



Safe Drugs Save Lives

**GUIDELINES ON GOOD MANUFACTURING
PRACTICE FOR MEDICINAL PRODUCTS
PART 1**

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INTRODUCTION

The Mandate

National Drug Authority (NDA) was established in 1993 by the National Drug Policy and Authority Statute which in 2000 became the National Drug Policy and Authority (NDP/A) Act, Cap. 206 of the Laws of Uganda (2000 Edition). The Act established a National Drug Policy and National Drug Authority to ensure the availability, at all times, of essential, efficacious and cost-effective drugs to the entire population of Uganda, as a means of providing satisfactory healthcare and safeguarding the appropriate use of drugs.

The Vision

“A Uganda with safe, effective and quality medicines and healthcare products ”.

The Mission

“Promoting and protecting public health through the effective regulation of human and animal medicines and healthcare products. ”.

The Core Values

- We *care* for the people of Uganda striving for excellence in service to our clients underpinned by professionalism and fairness.
- We take *pride* in what we do, motivated and passionate about achieving the highest standards of service.
- We serve with *integrity* and are honest, transparent and accountable at all times.
- We continuously nurture *team spirit* respecting and supporting each other, working together to achieve our common objectives.
- We take advantage of new opportunities for *learning* and use our knowledge and skills to innovate, creating value for our clients and the public.

Objective of these guidelines

These guidelines (and the Annexes) are intended to provide guidance to the pharmaceutical manufacturer on how to comply with GMP.

These guidelines shall form the basis of GMP inspection by NDA as one of the requirements for registration of pharmaceutical products in Uganda.

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Policy

The National Drug Policy and Authority Act, Sections 2(d) and 5(e) mandate NDA to exercise control on manufacture, production and on the quality of drugs. One of the means of achieving this is through compliance with Good Manufacturing Practice (GMP) requirements as laid down in these guidelines.

These guidelines are developed in accordance with the Statutory Instruments No. 35; The National Drug Policy and Authority (Licensing) Regulations, 2014:

Section 19(1): *"The Authority shall, for the purposes of assessing the manufacturing practices of the manufacturer, adopt with the necessary modifications, internationally accepted Good Manufacturing Practice Guidelines";* and

Section 19(2): *"A manufacturer who manufactures drugs in Uganda or outside Uganda for importation into Uganda shall comply with the Good Manufacturing Practice Guidelines adopted by the Authority".*

Scope

These guidelines (and the Annexes) shall be used for periodic GMP inspection of all manufacturers of medicinal products within and outside Uganda whose products are registered or subjected to registration in Uganda; irrespective of their size, type of products, product range or location of the manufacturing facilities. Manufacturers that are GMP compliant shall be issued with GMP compliance certificates.

These guidelines do not apply to hospital pharmaceutical production units.

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INTERPRETATION

Action limit: Established criteria, requiring immediate follow-up and corrective action if exceeded.

Active pharmaceutical ingredient (API) or Drug substance: Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug 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.

API Starting Material: A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

Air lock: An enclosed space with two or more doors, and 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 they need to be entered. An air-lock is designed for and used by either people or goods.

Alert limit: Established criteria giving early warning of potential drift from normal conditions which are not necessarily grounds for definitive corrective action but which require follow-up investigation.

Authorized person: Person recognised by the authority as having the necessary basic scientific and technical background and experience. Authorized person(s) is responsible for the release of batches of finished product for sale or distribution. The batch documentation of a batch of a finished product must be signed by an authorized person from the production department and the batch test results by an authorized person from the quality control department for batch release.

Batch (or lot): A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

Note: To complete certain stages of manufacture, it may 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 continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity. For the control of the finished product, a batch of a medicinal products comprises all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilisation operation or, in the case of a continuous production process, all the units manufactured in a given period of time.

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

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batch numbering.

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

Biogenerator: A contained system, such as a fermenter, into which biological agents are introduced along with other materials so as to effect their multiplication or their production of other substances by reaction with the other materials. Biogenerators are generally fitted with devices for regulation, control, connection, material addition and material withdrawal.

