or pipes for waste materials should be clearly identified

Sanitation

- 3.57. Any building used in the manufacture, processing, packaging or holding of a pharmaceutical product should be maintained in a clean and sanitary condition. There should be standard operating procedures assigning responsibility for sanitation and describing in sufficient detail, the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; and should be followed.
- 3.58. The building should be free of infestation by rodents, birds, insects, and other vermin.
- 3.59. There should be standard operating procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, cleaning and sanitizing agents. Such standard operating procedures should be designed to protect personnel and prevent the contamination of equipment, materials, pharmaceutical product containers, closures, packaging, labelling materials, or pharmaceutical products and should be followed. Rodenticides, insecticides, and fungicides should not be used unless registered in accordance with the Food and Drug Act and the Pesticide Registration Regulations of the Agency.

Equipment

- 3.60. Equipment should be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.
- 3.61. Equipment should be installed in such a way as to minimize any risk of error or contamination.
- 3.62. 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, adsorptive or absorptive to an extent that would affect the quality of the product and thus present any hazard.
- 3.63. Manufacturing equipment should be designed so that it can be easily

and thoroughly cleaned. It should be cleaned according to detailed written procedures and stored only in a clean and dry condition.

- 3.64. Repair and maintenance operations should not present any hazard to the quality of the products.
- 3.65. Washing, cleaning and drying equipment should be chosen and used so as not to be a source of contamination.
- 3.66. Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.
- 3.67. Production equipment should be thoroughly cleaned according to a fixed schedule.
- 3.68. Laboratory equipment and instruments should be suited to the testing procedures undertaken.
- 3.69. Measuring, weighing, recording and control equipment should be calibrated by certified bodies and checked at defined intervals by appropriate methods. Adequate records should be maintained
- 3.70. Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.
- 3.71. All service pipework and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.
- 3.72. Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is opened, precautions should be taken to minimize contamination.
- 3.73. Non-dedicated equipment used for the production of different pharmaceutical products should be cleaned according to validated cleaning procedures to prevent cross-contamination.
- 3.74. Defective equipment should be removed from production and quality control areas. If this is not possible, it should be clearly labelled as defective to prevent use.
- 3.75. Current drawings of critical equipment and support systems should be maintained.

Cleaning and maintenance

- 3.76. Any building used in the manufacture, processing, packaging, or

holding of a pharmaceutical product should be maintained in a good state of repair.

- 3.77. Repair and maintenance operations should not present any hazard to the quality of products.
- 3.78. Schedules and procedures (including assignments of responsibilities) should be established for the preventive maintenance of equipment
- 3.79. Equipment and utensils should be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the pharmaceutical product beyond the official or other established specifications.
- 3.80. Standard operating procedures should be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packaging, or holding of a pharmaceutical product. These procedures should include, but are not necessarily limited to, the following:
 - a. Assignment of responsibility for cleaning and maintaining equipment;
 - b. Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;
 - c. A description in sufficient detail of the methods, equipment, and materials used (including dilution of cleaning agents) in cleaning and maintenance operations,
 - d. Where appropriate, instructions for disassembling and reassembling equipment to ensure proper cleaning and maintenance should be provided;
 - e. Instructions for the removal or obliteration of previous batch identification;
 - f. Instructions for the protection of clean equipment from contamination prior to use;
 - g. Inspection of equipment for cleanliness immediately before use.
 - h. Proper records should be kept of maintenance, cleaning, sanitizing, and inspection as described in **Chapter 5**

4 QUALIFICATION AND VALIDATION

Qualification and validation

Principle

- 4.1. It is a requirement of GMP that manufacturers identify what validation work is needed to prove that the critical aspects of their particular operations are controlled. Significant changes to the facilities, the equipment and the processes, which may affect the quality of the product, should be validated. A risk assessment approach should be used to determine the scope and extent of validation.

General

- 4.2. The key elements of a qualification and validation programme of a company should be clearly defined and documented in a validation master plan.
- 4.3. Qualification and validation should establish and provide documentary evidence that:
 - a. The premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP (design qualification {DQ});
 - b. The premises, supporting utilities and equipment have been built and installed in compliance with their design specifications (installation qualification {IQ});
 - c. The premises, supporting utilities and equipment operate in accordance with their design specifications (operational qualification {OQ});
 - d. A specific process will consistently produce a product meeting its predetermined specifications and quality attributes (Process Validation {PV} also called Process Performance Qualification {PPQ}).
- 4.4. Any aspect of operation, including significant changes to the

premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, should be qualified and validated. Qualification and validation should not be considered as one-off exercises. An on-going programme should follow their first implementation and should be based on a periodic review.

- 4.5. The commitment to maintain continued validation status should be stated in the relevant company documentation, such as the quality manual or validation master plan.
- 4.6. The responsibility of performing validation should be clearly defined.
- 4.7. Validation studies are an essential part of GMP and should be conducted in accordance with predefined and approved protocols.
- 4.8. A written report summarizing the results recorded and the conclusions reached should be prepared and stored.
- 4.9. Processes and procedures should be established on the basis of the results of the validation performed.
- 4.10. Particular attention should be paid to the validation of processes, analytical test methods, automated systems and cleaning procedures.

Planning for validation

- 4.11. All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a Validation Master Plan (VMP).
- 4.12. The VMP should be a summary document which is brief, concise and clear.
- 4.13. The VMP should contain at least the following:
 - a. Validation policy;
 - b. Organizational structure of validation activities;
 - c. Summary of facilities, systems, equipment and processes to be validated;
 - d. Documentation format: the format to be used for protocols and reports;

- e. Planning and scheduling;
 - f. Change control;
 - g. Reference to existing documents.
- 4.14. In case of large projects like the construction of a new facility, often the best approach is to create a separate VMP, (in such situations the VMP should be part of the total project management.)

Documentation

- 4.15. Written protocol that specifies how qualification and validation will be conducted should be established. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria.
- 4.16. A report that cross-references the qualification and/or validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification.
- 4.17. After completion of a satisfactory qualification, a formal release for the next step in qualification and validation should be made as a written authorization.

Qualification

Qualification prerequisites

User requirement specification (URS)

- 4.18. This document describes what the equipment is intended to do and all the essential requirements such as production rates, operating ranges etc. The user usually develops this document and it links to the performance qualification document which tests for each of the requirements.

Functional Requirement Specification (FRS)

- 4.19. This document describes the detailed functionality of the equipment. The supplier usually develops this document and this document links to the operational qualification document

which tests for each function.

Factory Acceptance Test (FAT)

- 4.20. FAT is a test conducted to determine if the requirement of the specification of the contract are met and this is usually conducted in the facility of the supplier.

Site Acceptance Test (SAT)

- 4.21. SAT is a test conducted to determine if the requirements of the specification of the contract are met and this is usually conducted in the facility of the user. It is done before commissioning.

Design qualification

- 4.22. The first element of the validation of new facilities, systems or equipment will be design qualification (DQ).
- 4.23. The compliance of the design with GMP should be demonstrated and documented.

Installation qualification

- 4.24. Installation qualification (IQ) should be performed on new or modified facilities, systems and equipment.
- 4.25. IQ should include, but not be limited to the following:
- a. Installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;
 - b. Collection and collation of supplier operating and working instructions and maintenance requirements;
 - c. Calibration requirements;
 - d. Verification of materials of construction.

Operational qualification

- 4.26. Operational qualification (OQ) should follow installation qualification.
- 4.27. OQ should include, but not be limited to the following:
- a. Tests that have been developed from knowledge of processes, systems and equipment;

- b. Tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as “worst case” conditions.
- 4.28. The completion of a successful operational qualification should allow the finalization of calibration, operating and cleaning procedures, operator training and preventive maintenance requirements. It should permit a formal "release" of the facilities, systems and equipment.

Performance qualification

- 4.29. Performance qualification (PQ) should follow successful completion of installation qualification and operational qualification.
- 4.30. PQ should include, but not be limited to the following:
- a. Tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;
 - b. Tests to include a condition or set of conditions encompassing upper and lower operating limits.
- 4.31. Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.

Qualification of established (in-use) facilities, systems and equipment

- 4.32. Evidence should be available to support and verify the operating parameters and limits for the critical variables of the operating equipment. Additionally, the calibration, cleaning, preventive maintenance, operating procedures and operator training procedures and records should be documented.

Process validation

General

- 4.33. The requirements and principles for process validation are applicable to the manufacture of pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes and re-validation.
- 4.34. Process validation should normally be completed prior to the

distribution and sale of the pharmaceutical product (prospective validation). In exceptional circumstances, where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes in use for some time should also be validated (retrospective validation). Retrospective validation is not permitted in the production of parenteral preparations.

- 4.35. Facilities, systems and equipment to be used should have been qualified and analytical testing methods should be validated or verified as appropriate. Personnel taking part in the validation programme should have been appropriately trained.
- 4.36. Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.

Prospective validation

- 4.37. Prospective validation should include, but not be limited to the following:
 - a. Short description of the process;
 - b. Summary of the critical processing steps to be investigated;
 - c. List of the equipment/facilities to be used (including measuring/ monitoring/recording equipment) together with its calibration status;
 - d. Finished product specifications for release;
 - e. List of analytical methods, as appropriate;
 - f. Proposed in-process controls with acceptance criteria;
 - g. Additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
 - h. Sampling plan;
 - i. Methods for recording and evaluating results;
 - j. Functions and responsibilities;
 - k. Proposed timetable.
- 4.38. Using this defined process (including specified materials) a

series of batches of the final product may be produced under routine conditions. In theory, the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation.

- 4.39. In keeping with principles of quality risk management, these guidelines recommend that process validation embraces the product life-cycle concept which involves the generation and evaluation of data throughout the process from development to full scale production.
- 4.40. Batches made for process validation should be the same size as the intended industrial scale batches.
- 4.41. If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise, and with the marketing authorization.

Concurrent validation

- 4.42. In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.
- 4.43. The decision to carry out concurrent validation must be justified, documented and approved by authorised personnel.
- 4.44. Documentation requirements for concurrent validation are the same as specified for prospective validation.