Biological agents: Microorganisms, including genetically engineered microorganisms, cell cultures and endoparasites, whether pathogenic or not.

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

Calibration: The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

Cell bank system: A cell bank system is a system whereby successive batches of a product are manufactured by culture in cells derived from the same master cell bank (fully characterised for identity and absence of contamination). A number of containers from the master cell bank are used to prepare a working cell bank. The cell bank system is validated for a passage level or number of population doublings beyond that achieved during routine production.

Cell culture: The result from the in-vitro growth of cells isolated from multicellular organisms.

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

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

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

Note: The different degrees of environmental control are defined in the Supplementary Guidelines for the Manufacture of sterile medicinal products.

Clean/contained area: An area constructed and operated in such a manner that will achieve the aims of both a clean area and a contained area at the same time.

Computerised system: A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic

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control.

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

Contained area: An area constructed and operated in such a manner (and equipped with appropriate air handling and filtration) so as to prevent contamination of the external environment by biological agents from within the area.

Containment: The action of confining a biological agent or other entity within a defined space.

Controlled area: An area constructed and operated in such a manner that some attempt is made to control the introduction of potential contamination (an air supply approximating to grade D may be appropriate), and the consequences of accidental release of living organisms. The level of control exercised should reflect the nature of the organism employed in the process. At a minimum, the area should be maintained at a pressure negative to the immediate external environment and allow for the efficient removal of small quantities of airborne contaminants.

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

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

Crude plant (vegetable drug): Fresh or dried medicinal plant or parts thereof.

Cryogenic vessel: A container designed to contain liquefied gas at extremely low temperature.

Cylinder: A container designed to contain gas at a high pressure.

Exotic organism: A biological agent where either the corresponding disease does not exist in a given country or geographical area, or where the disease is the subject of prophylactic measures or an eradication programme undertaken in the given country or geographical area.

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

Herbal medicinal products: Medicinal products containing, as active ingredients, exclusively plant material and/or vegetable drug preparations.

Infected: Contaminated with extraneous biological agents and therefore capable of spreading infection.

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.

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

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

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

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

Liquifiable gases: Those which, at the normal filling temperature and pressure, remain as a liquid in the cylinder.

Manifold: Equipment or apparatus designed to enable one or more gas containers to be filled simultaneously from the same source.

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

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

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

Marketing authorization (product licence, registration certificate): A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling and shelf-life.

Master cell bank: A culture of (fully characterised) cells distributed into containers in a single operation, processed together in such a manner as to ensure uniformity and stored in such a manner as to ensure stability. A master cell bank is usually stored at -70°C or lower.

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

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

Master seed lot: A culture of a micro-organism distributed from a single bulk into containers in a single operation in such a manner as to ensure uniformity, to prevent contamination and to ensure stability. A master seed lot in liquid form

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is usually stored at or below -70°C . A freeze-dried master seed lot is stored at a temperature known to ensure stability.

Media fill: Method of evaluating an aseptic process using a microbial growth medium. (Media fills are synonymous to simulated product fills, broth trials, broth fills etc.).

Medicinal plant: Plant the whole or part of which is used for pharmaceutical purpose.

Medicinal products: Any medicine or similar product intended for human use, which is subject to control under health legislation in the manufacturing or importing State.

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

Packaging material: Any material employed in the packaging of a medicinal products, 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.

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

Packaging: All operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product.

Note: Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not finally packaged, primary containers.

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

Primary containment: A system of containment which prevents the escape of a biological agent into the immediate working environment. It involves the use of closed containers or safety biological cabinets along with secure operating procedures.

Procedures: Description of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of a medicinal products.

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

Qualification: Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to

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incorporate the concept of qualification.

Quality assurance: Part of quality management focused on providing confidence that quality requirements will be fulfilled.

Quality control: Part of quality management focused on fulfilling quality requirements

Quality Unit(s): An organizational unit independent of production which fulfils both quality assurance (QA) and quality control (QC) 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.