Retrospective validation

- 4.45. Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.
- 4.46. Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.
- 4.47. The source of data for this validation should include, but not be

limited to batch processing and packaging records, process control charts, maintenance log books, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results.

- 4.48. Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.
- 4.49. For retrospective validation generally, data from ten to thirty consecutive batches should be examined to assess process consistency.

Cleaning validation

- 4.50. Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carryover of product residues, cleaning agents and microbial contamination should be logically based on the materials involved. The limits should be achievable and verifiable.
- 4.51. Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant.
- 4.52. Normally, only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to non-contact parts. The intervals between use and cleaning as well as cleaning and re-use should be validated. Cleaning intervals and methods should be determined.
- 4.53. For cleaning procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilizing a “worst case” approach can be carried out which takes account of the critical issues.
- 4.54. Typically, three consecutive applications of the cleaning

5 DOCUMENTATION

DOCUMENTATION

Principle

- 5.1. Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a pharmaceutical product for sale; to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis.
- 5.2. The various types of documents and media used should be fully defined in the manufacturer's PQS. Documentation may exist in a variety of forms, including paper-based, electronic or photographic media. The main objective of the system of documentation utilised must be to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of pharmaceutical products.
- 5.3. The Pharmaceutical Quality System should include sufficient instructional detail to facilitate a common understanding of the requirements, in addition to providing for sufficient recording of the various processes and evaluation of any observations, so that ongoing application of the requirements may be demonstrated. 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

- 5.4. Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of Product Specification Files, Manufacturing and Marketing Authorization dossiers, as appropriate.
- 5.5. Documents containing instructions should be approved, signed and dated by appropriate and authorised persons.

- 5.6. Documents should have unambiguous contents; the title, nature and purpose should be clearly stated and be uniquely identifiable. The effective date should be defined. No document should be changed without authorization and approval.
- 5.7. Documents containing instructions should be laid out in an orderly fashion and should be easy to check. The style and language of documents should fit with their intended use. Standard Operating Procedures, Work Instructions and Methods should be written in an imperative mandatory style.
- 5.8. 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.
- 5.9. Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.
- 5.10. Documents should not be hand-written; although, where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.
- 5.11. Any alteration made to a document should be signed and dated; that alteration should be done in such a way as to permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.
- 5.12. Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records should be retained for at least one year after the expiry date of the finished product.
- 5.13. Data (and records for storage) may be recorded by electronic data processing systems or by photographic or other reliable means. Master formulae and detailed SOPs 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 system, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked. Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, electronic discs, paper printouts or other means. It is particularly important that, during the period of retention, the data are readily available.
- 5.14. Complex systems need to be understood, well documented, validated, and adequate controls should be in place.
- 5.15. Many documents (instructions and/or records) may exist in hybrid forms, i.e. some

- elements as electronic and others as paper based. Relationships and control measures for master documents, official copies, data handling and records need to be stated for both hybrid and homogenous systems.
- 5.16. Appropriate controls for electronic documents such as templates, forms, and master documents should be implemented. Appropriate controls should be in place to ensure the integrity of the record throughout the retention period.
- 5.17. It should be clearly defined which record is related to each manufacturing activity and where this record is located. Secure controls must be in place to ensure the integrity of the record throughout the retention period and validated where appropriate.
- 5.18. Specific requirements apply to batch documentation which must be kept for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the authorized Person, whichever is the longer.
- 5.19. For investigational pharmaceutical products (clinical trials), the batch documentation must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used.
- 5.20. For other types of documentation, the retention period will depend on the business activity which the documentation supports. Critical documentation, including raw data (for example relating to validation or stability), which supports information in the Marketing Authorisation should be retained whilst the authorisation remains in force. It may be considered acceptable to retire certain documentation (e.g. raw data supporting validation reports or stability reports) where the data has been superseded by a full set of new data. Justification for this should be documented and should take into account the requirements for retention of batch documentation; for example, in the case of process validation data, the accompanying raw data should be retained for a period at least as long as the records for all batches whose release has been supported on the basis of that validation exercise.
- 5.21. The following section gives some examples of required documents. The pharmaceutical quality system should describe all documents required to ensure product quality and patient safety.

Required GMP documentation (by type)

- 5.22. There are two primary types of documentation used to manage and record GMP compliance: Instructions (directions, requirements) and Records/Reports. Appropriate good documentation practice should be applied with respect to the type of document.
- 5.23. Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents. Instruction documents should be free from errors and

available in writing. The term 'written' means recorded, or documented on media from which data may be rendered in a human readable form.

Instructions (Directions or Requirements):

- 5.24. **Labels:** A document which is used to identify a container, product, equipment or location providing information on the item's origin, contents, use, destination or status.
- 5.25. 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 (e.g. quarantined, accepted, rejected, and clean).
- 5.26. All finished pharmaceutical products should be identified by labelling, as required by the Agency.
- 5.27. For reference standards, the label and/or accompanying document should indicate potency or concentration, date of manufacture, expiry date, date the closure was first opened, storage conditions and control number, as appropriate.
- 5.28. **Specifications:** Describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.
- 5.29. There should be appropriately authorized and dated specifications, including tests on identity, content, purity and quality, for starting and packaging materials and for finished products; where appropriate, they should also be available for intermediate or bulk products. Specifications for water, solvents and reagents (e.g. acids and bases) used in production should be included.
- 5.30. Each specification should be approved, signed, dated, and maintained by quality control.
- 5.31. Periodic revisions of the specifications may be necessary to comply with new editions of compendia.
- 5.32. Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routine testing.
- 5.33. Pharmacopoeias, reference standards, reference spectra and other reference materials should be available in the QC laboratory

Specifications for starting and packaging materials

- 5.34. Specifications for starting and primary or printed packaging materials should include or provide reference to, if applicable:
- a. A description of the materials, including:

- i. The designated name (if applicable, the International Non Proprietary Name (INN) and the internal code reference;
 - ii. The reference, if any, to a pharmacopoeial monograph;
 - iii. The approved suppliers and the original producer of the material;
 - iv. A specimen of printed materials;
 - b. Directions for sampling and testing;
 - c. Qualitative and quantitative requirements with acceptance limits;
 - d. Storage conditions and precautions;
 - e. The maximum period of storage before re-examination.
- 5.35. Packaging material should conform to specifications, and should be compatible with the material and/or with the pharmaceutical product it contains.
- 5.36. The material should be examined for compliance with the specification, and for defects as well as for the correctness of identity markings.
- 5.37. 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

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

Specifications for finished products

- 5.39. Specifications for finished products should include or provide reference to:
- 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, with the INN(s));
 - c. The formula or a reference to the formula;
 - d. A description of the pharmaceutical form and package details;
 - e. Directions for sampling and testing or a reference to procedures;
 - f. The qualitative and quantitative requirements, with the acceptance limits;
 - g. The storage conditions and any special handling precautions, where

applicable;

h. The shelf-life.

- 5.40. **Manufacturing Formulae, Processing, Packaging and Testing Instructions:**
Provide the details for all the starting materials, equipment and computerized systems (if any) to be used and specify all processing, packaging, sampling and testing instructions. In-process controls and process analytical technologies to be employed should be specified where relevant, together with acceptance criteria.
- 5.41. Approved, written Master Formula and Processing Instructions should exist for each product and batch size to be manufactured.
- 5.42. 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 pharmaceutical dosage form, strength of the product and batch size;
 - c. A list of all starting materials to be used (if applicable with the INNs), with the amount of each described; 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.
- 5.43. 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, sterilising and use;
 - c. Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use;
 - d. Detailed stepwise processing instructions (e.g. checks on materials, pre-treatments, sequence for adding materials, critical process parameters such as time, temperature etc.);
 - e. The instructions for any in-process controls with their limits;
 - f. Where necessary, the requirements for bulk storage of the products; including the container, labelling and special storage conditions where applicable;

- g. Any special precautions to be observed.

Packaging Instructions

- 5.44. Approved packaging instructions for each product, pack size and type should exist. These should include, or have a reference to the following:
- a. Name of the product; including the batch number of bulk and finished product;
 - b. Description of its pharmaceutical form and strength where applicable;
 - c. The pack size expressed in terms of the number, weight or volume of the product in the final container;
 - d. A complete list of all the packaging materials required, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
 - e. Where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;
 - f. Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations (line clearance), and that equipment is clean and suitable for use;
 - g. Special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before and after packaging operations;
 - h. A description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
 - i. Details of in-process controls with instructions for sampling and acceptance limits.

Batch manufacturing/processing records

- 5.45. A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)
- 5.46. 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.

- 5.47. 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:
- The name of the product;
 - The number of the batch being manufactured;
 - Dates and times of commencement, of significant intermediate stages, and of completion of production;
 - The name of the person responsible for each stage of production;
 - 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);
 - 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);
 - Any relevant processing operation or event and the major equipment used;
 - The in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
 - 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;
 - Notes on special problems including details, with signed authorization for any deviation from the master formula (manufacturing formula and processing instruction).
 - Approval by the person responsible for the processing operations
- 5.48. **Note:** Where a validated process is continuously monitored and controlled, then automatically generated reports may be limited to compliance summaries and exception / out-of-specification (OOS) data reports.

Batch packaging records

- 5.49. A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)
- 5.50. 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.

- 5.51. The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:
- a. The name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;
 - b. The date(s) and time(s) of the packaging operations;
 - c. The name of the responsible person carrying out the packaging operation;
 - d. The initials of the operators of the different significant steps;
 - e. The checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
 - f. Details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;
 - g. Samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;
 - h. Notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
 - i. The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit adequate reconciliation.
- 5.52. **Standard Operating Procedures (SOPs):** give directions for performing certain operations.
- 5.53. SOPs and associated records of actions taken should be available for but not limited to:
- a. Equipment assembly and validation;
 - b. Analytical apparatus and calibration;

- c. Maintenance, cleaning and sanitization;
 - d. Personnel matters including qualification, training, clothing and hygiene;
 - e. Environmental monitoring;
 - f. Pest control;
 - g. Complaints;
 - h. Recalls;
 - i. Returns;
 - j. Change control;
 - k. Investigations into deviations and non-conformances;
 - l. Internal quality/GMP compliance audits;
 - m. Summaries of records where appropriate (e.g. product quality review);
 - n. Supplier audits
 - o. Technology Transfer.
- 5.54. There should be SOPs and records for the receipt of each delivery of starting material and primary and printed packaging material.
- 5.55. 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).
- 5.56. There should be SOPs for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.
- 5.57. SOPs should be available for each instrument and piece of equipment (e.g. use, calibration, cleaning, maintenance) and placed in close proximity to the equipment.
- 5.58. There should be SOPs for sampling, which specify the person(s) authorized to take samples.

- 5.59. The sampling instructions should include:
- The method of sampling and the sampling plan;
 - The equipment to be used;
 - Any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
 - The amount(s) of sample(s) to be taken;
 - Instructions for any required subdivision of the sample;
 - The type of sample container(s) to be used; and whether they are for aseptic sampling or for normal sampling, and labelling;
 - Any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.
- 5.60. There should be an SOP describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.
- 5.61. The SOPs for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.
- 5.62. The SOP for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.
- 5.63. Batch-number allocation should be immediately recorded, e.g. in a logbook. The record should include at least the date of allocation, product identity and size of batch.
- 5.64. 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.
- 5.65. Analysis records should include at least the following data:
- The name of the material or product and, where applicable, dosage form;
 - The batch number and, where appropriate, the manufacturer and/or supplier;
 - References to the relevant specifications and testing procedures;
 - Test results, including observations and calculations, and reference to any specifications (limits);
 - Date(s) and reference number(s) of testing;
 - The initials of the persons who performed the testing;

- g. The date and initials of the persons who verified the testing and the calculations, where appropriate;
 - h. A clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.
- 5.66. 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. All records should be available to the authorised person. A system should be in place to indicate special observations and any changes to critical data.
- 5.67. Records should be maintained of the distribution of each batch of a product in order, e.g. to facilitate the recall of the batch if necessary.
- 5.68. Records should be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried out these operations.
- 5.69. The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.
- 5.70. Logbooks should be kept for major or critical analytical testing, production equipment and areas where product has been processed. They should be used to record in chronological order, as appropriate, any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried out these operations.
- 5.71. There should be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned. Such written procedures should be followed.
- 5.72. An inventory of all SOPs and other documents within the quality management system should be maintained.
- 5.73. **Protocols:** These give instructions for performing and recording certain discreet operations.
- 5.74. **Contracts:** These are written agreements between contract givers and acceptors for outsourced activities.

Record/Report type:

- 5.75. **Records:** These provide evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events, investigations, and in the case of manufactured batches a history of each batch of product, including its distribution. Records include the raw data which is used to generate other records. For electronic records regulated users should define which data are to be used as raw data. At least,

all data on which quality decisions are based should be defined as raw data.

Laboratory Records

- 5.76. Laboratory records should include complete data derived from all tests necessary to ensure compliance with established specifications and standards, including examinations and assays, as follows:
- a. A description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, batch number or other distinctive code, date sample was taken and date sample was received for testing.
 - b. A statement of each method used in the testing of the sample. The statement should indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. Where the method employed is in the current edition of a recognized standard reference (e.g. British Pharmacopoeia, United States Pharmacopoeia, International Pharmacopoeia), and the referenced method is not modified, a statement indicating the method and reference will suffice. The suitability of all testing methods used should be verified under actual conditions of use.
 - c. A statement of the weight or measure of sample used for each test, where appropriate.
 - d. A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material, pharmaceutical product container, closure, in-process material, or pharmaceutical product, and batch tested.
 - e. A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.
 - f. A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the material, pharmaceutical product container, closure, in-process material, or pharmaceutical product tested.
 - g. The initials or signature of the person who performs each test and the date(s) the tests were performed.
 - h. The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.
- 5.77. Complete records of any modification of an established method employed in testing

should be maintained. Such records should include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

- 5.78. Complete records of all out-of-specification (OOS) and out-of-trend (OOT) investigations should be maintained.
- 5.79. Complete records of any testing and standardization of laboratory reference standards, reagents, and standard solutions should be maintained.
- 5.80. Complete records of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices should be maintained.
- 5.81. Complete records of all stability testing performed as described in ***Stability Studies 8.55 to 8.73*** should be maintained.

Distribution records

- 5.82. Distribution records should contain the following:
 - a. Name, strength and dosage form of the product
 - b. Description of the dosage form,
 - c. Name and address of the consignee,
 - d. Date and quantity shipped,
 - e. Batch or control number of the pharmaceutical product.
 - f. Date of Manufacture and Expiration date.
- 5.83. **Certificates of Analysis:** These provide a summary of test results on samples of products or materials together with the evaluation for compliance to a stated specification.
- 5.84. Alternatively the certification may be based, in-whole or in-part, on the assessment of real time data (summaries and exception reports) from batch related process analytical technology (PAT), parameters or metrics as per the approved marketing authorisation dossier.
- 5.85. **Reports:** These document the conduct of particular exercises, projects or investigations, together with results, conclusions and recommendations.

Site Master File (SMF):

Introduction

- 5.86. The Site Master File (SMF) is a document which describes the GMP related activities of the manufacturer at a particular site.
- 5.87. The SMF is prepared by the pharmaceutical manufacturer and should contain specific

information about the quality management policies and activities of the site, the production and/or quality control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a pharmaceutical operation is carried out on the site, a site master file needs only to describe those operations, e.g. analysis, packaging, etc.

- 5.88. When submitted to the Agency, the SMF should provide clear information on the manufacturer's GMP related activities that can be useful in general supervision and in the efficient planning and undertaking of GMP inspections.
- 5.89. A site master file should contain adequate information but, as far as possible, not exceed 25-30 A4 pages plus appendices. Simple plans, outline drawings or schematic layouts are preferred instead of narratives.
- 5.90. The SMF file should be a part of documentation belonging to the quality management system of the manufacturer and kept updated accordingly. The SMF should have an edition number, the date it becomes effective and the review date. It should be subject to regular reviews to ensure that it is up to date and representative of current activities. Each appendix can have an individual effective date, allowing for independent updating.

Contents of Site Master File

- 5.91. The SMF should contain at least the following:

a. General Information on the Manufacturer

- i. Name and official address of the manufacturer;
- ii. Names and street addresses of the site, buildings and production units located on the site;
- iii. Phone (office and mobile) numbers and e-mail address of the manufacturer
- iv. A 24-hour telephone number(s) of the contact personnel in the case of product defects or recalls.

b. Authorized pharmaceutical manufacturing activities of the site.

- i. A brief description of manufacture, import, export, distribution and other activities as authorized by the Agency including foreign authorities with authorized dosage forms/activities, respectively; where not covered by the manufacturing authorization.
- ii. Type of products currently manufactured on-site where not covered by the manufacturing authorization in Appendix 1 should be attached as Appendix 2.

- iii. List of GMP inspections of the site within the last 5 years; including dates and name/country of the Competent Authority having performed the inspection. A copy of the current GMP certificate should be attached as Appendix 3 if available.
- c. **Any other manufacturing activities carried out on the site**
- i. Description of non-pharmaceutical activities on-site, if any.

Quality Management System of the Manufacturer

- 5.92. Description of the quality management system
- a. Brief description of the quality management systems run by the company and reference to the standards used (e.g. ICH Q10, ISO 9001);
 - b. Responsibilities related to the maintaining of quality system including top management;
 - c. Information of activities for which the site is accredited and certified, including dates and contents of accreditations, names of accrediting bodies.
- 5.93. Release procedure for finished products
- a. Name(s) of authorised person(s) responsible for batch certification and release procedures
 - b. Detailed description of qualification requirements (education and work experience) of the authorised person(s) responsible for batch certification and release procedures;
 - c. General description of batch certification and release procedure;
 - d. Role of authorised person in quarantine and release of finished products and in assessment of compliance with the marketing authorization;
 - e. Statement on whether the control strategy employs Process Analytical Technology (PAT) and/or Real Time Release or Parametric Release;
- 5.94. Management of suppliers and contractors
- a. A brief summary of the establishment/knowledge of supply chain and the external audit program;
 - b. Brief description of the qualification system of contractors, manufacturers of active pharmaceutical ingredients (API) and other critical materials suppliers;
 - c. Measures taken to ensure that products manufactured are compliant with Transmissible Spongiform Encephalopathy (TSE) guidelines.

- d. Measures adopted where counterfeit/falsified products, bulk products (e.g. unpacked tablets), active pharmaceutical ingredients or excipients are suspected or identified.
 - e. Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;
 - f. List of contract manufacturers and laboratories including the addresses and contact information and flow charts of supply-chains for outsourced manufacturing and Quality Control activities; e.g. sterilization of primary packaging material for aseptic processes, testing of starting materials etc., should be presented in Appendix 4
 - g. Brief overview of the responsibility sharing between the contract giver and acceptor with respect to compliance with the Marketing Authorization.
- 5.95. Quality Risk Management (QRM)
- a. Brief description of QRM methodologies used by the manufacturer;
 - b. Scope and focus of QRM including brief description of any activities which are performed at corporate level, and those which are performed locally. Any application of the QRM system to assess continuity of supply should be mentioned;
- 5.96. Product Quality Reviews
- a. Brief description of methodologies used
- 5.97. Personnel
- a. Organizational chart showing the arrangements for quality management, production and quality control positions/titles in Appendix 5 including top management and authorized person.
 - b. Number of employees engaged in the quality management, production, quality control, storage and distribution respectively;

Premises and Equipment

- 5.98. Premises
- a. Short description of plant; size of the site and list of buildings. If the production for different markets, i.e. for local and foreign countries takes place in different buildings on the site, the buildings should be listed with destined markets identified;
 - b. Simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings are not required);