Radiopharmaceutical: Any medicinal products which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a pharmaceutical purpose.

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

Record: A document stating results achieved or providing evidence of activities performed.

Recovery: The introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.

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

Return: Sending back to the manufacturer or distributor of a medicinal products which may or may not present a quality defect.

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

Secondary containment: A system of containment which prevents the escape of a biological agent into the external environment or into other working areas. It involves the use of rooms with specially designed air handling, the existence of airlocks and/or sterilises for the exit of materials and secure operating procedures. In many cases it may add to the effectiveness of primary containment.

Seed lot: Seed lot system: A seed lot system is a system according to which successive batches of a product are derived from the same master seed lot at a given passage level. For routine production, a working seed lot is prepared from the master seed lot. The final product is derived from the working seed lot and has not undergone more passages from the master seed lot than the vaccine shown in clinical studies to be satisfactory with respect to safety and efficacy. The origin and the passage history of the master seed lot and the working seed lot are recorded.

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

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

Starting material: Any substance used in the production of a medicinal products, but excluding packaging materials.

Sterility: Sterility is the absence of living organisms. The conditions of the sterility tests are given in the European (or other relevant) Pharmacopoeia.

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

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

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

Validation: Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

Working cell bank: A culture of cells derived from the master cell bank and intended for use in the preparation of production cell cultures. The working cell bank is usually stored at -70°C or lower.

Working seed lot: A culture of a micro-organism derived from the master seed lot and intended for use in production. Working seed lots are distributed into containers and stored as described above for master seed lots.

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CHAPTER 1: PHARMACEUTICAL QUALITY SYSTEM

PRINCIPLE

The holder of a Manufacturing Authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation or Clinical Trial Authorisation, as appropriate, and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by its distributors. To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented Pharmaceutical Quality System incorporating Good Manufacturing Practice and Quality Risk Management. It should be fully documented and its effectiveness monitored. All parts of the Pharmaceutical Quality System should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. There are additional legal responsibilities for the holder of the Manufacturing Authorisation and for the Authorised Person(s).

The basic concepts of Quality Management, Good Manufacturing Practice (GMP) and Quality Risk Management are inter-related. They are described here in order to emphasise their relationships and their fundamental importance to the production and control of medicinal products.

PHARMACEUTICAL QUALITY SYSTEM¹

- 1.1 Quality Management is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Management therefore incorporates Good Manufacturing Practice.
- 1.2 GMP applies to the lifecycle stages from the manufacture of investigational medicinal products, technology transfer, commercial manufacturing through to product discontinuation. However the Pharmaceutical Quality System can extend to the pharmaceutical development lifecycle stage as described in ICH Q10, which while optional, should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

¹ National requirements require manufacturers to establish and implement an effective pharmaceutical quality assurance system. The term Pharmaceutical Quality System is used in this chapter in the interests of consistency with ICH Q10 terminology. For the purposes of this chapter these terms can be considered interchangeable.

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- 1.3 The size and complexity of the company's activities should be taken into consideration when developing a new Pharmaceutical Quality System or modifying an existing one. The design of the system should incorporate appropriate risk management principles including the use of appropriate tools. While some aspects of the system can be company-wide and others site-specific, the effectiveness of the system is normally demonstrated at the site level.
- 1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that:
- a) Product realisation is achieved by designing, 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) Medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice;
 - d) Production and control operations are clearly specified and Good Manufacturing Practice adopted;
 - e) Managerial responsibilities are clearly specified;
 - 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 from the approved supply chain;
 - g) Processes are in place to assure the management of outsourced activities;
 - h) A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality;
 - i) The results of product and processes monitoring are 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 the future;
 - j) All necessary controls on intermediate products, and any other in-process controls and validations are carried out;
 - k) Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge;
 - l) Arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required;

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- m) After implementation of any change, an evaluation is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality;
- n) An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems.