- c. Lay-outs and flow charts of the production areas (in appendix 6) showing the room classification and pressure differentials between adjoining areas and indicating the production activities (i.e. compounding, filling, storage, packaging, etc.) in the rooms.;
 - d. Lay-outs of warehouses and storage areas, with special areas for the storage and handling of highly toxic, hazardous and sensitizing materials indicated, if applicable;
 - e. Brief description of specific storage conditions if applicable, but not indicated on the lay-outs;
 - f. Brief description of heating, ventilation and air conditioning (HVAC) systems
 - g. Principles for defining the air supply, temperature, humidity, pressure differentials and air change rates, policy of air recirculation;
 - h. Brief description of water systems
 - i. Quality references of water produced
 - j. Schematic drawings of the systems in appendix 7
 - k. Brief description of other relevant utilities, such as steam, compressed air, nitrogen, etc.
- 5.99. Equipment
- a. Listing of major production and control laboratory equipment with critical pieces of equipment identified should be provided in appendix 8.
- 5.100. Preventive maintenance and Calibration
- a. Description of preventive maintenance and calibration system, responsibilities and recording system
- 5.101. Qualification and Validation
- a. Brief description of the company's general policy for qualification and validation
- 5.102. Cleaning and sanitation
- a. Brief description of cleaning and sanitation methods of product contact surfaces (i.e. manual cleaning, automatic Clean-in-Place, etc.).
 - b. Cleaning validation policy of the company and method of evaluation of the effectiveness of cleaning; principles for establishing allowable residue limits

- c. Cleaning agents and quality of water used for cleaning
 - d. Arrangements for the handling of spillages of potent/toxic substances where applicable
- 5.103. GMP critical computerized systems
- a. Description of GMP critical computerized systems (excluding equipment specific Programmable Logic Controllers (PLCs))
- 5.104. Documentation
- a. Description of documentation system (i.e. electronic, manual);
 - b. When documents and records are stored or archived off-site (including pharmacovigilance data, when applicable): List of types of documents/records; Name and address of storage site and an estimate of time required for retrieving documents from the off-site archive.
- 5.105. Production
- a. Type of products manufactured including list of dosage forms of both human and veterinary products which are manufactured on the site(appendices 1 and 2)
 - b. List of dosage forms of Investigational Medicinal Products (IMP) manufactured for any clinical trials on the site, and when different from the commercial manufacturing, information of production areas and personnel
 - c. Toxic or hazardous substances handled (e.g. with high pharmacological activity and/or with sensitizing properties);
 - d. Product types manufactured in a dedicated facility or on a campaign basis, if applicable;
 - e. Process Analytical Technology (PAT) applications, if applicable: general statement of the relevant technology, and associated computerized systems;
- 5.106. Process validation
- a. Brief description of general policy for process validation;
 - b. Policy for reprocessing;
- 5.107. Material management and warehousing
- a. Arrangements for the handling of starting materials, packaging materials, bulk and finished products including sampling, quarantine, release and storage
 - b. Arrangements for the handling of rejected materials and products

- 5.108. Quality Control (QC)
- a. Description of the quality control activities carried out on the site in terms of physical, chemical, and microbiological and biological testing.

Distribution, Complaints, Product Defects and Recalls

- 5.109. Distribution (under the responsibility of the manufacturer)
- a. Types of companies (wholesale licence holders, establishment licence holders, etc.) and locations (within Nigeria, other countries etc.) to which the products are shipped from the site;
 - b. Description of the system used to verify that each customer/recipient is legally entitled to receive pharmaceutical products from the manufacturer
 - c. Brief description of the system to ensure appropriate environmental conditions during transit, e.g. temperature monitoring/control;
 - d. Arrangements for product distribution and methods by which product traceability is maintained;
 - e. Measures taken to prevent manufacturers' products from entering the illegal supply chain.
- 5.110. Complaints, product defects and recalls
- a. Brief description of the system for handling complaints, product defects and recalls
- 5.111. Self-Inspections
- b. Short description of the self-inspection system with focus on criteria used for selection of the areas to be covered during planned inspections, practical arrangements and follow-up activities
- 5.112. **Quality Manual:** A document produced by a manufacturer that details how its quality management system operates.
- 5.113. This should contain at least the following:
- a. Quality policy
 - b. Quality objectives
 - c. Administrative structure
 - d. Organization and management
 - e. Documentation and change control
 - f. Records
 - g. Material management
 - h. Production processes
 - i. Laboratory control
 - j. Personnel
 - k. Management review and internal audit
 - l. Non-conformances/CAPA
 - m. Complaints and recall

- n. Contract manufacturing and analysis
- o. Self-inspection

Appendices

Appendix 1	Copy of valid manufacturing authorization
Appendix 2	List of dosage forms manufactured including the INN-names or common name (as available) of active pharmaceutical ingredients (API) used
Appendix 3	Copy of valid GMP Certificate
Appendix 4	List of contract manufacturers and laboratories including the addresses and contact information, and flow-charts of the supply chains for these outsourced activities
Appendix 5	Organizational charts
Appendix 6	Lay outs of production areas including material and personnel flows, general flow charts of manufacturing processes of each product type (dosage form)
Appendix 7	Schematic drawings of water systems
Appendix 8	List of major production and laboratory equipment

6 PRODUCTION

Principle

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

General

- 6.2. Production should be performed and supervised by competent persons.
- 6.3. All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging, releasing and distribution should be done in accordance with written procedures or instructions and recorded.
- 6.4. 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 unit.
- 6.5. All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.
- 6.6. Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the quality unit.
- 6.7. Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.
- 6.8. Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.
- 6.9. 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.
- 6.10. Checks on yields, and reconciliation of quantities, should be carried out as

necessary to ensure that there are no discrepancies outside acceptable limits.

- 6.11. Operations on different products should not be carried out simultaneously or consecutively in the same room or area.
- 6.12. At every stage of processing, products and materials should be protected from microbial and other contaminations.
- 6.13. When working with dry materials and products, special precautions 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). This applies particularly to the handling of highly active or sensitizing materials.
- 6.14. At all times during processing, all materials, bulk containers, major items of equipment, the rooms and packaging lines being used should be labelled or otherwise identified with an indication of the product or material being processed, its strength and the batch number. Where applicable, this indication should also mention the stage of production. It is important to also record the name of the previous product that has been processed.
- 6.15. 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, clean etc.).
- 6.16. 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.
- 6.17. Access to production premises should be restricted to authorized personnel.
- 6.18. The production of toxic non-pharmaceutical products should not be carried out in plants meant for the production of pharmaceutical products.
- 6.19. In-process controls should be performed within the production area. The performance of such in-process controls should not have any negative effect on the quality of the product or another product (e.g. cross-contamination or mix up).

Prevention of cross-contamination in production

- 6.20. Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, particles, 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. These should be manufactured in dedicated facilities. 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.

- 6.21. A toxicological evaluation should be the basis for the establishment of threshold values in relation to the products manufactured. Where the toxicological evaluation supports a threshold value, this should be used as an input parameter in risk assessment. A quality risk management approach should be used based on this toxicological evaluation and the potential cross contamination risks presented by the products manufactured. Factors including facility/equipment design, personnel flow, physicochemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the threshold values for products should also be taken into account. The outcome of the quality risk management process should be the basis for determining the necessity for and extent to which equipment and facilities should be dedicated to a particular product or product family. This may range from dedicating specific product contact parts to dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a segregated, self-contained production area within a multiproduct facility, where justified.
- 6.22. Technical and organizational measures to mitigate risks of cross-contamination could include, but are not limited to, the following:

Technical Measures

- a. Dedicated manufacturing facilities; production in dedicated facilities is required for products such as β -lactams, live vaccines, live bacteria preparations and some other biologics
- b. Self-contained production areas having separate processing equipment and separate HVAC systems. It may also be desirable to isolate certain utilities from those used in other areas.
- c. Design of manufacturing process, facility and equipment to minimize opportunities for cross contamination during processing, maintenance and cleaning

- d. Use of “closed systems” for processing and material/product transfer between equipment,
- e. Use of physical barrier systems, including isolators, as containment measures
- f. Controlled removal of dust close to source of the contaminant e.g. through localised extraction
- g. Dedication of processing equipment, dedication of product contact parts or dedication of selected parts which are harder to clean (e.g. filters), dedication of maintenance tools
- h. Use of disposable technologies
- i. Use of equipment designed for ease of cleaning
- j. Appropriate use of airlocks and pressure cascade to confine potential airborne contaminants within a specified area
- k. Minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air
- l. Use of automatic clean-in-place systems of validated effectiveness,
- m. For common general wash areas, separation of equipment washing, drying and storage areas,

Organizational Measures

- a. Dedicating the whole manufacturing facility or a self-contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness,
- b. Keeping protective clothing inside areas where products with high risk of cross contamination are processed,
- c. Cleaning verification after each product campaign instead of a cleaning validation should be considered as a detectability tool to support effectiveness of the quality risk management approach,
- d. Cleaning of working areas and surfaces followed by execution of a comprehensive sampling protocol for critical surfaces
- e. Use of air samples and wipe/swab samples taken in adjoining areas outside the working area to demonstrate the efficiency of mitigation measures for airborne and mechanical transfer of contaminant,
- f. Specific measures for waste handling, contaminated rinsing water and soiled gowning,

- g. Recording of spills, accidental events or deviations from procedures
 - h. Design of cleaning processes for manufacturing equipment and building facilities such that the cleaning processes in themselves do not present a cross contamination risk.
 - i. Design of detailed records for cleaning processes to assure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas,
 - j. Use of common general wash areas on a campaign basis.
 - k. Monitoring of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls.
- 6.23. Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological monitoring and particulate matter where appropriate).
- 6.24. Periodic checks of effectiveness of measures to prevent cross-contamination according to set procedures.

Validation

1. When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.
2. 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.
3. Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

Equipment identification

- 6.25. All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a pharmaceutical product should be properly identified at all times to indicate the product or material being processed, its strength (where applicable) batch number and, when necessary, the phase of processing of the batch.
- 6.26. Major equipment should be identified by a distinctive identification number or code that should be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a pharmaceutical product.

Charge-in of materials

- 6.27. Standard operating production and control procedures that describe the following, are designed to ensure that the pharmaceutical products manufactured have the identity, strength, quality, and purity specifications for the intended use they purport or are represented to possess:
- a. The batch should be formulated with the intent to provide not less than 100 per cent of the labelled or established amount of active ingredient.
 - b. Materials for pharmaceutical product manufacturing should be weighed, measured, or subdivided as appropriate. Where a material is removed from the original container to another, the new container should be identified with the following information:
 - i. Material name or item code;
 - ii. Receiving or control number;
 - iii. Weight or measure in new container;
 - iv. Batch for which material was dispensed, including its product name, strength, and lot number.
 - c. Weighing, measuring, or subdividing operations for materials should be adequately supervised. Each container of material dispensed to manufacturing should be examined by a second person to ensure that:
 - i. The material was released by the quality control unit;
 - ii. The weight or measure is correct as stated in the batch production records;
 - iii. The containers are properly identified.
 - d. Each material should be added to the batch by one person and verified by a second person.
 - e. The identification of personnel performing each step of the process and of the person who checked each of these steps should be clearly stated.

Calculation of yield

- 6.28. Actual yields and percentages of theoretical yield should be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the pharmaceutical product. Such calculations should be performed by one person and independently verified by a second person. Deviation from validated yield range should be treated as described in ***Change***

Control 6.39 to 6.41.***Sampling and testing of in-process materials and pharmaceutical products***

- 6.29. To ensure batch uniformity and integrity of pharmaceutical products, standard operating procedures that describe the in-process controls and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch should be established and followed. Such control procedures should be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the pharmaceutical product.
- 6.30. Valid in-process specifications should be consistent with pharmaceutical product final specifications and should be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples should ensure that the pharmaceutical product and in-process material conform to specifications.
- 6.31. In-process materials should be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, for example, at commencement or completion of significant phases or after storage for long periods.
- 6.32. Rejected in-process materials should be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

Time limitations on production

- 6.33. When appropriate, time limits for the completion of each phase of production should be established to ensure the quality of the pharmaceutical product.
- 6.34. Deviations from established time limits may be acceptable where such deviations do not compromise the quality of the pharmaceutical product. Such deviations should be justified and documented.

Control of microbiological contamination

- 6.35. Standard operating procedures designed to prevent objectionable microorganisms in pharmaceutical products not required to be sterile, should be established and followed.
- 6.36. Standard operating procedures designed to prevent microbiological contamination of pharmaceutical products purporting to be sterile, should

be established and followed. Such procedures should include validation of any sterilization process.

Reprocessing

- 6.37. Standard operating procedures prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps to be taken to ensure that the reprocessed batches will conform to all established standards, specifications, and characteristics should be established and followed.
- 6.38. Reprocessing should not be performed without the review and approval of the quality unit.

Change control

- 6.39. A formal change control system should be established to evaluate all changes that may affect the production and control of the pharmaceutical product, intermediate or API
- 6.40. Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials, computer software.
- 6.41. Any proposals for GMP-relevant changes should be drafted, reviewed, and approved by the appropriate organizational unit and reviewed and approved by the quality unit.

Packaging and labelling control

Material examination and usage criteria

- 6.42. Standard operating procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labelling and packaging materials should be established and followed.
- 6.43. Labelling and packaging materials should be representatively sampled, and examined or tested upon receipt and before use in packaging or labelling of a pharmaceutical product.
- 6.44. Any labelling or packaging material meeting appropriate written specifications may be approved and released for use. Any labelling or packaging material that does not meet such specifications should be rejected to prevent their use in operations for which they are unsuitable.
- 6.45. Records of each different labelling and packaging material indicating receipt,

examination or testing, and whether accepted or rejected should be maintained for each shipment received.

Packaging Materials

- 6.46. Containers should provide adequate protection against deterioration or contamination of the intermediate, API or finished pharmaceutical product that may occur during transportation and recommended storage.
- 6.47. Containers should be clean and, where indicated by the nature of the intermediate, API or finished pharmaceutical product, sanitized to ensure that they are suitable for their intended use.
- 6.48. These containers should not be reactive, additive, adsorptive or absorptive so as to alter the quality of the intermediate, API or finished pharmaceutical product beyond the specified limits.

Label Issuance and Control

- 6.49. Labels and other labelling materials for each different pharmaceutical product, strength, dosage form, or quantity of contents should be stored separately and securely with suitable identification.
- 6.50. Obsolete and out-dated labels, labelling, and other packaging materials should be destroyed.
- 6.51. Use of gang printing of labelling for different pharmaceutical products or different strengths or net contents of the same pharmaceutical product, is prohibited..
- 6.52. Where cut labelling is used, packaging and labelling operations should include one of the following special control procedures:
 - a. Dedication of labelling and packaging lines to each different strength of each different pharmaceutical product.
 - b. Use of appropriate electronic or electromechanical equipment to conduct a 100 per cent examination for correct labelling during or after completion of finishing operations; or
 - c. Use of visual inspection to conduct a 100 per cent examination for correct labelling during or after completion of finishing operations for hand- applied labelling. Such examination should be performed by one person for not more than 30minutes at each sitting and independently verified by a second person.
- 6.53. Printing devices on/or associated with manufacturing lines used to imprint/overprint labelling upon the pharmaceutical product unit label or case should be monitored to ensure that all imprinting/overprinting conform

to the print specified in the batch production record.

- 6.54. Procedures should be used to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labelled and the number of labels issued. Such discrepancies should be investigated, documented and approved by the quality unit.
- 6.55. All excess labelling bearing lot or control numbers should be destroyed.
- 6.56. Returned labelling should be maintained and stored in a manner to prevent mix-ups and provide proper identification.

Packaging and labelling operations

- 6.57. Standard operating procedures designed to ensure that correct labels, labelling, and packaging materials are used for pharmaceutical products should be established and followed. These procedures should incorporate the following features:
 - a. Designs to prevent mix-ups and cross-contamination by physical or spatial separation from operations involving other pharmaceutical products.
 - b. Identification and handling of filled pharmaceutical product containers that are set aside and held in unlabelled conditions for future labelling operations to preclude mislabelling of individual containers, batches, or portions of batches. Identification need not be applied to each individual container but should be sufficient to determine name, strength, quantity of contents, and batch or control number of each container.
 - c. Identification of the pharmaceutical product with a lot or control number that permits determination of the history of the manufacture and control of the batch.
 - d. Examination of packaging and labelling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.
 - e. Inspection of the packaging and labelling facilities immediately before use to ensure that all pharmaceutical products have been removed from previous operations. Inspection should also be made to ensure that packaging and labelling materials not suitable for subsequent operations have been removed. Results of inspection should be documented in the batch production records.
- 6.58. Marketing authorisation holders for pharmaceutical products should obtain approval from the Agency for changes in packaging and labelling.

Tamper-resistant packaging

- 6.59. A pharmaceutical product that has tamper-resistant packaging should be designed to remain intact when handled in a reasonable manner during manufacture, distribution and retail.
- 6.60. There should be a statement that is prominently placed so that consumers are alerted to the specific tamper-resistant feature of the package
- 6.61. The tamper-resistant labelling should be so placed that it will be unaffected where the tamper-resistant feature of the package is breached or missing.
- 6.62. To reduce the likelihood of successful tampering and to increase the likelihood that consumers will discover where a product has been tampered with, tamper-resistant packaging should not be easily duplicated by the use of commonly available materials or through use of commonly available processes.

Expiration dating

- 6.63. To ensure that a pharmaceutical product meets applicable standards of identity, strength, quality, and purity at the time of use, it should bear an expiration date determined by appropriate stability testing.
- 6.64. Expiration dates should be related to any storage conditions stated on the labelling, as determined by stability studies.
- 6.65. Where the pharmaceutical product is to be reconstituted at the time of dispensing, its labelling should bear expiration information for both the reconstituted and un-reconstituted pharmaceutical products.
- 6.66. Expiration dates should appear on labelling in accordance with the NAFDAC Drug Labelling Regulations.

Pharmaceutical product inspection

- 6.67. Packaged and labelled products should be examined during finishing operations to provide assurance that containers and packages in the batch have the correct label.
- 6.68. A representative sample of units should be collected at the completion of operations and should be visually examined for correct labelling.
- 6.69. Results of these examinations should be recorded in the batch production or control records.

Production record review

- 6.70. All pharmaceutical product manufacture and control records, including those for packaging and labelling, should be reviewed and approved by the quality

CHAPTER

7 MATERIALS MANAGEMENT

Principle

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

General

- 7.2. 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.
- 7.3. All incoming materials and finished products should be quarantined immediately after receipt or processing, until they have been sampled, examined or tested, as appropriate and are released for use or distribution.
- 7.4. All materials and products should be stored under the appropriate conditions established by the manufacturer, and in an orderly fashion, to permit batch segregation and stock rotation by a first-expire, first-out rule (FEFO).
- 7.5. Water used in the manufacture of pharmaceutical products should be suitable for its intended use.
- 7.6. There should be written procedures describing in sufficient detail the receipt, identification/internal labelling, storage, handling, sampling, testing, and approval or rejection of starting materials and packaging materials; such written procedures should be followed.

Suppliers' audits and approval

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

- 7.8. Before suppliers are approved and included in the approved list of suppliers or specifications, they should be evaluated. The approval process should clearly define identity, location address and GMP level of the manufacturer of the material.
- 7.9. The process should define minimum acceptable conditions for approval. Agents and suppliers in the supply chain should be identifiable and their activities should be adequately controlled, so as not to jeopardize the identity, performance or quality of the material.
- 7.10. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier's ability to conform with GMP standards.