This can be determined using Quality Risk Management principles. In cases where the true root cause(s) of the issue cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those. Where human error is suspected or identified as the cause, this should be justified having taken care to ensure that process, procedural or system based errors or problems have not been overlooked, if present. Appropriate corrective actions and/or preventive actions (CAPAs) should be identified and taken in response to investigations. The effectiveness of such actions should be monitored and assessed, in line with Quality Risk Management principles;

- o) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products;
 - p) Satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;
 - q) There is a process for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Pharmaceutical Quality System.
- 1.5 Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the Pharmaceutical Quality System is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organisation to the Pharmaceutical Quality System.
- 1.6 There should be periodic management review, with the involvement of senior management, of the operation of the Pharmaceutical Quality System to identify opportunities for continual improvement of products, processes and the system itself.
- 1.7 The Pharmaceutical Quality System should be defined and documented. A Quality Manual or equivalent documentation should be established and should contain a description of the quality management system including

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management responsibilities.

GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS

1.8 Good Manufacturing Practice is that part of Quality Management which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation, Clinical Trial Authorisation or product specification. Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

- a) All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality 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) Correct materials, containers and labels;
 - (v) Approved procedures and instructions, in accordance with Quality System;
 - (vi) Suitable storage and transport.
- d) Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
- e) Procedures are carried out correctly and operators are trained to do so;
- f) 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;
- g) Any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented;
- h) Records of manufacture including distribution which enable the

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complete history of a batch to be traced are retained in a comprehensible and accessible form;

- i) The distribution of the products minimises any risk to their quality and takes account of good distribution practice;
- j) A system is available to recall any batch of product, from sale or supply; and
- k) Complaints about products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence.

QUALITY CONTROL

1.9 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 judged to be satisfactory. The basic requirements of Quality Control are that:

- a) Adequate facilities, trained personnel and approved procedures are available for sampling and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
- b) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by approved personnel and methods;
- 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 or Clinical Trial 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;

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- 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 reference samples of starting materials and products are retained in accordance with Annex 19 to permit future examination of the product if necessary and that the sample is retained in the final pack.

PRODUCT QUALITY REVIEW

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

- a) 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 taken;
- e) A review of all changes carried out to the processes or analytical methods; (vi) A review of Marketing Authorisation variations submitted, granted or refused, including those for third country (export only) dossiers;
- f) A review of the results of the stability monitoring programme and any adverse trends;
- g) A review of all quality-related returns, complaints and recalls and the investigations performed at the time;
- h) A review of adequacy of any other previous product process or equipment corrective actions;
- i) For new Marketing Authorisations and variations to Marketing Authorisations, a review of post-marketing commitments;
- j) The qualification status of relevant equipment and utilities, e.g.

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HVAC, water, compressed gases, etc;

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

1.11 The manufacturer and, where different, Marketing Authorisation holder should evaluate the results of the review and an assessment made as to whether corrective and preventive action or any revalidation should be undertaken, under the Pharmaceutical Quality System. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified.

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

QUALITY RISK MANAGEMENT

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

1.13 The principles of Quality Risk Management are 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;
- b) The level of effort, formality and documentation of the Quality Risk Management process is commensurate with the level of risk.

Examples of the processes and applications of Quality Risk Management can be found inter alia in Annex 20 or ICHQ9.

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CHAPTER 2: PERSONNEL

PRINCIPLE

The correct manufacture of medicinal products relies upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

GENERAL

- 2.1 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. Senior management should determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the Pharmaceutical Quality System and continually improve its effectiveness. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.
- 2.2 The manufacturer must have an organisation chart in which the relationships between the heads of Production, Quality Control and where applicable Head of Quality Assurance or Quality Unit referred to in point 2.5 and the position of the Authorised Person(s) are clearly shown in the managerial hierarchy.
- 2.3 People 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 a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice.
- 2.4 Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place to achieve the *quality objectives*, and, that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality and should ensure continuing suitability and effectiveness of the Pharmaceutical Quality System and GMP compliance through participation in management review.