Starting materials

- 7.11. The purchase of starting materials is an important operation that should involve staff who have particular and thorough knowledge of the products and suppliers.
- 7.12. Starting materials should be purchased only from approved suppliers and, where possible, directly from the producer against an agreed specification. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is beneficial for all critical aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements as well as complaints and rejection procedures, to be contractually agreed between the manufacturer and the supplier.
- 7.13. Where the supplier of a critical material is not the manufacturer of that material, the name and address of the latter should be known by the finished product manufacturer.
- 7.14. Changes in materials or the source of supply of raw materials should be handled through the formal change control system of the manufacturer to evaluate the effect of the change on the product quality.
- 7.15. There should be written procedures and records for the receipt of each delivery of each starting material.
- 7.16. For each consignment, at a minimum, the containers should be checked at least for integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.
- 7.17. All incoming materials should be checked to ensure that the consignment

- corresponds to the order. Containers should be cleaned where necessary and labelled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.
- 7.18. Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the quality unit and investigated.
 - 7.19. If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release.
 - 7.20. Bagged or boxed materials should not be stored on the floor and should be suitably spaced to permit cleaning and inspection.
 - 7.21. Starting materials in the storage area should be appropriately labelled.
 - 7.22. Labels should bear at least the following information:
 - a. The designated name of the product and the internal code reference where applicable;
 - b. The batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;
 - c. The status of the contents (e.g. in quarantine, on test, released, rejected, returned, recalled);
 - d. An expiry date and a retest date (within the shelf life of the material) where applicable. When fully validated computerized storage systems are used, not all of the above information need be in a legible form on the label.
 - 7.23. There should be written procedures for sampling, which include the person(s) authorised to take samples, the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.
 - 7.24. Representative samples of each shipment of each batch should be collected for testing.
 - 7.25. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The sampling method should be based on appropriate criteria such as:
 - a. Statistical criteria (variability, confidence levels, degree of precision desired)
 - b. Criticality of the material,

- c. Past quality history of the supplier;
 - d. Quantity needed for analysis and retention as described in ***Sampling 8.15 to 8.29.***
- 7.26. Samples should be collected in accordance with the following procedures:
- a. The containers of materials selected should be cleaned where necessary, by appropriate means.
 - b. The containers should be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other materials.
 - c. Sterile equipment and aseptic sampling techniques should be used when necessary.
 - d. Where it is necessary to sample a material from the top, middle, and bottom of its container, such sample subdivisions should not be composited for testing.
 - e. Sample containers should be identified so that the following information can be determined:
 - i. Name of the material sampled
 - ii. The batch number
 - iii. The container from which the sample was taken
 - iv. The date on which the sample was taken
 - v. The name and signature of the person who collected the sample.
 - f. Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.
 - g. Containers from which samples are withdrawn should be opened carefully and subsequently re-closed. They should be marked to indicate that a sample has been taken from them.
- 7.27. Samples should be examined and tested as follows:
- a. Tests should be conducted to verify the identity of each material. Specific identity tests, where they exist, should be used.
 - b. Each material should be tested for conformity with all appropriate written specifications for purity, strength and quality. In lieu of such

- testing by the manufacturer, a report of analysis may be accepted from the supplier of a material, provided that at least one specific identity test is conducted on such material by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.
- c. Containers and closures should be tested for conformance with appropriate standard operating procedures. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.
 - d. When appropriate, materials should be microscopically examined.
 - e. Each batch of material that is liable to contamination with filth, insect infestation, or other extraneous adulterant should be examined against established specifications for such contamination.
 - f. Each batch of material that is liable to microbiological contamination that is objectionable in view of its intended use should be subjected to microbiological tests before use.
 - g. Any batch of material that meets the appropriate written specifications of identity, strength, quality, purity and related tests may be approved and released for use in accordance with written procedures. Any batch of such material that does not meet such specifications should be rejected as specified in written procedures.
- 7.28. Only starting materials released by the quality unit and within their shelf-life should be used.
- 7.29. Materials approved for use should be rotated so that the oldest approved stock is used first. Deviation from this requirement is only permitted where such deviation is temporary and appropriate.
- 7.30. Materials should be retested or re-examined, as appropriate within the shelf-life of the material, for identity, strength, quality, and purity and approved or rejected by quality control as necessary, for example, after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the material.
- 7.31. Starting materials should be dispensed only by designated person(s),

- following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.
- 7.32. Each dispensed material and its weight or volume should be independently checked and the check recorded.
 - 7.33. Materials dispensed for each batch of the final product should be kept together and conspicuously labelled as such.
 - 7.34. 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.
 - 7.35. All handling of materials and products, such as receipt, quarantine, sampling, storage, labelling etc. should be done in accordance with written procedures or instructions and recorded.
 - 7.36. At all times during processing, all materials and bulk containers, should be labelled with the identity of the product or material being processed, its strength (where applicable) and batch number.
 - 7.37. 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, approved, rejected, clean etc.).

Packaging materials

- 7.38. The purchase, handling and control of primary and printed packaging materials should be as for starting materials.
- 7.39. 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.
- 7.40. Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.
- 7.41. Out-dated or obsolete primary packaging material or printed packaging material should be destroyed in line with the Agency's requirements and its disposal recorded.

- 7.42. All packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.
- 7.43. Packaging materials should provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the intermediate, API or finished pharmaceutical product or that may occur during transportation.
- 7.44. These containers should not be reactive, additive, adsorptive or absorptive so as to alter the quality of the intermediate, API or finished pharmaceutical product beyond the specified limits.
- 7.45. Containers should be clean and, where indicated by the nature of the Intermediate, API or finished pharmaceutical product, sanitized, sterilized and processed to remove pyrogenic properties and ensure that they are suitable for their intended use.
- 7.46. Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties should be written and followed for pharmaceutical product containers and closures.
- 7.47. Where containers are re-used during production process, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.
- 7.48. All handling of packaging materials should be done in accordance with written procedures or instructions and recorded.

Intermediate and bulk products

- 7.49. Intermediate and bulk products should be kept under appropriate conditions.
- 7.50. Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

Finished products

- 7.51. 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.
- 7.52. The evaluation of finished products and the documentation necessary for release of a product for sale are described in ***Chapter 8 "Quality Control"***.

- 7.53. Written release and rejection procedures should be available for products, and in particular for the release for sale of the finished product by the Quality unit.
- 7.54. Standard Operating Procedures for the distribution of pharmaceutical products should be established, and followed. They should include:
- A procedure whereby the oldest approved stock of a pharmaceutical product is distributed first. Deviation from this requirement is only permitted where such deviation is temporary, appropriate and documented.
 - A system by which the distribution of each lot of pharmaceutical product can be traceable to facilitate its recall where necessary

Rejected, recovered, reprocessed and reworked materials

- 7.55. Rejected materials should be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.
- 7.56. Where there are rejected materials, the manufacturer should notify the Agency before the materials are either returned to the suppliers or destroyed in a timely manner and in line with the guidelines of the Agency. Whatever action is taken should be approved and recorded by authorised personnel.
- 7.57. Disposal of rejected materials should be conducted in accordance with standard operating procedures and environmental regulations.
- 7.58. The reworking of finished pharmaceutical products is not permitted by the Agency
- 7.59. A pharmaceutical product may be reprocessed provided the subsequent product meets appropriate standards, specifications, and characteristics.
- 7.60. The recovery of all or part of earlier batches, which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorised 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.
- 7.61. The need for additional testing of any finished product that has been reprocessed should be considered by the quality unit.

Recalled products

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

Returned goods

- 7.63. Pharmaceutical products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or re-labelling, or alternative action taken only after they have been critically assessed by QC in accordance with a written procedure. The nature of the pharmaceutical 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.
- 7.64. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse.
- 7.65. Records of returned pharmaceutical products should be maintained and should include the name and labelled potency of the pharmaceutical product dosage form, batch number or control number, reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned pharmaceutical product.
- 7.66. Where the reason for a pharmaceutical product being returned implicates associated batches, an appropriate investigation should be conducted.

Pharmaceutical product salvaging

- 7.67. Pharmaceutical products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, expiry, or radiation due to natural disasters, fires, accidents, or equipment failures should not be salvaged and returned to the market place.
- 7.68. Whenever there is doubt whether pharmaceutical products have been subjected to such conditions, salvaging operations may be conducted only where there is:
- a. Evidence from laboratory tests and assays (including animal feeding studies where applicable) that the pharmaceutical products meet all applicable standards of identity, strength, quality, and purity and;
 - b. Evidence from inspection of the premises that the pharmaceutical products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident.
- 7.69. Organoleptic examinations may be acceptable only as supplemental evidence that the pharmaceutical products meet appropriate standards of identity, strength, quality, and purity.

- 7.70. Records including name, batch number, and disposition should be maintained for salvaged pharmaceutical products

Reagents and culture media

- 7.71. There should be records for the receipt and preparation of reagents and culture media. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.
- 7.72. Reagents made up in the laboratory should be prepared according to written procedures and appropriately labelled. The label should indicate the concentration, standardization factor, the date of preparation, the date when re-standardization is due, shelf-life, and the storage conditions. The label should be signed and dated by the person preparing the reagent.
- 7.73. Both positive and negative controls should be applied to verify the suitability of culture media each time they are prepared and used. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

Reference standards

- 7.74. Whenever official reference standards exist, these should preferably be used.
- 7.75. Official reference standards should be used only for the purpose described in the appropriate monograph.
- 7.76. Reference standards developed by the manufacturer should be tested or validated, released and stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.
- 7.77. Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization. Their traceability to primary standards should be demonstrated and documented.
- 7.78. 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;

Principle

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

General

- 8.3. Each manufacturer of pharmaceutical products 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 available must meet minimum NAFDAC GLP requirements to ensure that all the quality control arrangements are effectively and reliably carried out.
- 8.4. The basic requirements for QC:
 - a. Adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting and testing starting materials, packaging materials and intermediate, bulk and finished products and for monitoring environmental conditions for GMP purposes.
 - b. Access to production areas for sampling and investigation as appropriate.
- 8.5. The responsibilities of QC are as follows:
 - a. Sampling of starting materials, packaging materials, intermediate products, bulk products and finished products by methods and personnel approved by the QC.