KEY PERSONNEL

- 2.5 Senior Management should appoint Key Management Personnel including

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the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the release of products the Authorised Person(s) designated for the purpose. Normally, key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other. In large organisations, it may be necessary to delegate some of the functions listed in 2.7, 2.8 and 2.9. Additionally, depending on the size and organisational structure of the company, a separate Head of Quality Assurance or Head of the Quality Unit may be appointed. Where such a function exists usually some of the responsibilities described in 2.7, 2.8 and 2.9 are shared with the Head of Quality Control and Head of Production and senior management should therefore take care that roles, responsibilities, and authorities are defined.

2.6 The duties of the Authorised Person(s) are described in the national requirements and can be summarised as follows:

- a) An Authorised Person must ensure that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that country and in accordance with the requirements of the Marketing Authorisation;
- b) The Authorised Person(s) must meet the qualification requirements laid down in the national legislation, they shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorisation to carry out their responsibilities;
- c) The responsibilities of an Authorised Person may be delegated, but only to other Authorised Person(s).

2.7 The head of Production generally has the following responsibilities:

- a) To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
- b) To approve the instructions relating to production operations and to ensure their strict implementation;
- c) To ensure that the production records are evaluated and signed by an authorised person;
- d) To ensure the qualification and maintenance of his department, premises and equipment;
- e) To ensure that the appropriate validations are done;
- f) To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

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2.8 The head of Quality Control generally has the following responsibilities:

- a) To approve or reject, as he/she sees fit, starting materials, packaging materials, intermediate, bulk and finished products;
- b) To ensure that all necessary testing is carried out and the associated records evaluated;
- c) To approve specifications, sampling instructions, test methods and other Quality Control procedures;
- d) To approve and monitor any contract analysts;
- e) To ensure the qualification and maintenance of his/her department, premises and equipment;
- f) To ensure that the appropriate validations are done;
- g) To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

Other duties of Quality Control are summarised in Chapter 6.

2.9 The heads of Production, Quality Control and where relevant, Head of Quality Assurance or Head of Quality Unit, generally have some shared, or jointly exercised, responsibilities relating to quality including in particular the design, effective implementation, monitoring and maintenance of the Pharmaceutical Quality System. These may include, subject to any national regulations:

- a) The authorisation of written procedures and other documents, including amendments;
- b) The monitoring and control of the manufacturing environment;
- c) Plant hygiene
- d) Process validation;
- e) Training;
- f) The approval and monitoring of suppliers of materials;
- g) The approval and monitoring of contract manufacturers and providers of other GMP related outsourced activities;
- h) The designation and monitoring of storage conditions for materials and products;
- i) The retention of records;
- j) The monitoring of compliance with the requirements of Good Manufacturing Practice;
- k) The inspection, investigation, and taking of samples, in order to

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monitor factors which may affect product quality;

- l) Participation in management reviews of process performance, product quality and of the Pharmaceutical Quality System and advocating continual improvement;
- m) Ensuring that a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management.

TRAINING

Personnel should be qualified to carry out operations assigned to them in accordance with the nature of, and potential risk of their operational activities. Appropriate qualifications for each position should be adequately defined for each position to help ensure that individuals are assigned appropriate responsibilities. Personnel should be selected based on their scientific and technical understanding, product knowledge, process knowledge and/or risk assessment abilities to appropriately execute certain quality functions.

- 2.10 The manufacturer should provide training for all the personnel whose duties take them into production and storage areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.
- 2.11 Besides the basic training on the theory and practice of the Pharmaceutical Quality System and Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training that is critical to ensure personnel remain proficient in their operational functions and in their understanding of GMP, and its practical effectiveness should be periodically assessed. Training programmes should be available that include; evaluation of the training needs, provision of training to satisfy these needs, evaluation of effectiveness of training and documentation of training and/or retraining. The training program should be approved by either the head of Production or the head of Quality Control, as appropriate and training records should be kept.
- 2.12 Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitising materials are handled, should be given specific training.
- 2.13 Visitors or untrained personnel should, preferably, not be taken into the production and quality control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.
- 2.14 The Pharmaceutical Quality System and all the measures capable of improving its understanding and implementation should be fully discussed

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during the training sessions.

PERSONNEL HYGIENE

- 2.15 Detailed hygiene programmes should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take him into the production and control areas. Hygiene programmes should be promoted by management and widely discussed during training sessions.
- 2.16 All personnel should receive medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.
- 2.17 Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of medicinal products.
- 2.18 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.
- 2.19 Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected should be forbidden.
- 2.20 Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.
- 2.21 Personnel should be instructed to use the hand-washing facilities before access in the production areas. Signs to this effect should be posted and instructions observed. Personal hygiene procedures including the use of protective clothing should apply to all persons entering production areas whether they are temporary or full time employees or non employees for example contractor's employees, visitors, senior managers and inspectors.
- 2.22 Any specific requirements for the manufacture of special groups of products, for example sterile preparations, are covered in the annexes.

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CONSULTANTS

2.23 Consultants should have adequate education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

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CHAPTER 3: PREMISES AND EQUIPMENT

PRINCIPLE

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

PREMISES

General

- 3.1. Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.
- 3.2. Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.
- 3.3. Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.
- 3.4. Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.
- 3.5. Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

Production Area

- 3.6. In order to minimise the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitising materials (e.g. penicillins) or biological preparations (e.g. from live micro-organisms). The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions

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are taken and the necessary

validations are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

- 3.7. Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
- 3.8. The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.
- 3.9. Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.
- 3.10. Pipe work, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.
- 3.11. Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.
- 3.12. Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.
- 3.13. Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.
- 3.14. In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross-contamination and facilitate cleaning.
- 3.15. Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.
- 3.16. Production areas should be well lit, particularly where visual on-line controls are carried out.

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

Storage Areas

- 3.18. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.
- 3.19. Storage areas should be designed or adapted to ensure good storage conditions.
In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.
- 3.20. Receiving and dispatch bays should protect materials and products from the weather. Receptions areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.
- 3.21. Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.
- 3.22. There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.
- 3.23. Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.
- 3.24. Highly active materials or products should be stored in safe and secure areas.
- 3.25. Printed packaging materials are considered critical to the conformity of the medicinal products and special attention should be paid to the safe and secure storage of these materials.

Quality Control Areas

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

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- 3.27. Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.
- 3.28. Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.
- 3.29. Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

Ancillary Areas

- 3.30. Rest and refreshment rooms should be separate from other areas.
- 3.31. Facilities for changing clothes, and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.
- 3.32. Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.
- 3.33. Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

EQUIPMENT

- 3.34. Manufacturing equipment should be designed, located, qualified and maintained to suit its intended purpose.
- 3.35. Repair and maintenance operations should not present any hazard to the quality of the products.
- 3.36. Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.
- 3.37. Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.
- 3.38. Equipment should be installed in such a way as to prevent any risk of error or of contamination.
- 3.39. Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.
- 3.40. Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.

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- 3.41. Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.
- 3.42. Fixed pipe work should be clearly labelled to indicate the contents and, where applicable, the direction of flow.
- 3.43. Distilled, deionized and, where appropriate, other water pipes should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.
- 3.44. Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

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CHAPTER 4: DOCUMENTATION

PRINCIPLE

Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements. The various types of documents and media used should be fully defined in the manufacturer's Quality Management System. 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 medicinal products. The Quality Management 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.

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.

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.

REQUIRED GMP DOCUMENTATION (BY TYPE)

Site Master File: A document describing the GMP related activities of the manufacturer.

Instructions (directions, or requirements) type:

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

Manufacturing Formulae, Processing, Packaging and Testing Instructions: Provide detail all the starting materials, equipment and computerised 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.

Procedures: (Otherwise known as Standard Operating Procedures, or SOPs), give directions for performing certain operations.

Protocols: Give instructions for performing and recording certain discreet operations.

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Technical Agreements: Are agreed between contract givers and acceptors for outsourced activities.

Record/Report type:

Records: 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.