- b. Qualification of equipment and validation of test methods.
 - c. Maintaining records (manually and/or by recording instruments) to demonstrate that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated
 - d. Ensuring that finished products contain ingredients that comply with the qualitative and quantitative composition of the product as described in the marketing authorization. They also ensure that the ingredients are of the required purity, in their proper container and correctly labelled
 - e. Maintains records of results of inspection and testing of materials, intermediate, bulk and finished products against specifications.
 - f. Ensures that sufficient samples of starting materials and products are 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.
 - g. Assessment of finished products including the review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures. Product assessment includes all relevant factors such as production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.
 - h. Establish, validate and implement all QC procedures
 - i. Evaluate, maintain, and store the reference standards for substances
 - j. Ensure the correct labelling of containers of materials and products
 - k. Ensure that the stability of the active pharmaceutical ingredients (APIs) and products is monitored
 - l. Participate in the investigation of complaints related to the quality of the product
 - m. Participate in environmental monitoring.
- 8.6. All these operations should be carried out in accordance with written procedures and recorded.

Good practices for pharmaceutical quality control

- 8.7. Space allocated for quality control laboratory and equipment should meet the general and specific requirements for quality control areas as specified in

NAFDAC GLP guidelines which shows the list of essential equipment that must be provided.

- 8.8. The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed in **Chapter 9 “Contract Manufacture and Analysis”**, can be accepted for particular reasons, but this should be stated in the quality control records.
- 8.9. The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, should be drafted by the quality control department and reviewed and approved by the authorized person.
- 8.10. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms should be recorded and justified.
- 8.11. Calibration of instruments, apparatus, gauges, and recording devices should be done at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met.
- 8.12. Instruments, apparatus, gauges, and recording devices not meeting established specifications should not be used.

Documentation

- 8.13. Laboratory documentation should follow the principles given in **Chapter 5 “Documentation”**. The following details should be readily available to QC:
 - a. Specifications;
 - b. Sampling procedures;
 - c. Testing procedures and records (including analytical worksheets and/or laboratory notebooks);
 - d. Analytical reports and/or certificates;
 - e. Data from environmental monitoring, where required;
 - f. Validation records of test methods, where applicable;
 - g. Procedures for and records of the calibration of instruments and maintenance of equipment

- h. Instrument and equipment installation qualification, operational qualification and performance qualification certificates.
 - i. Inventory of all laboratory equipment and reagents.
 - j. Audit certificates of suppliers of laboratory reagents.
- 8.14. Any QC documentation relating to a batch record should be retained for one year after the expiry date of the batch. For some kinds of data (e.g. analytical tests results, yields, environmental controls, etc.) it is recommended that records in a manner permitting trend evaluation be kept. 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

- 8.15. Sample taking should be done in accordance with approved written procedures that describe:
- a. The method of sampling;
 - b. The equipment to be used;
 - c. The amount of the sample to be taken
 - d. Instructions for any required sub-division of the sample;
 - e. The type and condition of the sample container to be used;
 - f. The identification of containers sampled;
 - g. Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
 - h. The storage conditions;
 - i. Instructions for the cleaning and storage of sampling equipment
- 8.16. 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;
 - f. The date of sampling
- 8.17. Retention samples should be representative of the batch of materials or

- products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process)
- 8.18. Retention samples from each batch of finished products should be retained till one year after the expiry date.
- 8.19. Finished products should 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.
- 8.20. Samples of active starting materials should be retained for at least one year beyond the expiry date of the corresponding finished product.
- 8.21. For an active ingredient in a radioactive pharmaceutical product, except for non-radioactive reagent kits, the retention sample should be retained for:
- Three months after the expiration date of the last lot of the pharmaceutical product containing the active ingredient where the expiration dating period of the pharmaceutical product is 30 days or less; or
 - Six months after the expiration date of the last lot of the pharmaceutical product containing the active ingredient where the expiration dating period of the pharmaceutical product is more than 30 days.
- 8.22. For a radioactive pharmaceutical product, except for non-radioactive reagent kits, the retention sample should be retained for:
- Three months after the expiration date of the pharmaceutical product where the expiration dating period of the pharmaceutical product is 30 days or less; or
 - Six months after the expiration date of the pharmaceutical product where the expiration dating period of the pharmaceutical product is more than 30 days.
- 8.23. Retention samples from representative sample lots or batches selected by acceptable statistical procedures should be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the retention sample.
- 8.24. Any evidence of pharmaceutical product deterioration should be investigated. The results of examination should be recorded and maintained with other stability data on the pharmaceutical product.
- 8.25. Retention samples of compressed medical gases need not be kept.

- 8.26. Other starting materials (except solvents, gases and water) should be retained for at least two years after the release of the product if their stability allows. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter.
- 8.27. Retention samples of materials and products should be of a size sufficient to permit at least two full re-examinations.
- 8.28. Out-of-specification (OOS)/out-of-trend (OOT) results obtained during testing of materials or products should be investigated in accordance with an approved procedure. Records should be maintained.
- 8.29. Records of quantity and traceability reference of reagent media and glassware used must be kept.

Test requirements

- 8.30. The accuracy, sensitivity, specificity, and reproducibility of test methods employed should be established, validated and documented. Such validation and documentation may be accomplished as described in **Chapter 4 “Qualification and Validation”**.
- 8.31. All testing operations described in the marketing authorization should be carried out according to the approved methods.
- 8.32. For each batch of pharmaceutical product purporting to be sterile and/or pyrogen-free, there should be appropriate laboratory testing to determine conformance to such requirements. The test procedures should be in writing and should be followed.
- 8.33. For each batch of ophthalmic ointment, there should be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures should be in writing and should be followed.
- 8.34. For each batch of controlled-release dosage form, there should be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures should be in writing and should be followed.

Starting and packaging materials

- 8.35. Before releasing a starting or packaging material for use, the authorized person should ensure that the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters.
- 8.36. An identity test should be conducted on a sample from each container of

starting material.

- 8.37. Each batch (lot) of printed packaging materials must be examined following receipt.
- 8.38. In lieu of full testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results and through on-site audits of the supplier's capabilities.
- 8.39. Certificates of analysis must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain at least the following information:
- a. Identification (name and address) of the issuing supplier;
 - b. Signature of the competent official, and statement of his or her qualifications;
 - c. The name of the material tested;
 - d. The batch number of the material tested;
 - e. The specifications and methods used;
 - f. The test results obtained;
 - g. The date of testing

In-process control

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

Finished products

- 8.41. For each batch of pharmaceutical product, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification, prior to release.
- 8.42. The results obtained should be recorded and checked to make sure that they are consistent with each other. Any calculations should be critically examined.
- 8.43. Where sterility and/or pyrogen testing are conducted on specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.
- 8.44. There should be appropriate laboratory testing, as necessary, of each batch

of pharmaceutical product required to be free of objectionable microorganisms.

- 8.45. Products failing to meet the established specifications or any other relevant quality criteria should be rejected.
- 8.46. The tests performed should be recorded and the records should include at least the following data:
- a. Name of the material or product and, where applicable, dosage form;
 - b. Batch number and, where appropriate, name of 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 certificates of analysis;
 - e. Dates of testing;
 - f. Initials of the persons who performed the testing
 - g. 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
- 8.47. All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by quality control and the results recorded.
- 8.48. Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media. They should be prepared in accordance with written procedures.
- 8.49. Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardization and the last current factor should be indicated.
- 8.50. Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

- 8.51. Animals used for testing materials or products, should be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.
- 8.52. Where a reasonable possibility exists that a non-beta-lactam pharmaceutical product has been exposed to cross-contamination with beta-lactam, the non-beta-lactam pharmaceutical product should be tested for the presence of beta-lactam. Such pharmaceutical product should not be marketed where detectable levels are found when tested by appropriate methods.

Batch record review

- 8.53. QC records should be reviewed as part of the approval process of batch release before transfer to the authorized person. 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.
- 8.54. Retention samples from each batch of finished product should be kept for at least one year after the expiry date.

Stability studies

- 8.55. After marketing, the stability of the pharmaceutical 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.
- 8.56. 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 labelled storage conditions.
- 8.57. This mainly applies to the pharmaceutical 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

- 8.58. QC should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.
- 8.59. QC should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.
- 8.60. A written programme for on-going stability determination should be developed and implemented to include elements such as:
- A complete description of the pharmaceutical product involved in the study;
 - The complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
 - Provision for the inclusion of a sufficient number of batches;
 - Testing of the pharmaceutical product in the same container-closure system as that in which the product is marketed
 - The testing schedule for each pharmaceutical product;
 - Provision for special storage conditions;
 - Provision for adequate sample retention;
 - A summary of all the data generated, including the evaluation and the conclusions of the study.
- 8.61. Stability should be determined prior to marketing and following any significant changes, for example, in processes, equipment or packaging materials.
- 8.62. Accelerated studies, combined with basic stability information on the materials, pharmaceutical products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted.
- 8.63. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including pharmaceutical product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.
- 8.64. For homeopathic pharmaceutical products, there should be a written

- assessment of stability based at least on testing or examination of the pharmaceutical product for compatibility of the ingredients, and based on marketing experience with the pharmaceutical product to indicate that there is no degradation of the product for the normal or expected period of use.
- 8.65. Evaluation of stability should be based on the same container-closure system in which the pharmaceutical product is being marketed.
- 8.66. The on-going stability programme should be described in a written protocol and results formalised as a report. The equipment used for the on-going stability programme (stability chambers among others) should be qualified and maintained.
- 8.67. The protocol for an on-going stability programme should extend to the end of the shelf life period and should include, but not be limited to, the following parameters:
- a. Number of batch(es) per strength and different batch sizes, if applicable
 - b. Relevant physical, chemical, microbiological and biological test methods
 - c. Acceptance criteria
 - d. Reference to test methods
 - e. Description of the container-closure system(s)
 - f. Testing intervals (time points)
 - g. Description of the conditions of storage
 - h. Other applicable parameters specific to the pharmaceutical product.
- 8.68. The protocol for the on-going stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorisation dossier provided that this is justified and documented in the protocol.
- 8.69. 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,

9 CONTRACT MANUFACTURE AND ANALYSIS

Principle

- 9.1. Contract manufacture, analysis, and any other activity covered by GMP must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or work or analysis of unsatisfactory quality.

General

- 9.2. There should be a written agreement covering the manufacture and/or analysis arranged under the contract and any technical arrangements made in connection with it.
- 9.3. All arrangements for contract manufacture and analysis including technology transfer and any proposed changes in technical or other arrangements should be in accordance with the marketing authorisation for the product concerned.
- 9.4. The contract should permit the contract giver to audit the facilities and activities of the contract acceptor or mutually agreed subcontractors.
- 9.5. In the case of contract analysis, the final approval for release must be given by the authorized person in accordance with GMP and the marketing authorization as specified in the contract.

The Responsibilities of the Contract Giver

- any hazards associated with the product, work or tests which might pose a hazard to his premises, equipment, personnel, other materials or other products.
- 9.9. The contract giver should review and assess the records and results related to the outsourced activities. The contract giver should ensure that all products and materials delivered by the contract acceptor have been processed in accordance with GMP and the marketing authorization; comply with their specifications and that the product has been released by the authorized person in accordance with GMP and the marketing authorization.
- 9.10. The contract giver should monitor and review the performance of the contract acceptor including the implementation of any needed improvements and their effectiveness.
- 9.11. The contract giver is responsible for ensuring that the contract acceptor understands that his or her activities may be subject to inspection by the Agency.

The Responsibilities of the Contract Acceptor

- 9.12. The contract acceptor should have adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily, the work ordered by the contract giver. Contract manufacture may be undertaken only by a manufacturer who is authorised by the Agency.
- 9.13. The contract acceptor should ensure that all products or materials delivered to him are suitable for their intended purpose.
- 9.14. The contract acceptor must not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract acceptor and any third party should ensure that information and knowledge including that from assessment of the suitability of the third party, are made available in the same way as between the original contract giver and contract acceptor.
- 9.15. The contract acceptor should refrain from any activity (including unauthorized changes outside the terms of the contract) which may adversely affect the quality of the product manufactured and/or analysed for the contract giver.

The Contract

- 9.16. There must be a written contract between the contract giver and the contract acceptor which clearly establishes the responsibilities of each party, covering the outsourced activities, the products or operations to which they are

- related, communication processes relating to the outsourced activities and any technical arrangements made in connection with it.
- 9.17. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and good manufacturing practice.
- 9.18. All arrangements for manufacture and analysis must be in accordance with the marketing authorisation and agreed by both parties.
- 9.19. The contract should clearly describe who is responsible for contracted activities, e.g. knowledge management, technology transfer, supply chain, subcontracting, testing and releasing materials and undertaking production and QC, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the contract acceptor should take samples at the premises of the manufacturer.
- 9.20. Manufacturing, analytical and distribution records, and retention 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.
- 9.21. The contract agreement must state that the contract giver and the Agency have the right to visit the facilities of the contract acceptor.
- 9.22. In case of contract analysis, the contract acceptor should understand that he is subject to inspection by the Agency.
- 9.23. 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 procedure to be followed if the contract analysis shows that the tested products must be rejected.

10 COMPLAINTS AND PRODUCT RECALL

Principle

- 10.1. All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken. 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

- 10.2. A person responsible for handling the complaints and deciding the measures to be taken should be designated, together with sufficient supporting personnel 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.
- 10.3. There should be written procedures describing the action(s) to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.
- 10.4. Special attention should be given to establishing that the product that gave rise to a complaint was defective or caused by counterfeiting.
- 10.5. Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated.
- 10.6. The person responsible for quality control should normally be involved in the investigation of such problems. The use of interdisciplinary teams should be considered including appropriately trained quality management personnel.
- 10.7. If a 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.
- 10.8. Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.
- 10.9. All the decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

- 10.10. Complaints' records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.
- 10.11. The Agency should be informed if a manufacturer is considering action following possible faulty manufacture, product deterioration, detection of counterfeiting or any other serious quality problems with a product.
- 10.12. Written records involving a pharmaceutical product should be maintained until at least 1 year after the expiration date of the pharmaceutical product, or 1 year after the date that the complaint was received, whichever is longer.

Recalls

- 10.13. There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.
- 10.14. A person should be designated as responsible for execution and co-ordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organisation. If this person is not the authorised person, the latter should be made aware of any recall operation.
- 10.15. There should be established written procedures, regularly checked and updated when necessary, in order to organise any recall activity.
- 10.16. Recall operations should be capable of being initiated promptly and at any time down to the required level in the distribution chain.
- 10.17. The Agency should be informed promptly if products are intended to be recalled because they are, or are suspected of being defective.
- 10.18. The distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with location and e-mail addresses, phone numbers inside and outside working hours, batches and amounts delivered), including those for exported products, samples for clinical trials and medical samples to permit an effective recall.
- 10.19. Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.
- 10.20. 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.

10.21. The effectiveness of the arrangements for recalls should be evaluated regularly (mock recall).

11 SELF-INSPECTION

Principle

- 11.1. 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.
- 11.2. Self-inspections should be performed routinely, and in addition, may be performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the Agency is announced.
- 11.3. Self-inspections should be conducted in an independent and detailed way by designated, competent persons from the company. Independent audits by external experts may also be useful.
- 11.4. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively.
- 11.5. All recommendations for corrective action(s) should be implemented.
- 11.6. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

Items for self-inspection

- 11.7. 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.
- p. Distribution of the pharmaceutical products

Self-inspection team

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

Frequency of self-inspection

11.9. 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

11.10. A report should be made at the completion of a self-inspection.

11.11. The report should include:

- a. Self-inspection results;
- b. Evaluation and conclusions; and
- c. Recommended corrective actions.

Follow-up action

11.12. 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

11.13. 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 should also be extended to suppliers and contractors (*see Chapter 9 "Contract Manufacture and Analysis"*).

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FURTHER READING

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GLOSSARY

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

Act	The NAFDAC Act, Cap N1, LFN 2004
Active pharmaceutical ingredients (API)	Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical product and which when used in the production of a pharmaceutical product, becomes an active ingredient of the product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.
Agency	National Agency for Food and Drug Administration and Control
Airlock	An enclosed space with two or more doors which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when either people, goods or equipment need to enter or leave them.
Authorized person	The person recognised by the Agency as having the necessary basic scientific and technical background and experience; and who is responsible for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with regulatory requirements.
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 is expected to be homogeneous. 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. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.
Batch (or lot) number	Any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packaging, holding, and distribution of a batch or lot of pharmaceutical product or other material can be determined.
Bulk product	Any product which 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.
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.
Commissioning	The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements as specified in the user requirement specification and capacities as specified by the designer or developer. It is carried out before qualification and validation.
Computerised system	A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.
Consignment (or delivery)	The quantity of a pharmaceutical or pharmaceuticals, 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.
Contamination	The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.
Contract	A written agreement between two or more parties which is enforceable by law.
Cross contamination	Contamination of a starting material, intermediate product or finished product with another starting material or product during production.
Finished product	A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling.
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.
In-process	Any material fabricated, compounded, blended, or derived by chemical

material	reaction that is produced for, and used in, the preparation of the pharmaceutical product.
Intermediate product	Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.
Manufacture	All operations of purchase of materials and products, production, quality control, release, storage and distribution of pharmaceutical products, and the related controls.
Manufacturer	A company that carries out operations such as production, packaging, repackaging, labelling and re-labelling of pharmaceuticals.
Marketing authorization	A legal document issued by a 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, labelling and shelf-life. This is also called product licence or registration certificate
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.
Materials	A general term used to denote components, raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs, product containers, closures, packaging and labelling materials and in-process materials.
Pharmaceutical product	Any substance or combination of substances which may be administered to human beings or animals with a view to preventing diseases, making a medical diagnosis or restoring, correcting or modifying physiological functions in human beings or in animals. Pharmaceutical products may also be referred to as medicinal products or drugs as defined under the NAFDAC Act.
Packaging	All operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product. Note: Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging

Packaging material	Any 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.
Production	All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging, to its completion as a finished product.
Qualification	Action of proving that any premises, systems and items of equipment work correctly and actually leads to the expected results. The word <i>validation</i> is sometimes widened to incorporate the concept of qualification.
Quality assurance (QA)	The sum total of the organised arrangements made with the object of ensuring that all pharmaceutical products are of the quality required for their use and that quality systems are maintained.
Quality control (QC)	Quality control is the part of GMP that is concerned with sampling, specifications, testing, documentation, and release procedures which ensures that materials are not released for use, and that pharmaceutical products are not released for sale or supply, until their quality has been deemed satisfactory.
Quality unit	An organizational unit independent of production which fulfils both quality assurance and quality control responsibilities. This can be in the form of 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, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal.
Regulatory action	Includes but not limited to product hold, recall, forfeiture, or destruction, sealing of manufacturing line or facility, withdrawal of GMP certificate or product license/registration certificate, prosecution
Representative sample	A sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to ensure that the sample accurately portrays the material being sampled.
Reconciliation	A comparison between the theoretical quantity and the actual quantity.

Recovery	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. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.
Reprocessing	Subjecting all or part of a batch or lot of an in-process product, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch or lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological products and, in such cases, are validated and pre-approved as part of the marketing authorization.
Radiopharmaceutical	Any pharmaceutical product which when ready for use contains one or more radionuclides (radioactive isotopes) included for medicinal purpose.
Retention sample	Retained sample of each batch of starting materials and finished pharmaceutical product and that is representative of the batch.
Signed (signature)	The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.
Specifications	A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.
Standard operating procedures (SOP)	An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (example 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.
Strength	The concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or The potency, that is, the therapeutic activity of the pharmaceutical product as indicated by appropriate laboratory tests or by adequately

	developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).
System	A regulated pattern of interacting activities and techniques which are united to form an organised whole.
Theoretical yield	The quantity that would be produced at any appropriate phase of manufacture, processing, or packaging of a particular pharmaceutical product, based upon the quantity of materials to be used, in the absence of any loss or error in actual production.
Validation	A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined criteria.