Certificates of Analysis: Provide a summary of testing results on samples of products or materials² together with the evaluation for compliance to a stated specification.

Reports: Document the conduct of particular exercises, projects or investigations, together with results, conclusions and recommendations.

GENERATION AND CONTROL OF DOCUMENTATION

- 4.1 All types of document should be defined and adhered to. The requirements apply equally to all forms of document media types. Complex systems need to be understood, well documented, validated, and adequate controls should be in place. 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. 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.
- 4.2 Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of Product Specification Files, Manufacturing and Marketing Authorisation dossiers, as appropriate. The reproduction of working documents from master documents should not allow any error to be introduced through the reproduction process.
- 4.3 Documents containing instructions should be approved, signed and dated by appropriate and authorised persons. Documents should have unambiguous contents and be uniquely identifiable. The effective date should be defined.

² 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.

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- 4.4 Documents containing instructions should be laid out in an orderly fashion and 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.
- 4.5 Documents within the Quality Management System should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.
- 4.6 Documents should not be hand-written; although, where documents require the entry of data, sufficient space should be provided for such entries.

GOOD DOCUMENTATION PRACTICES

- 4.7 Handwritten entries should be made in clear, legible, indelible way.
- 4.8 Records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable.
- 4.9 Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

RETENTION OF DOCUMENTS

- 4.10 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.
- 4.11 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 Authorised Person, whichever is the longer. For investigational medicinal products, 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. Other requirements for retention of documentation may be described in legislation in relation to specific types of product (e.g. Advanced Therapy Medicinal Products) and specify that longer retention periods be applied to certain documents.
- 4.12 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

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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.

The following section gives some examples of required documents. The quality management system should describe all documents required to ensure product quality and patient safety.

SPECIFICATIONS

- 4.13 There should be appropriately authorised and dated specifications for starting and packaging materials, and finished products.

Specifications for starting and packaging materials

- 4.14 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 and the internal code reference;
 - (ii) The reference, if any, to a pharmacopoeial monograph;
 - (iii) The approved suppliers and, if reasonable, 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.

Specifications for intermediate and bulk products

- 4.15 Specifications for intermediate and bulk products should be available for critical steps or if these are purchased or dispatched. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

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Specifications for finished products

- 4.16 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 formula;
 - c) A description of the pharmaceutical form and package details;
 - d) Directions for sampling and testing;
 - e) The qualitative and quantitative requirements, with the acceptance limits;
 - f) The storage conditions and any special handling precautions, where applicable;
 - g) The shelf-life.
 - h) The reference, if any, to a pharmacopoeial monograph;

MANUFACTURING FORMULA AND PROCESSING INSTRUCTIONS

Approved, written Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured.

4.17 The Manufacturing Formula should include:

- a) The name of the product, with a product reference code relating to its specification;
- b) A description of the pharmaceutical form, strength of the product and batch size;
- c) A list of all starting materials to be used, with the amount of each, described; mention should be made of any substance that may disappear in the course of processing;
- d) A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

4.18 The Processing Instructions should include:

- a) A statement of the processing location and the principal equipment to be used;
- b) The methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);
- 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;

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- d) Detailed stepwise processing instructions [e.g. checks on materials, pre-treatments, sequence for adding materials, critical process parameters (time, temp 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, labeling and special storage conditions where applicable
- g) Any special precautions to be observed.

Packaging Instructions

4.19 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 operations begin;
- 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.

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Batch Processing Record

4.20 A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions, and should contain the following information:

- a) The name and batch number of the product;
- b) Dates and times of commencement, of significant intermediate stages and of completion of production;
- c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;
- d) The batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
- e) Any relevant processing operation or event and major equipment used;
- f) A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
- g) The product yield obtained at different and pertinent stages of manufacture;
- h) Notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions;
- i) Approval by the person responsible for the processing operations.

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 Record

4.21 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions.

The batch packaging record should contain the following information:

- a) The name and batch number of the product;

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- b) The date(s) and times of the packaging operations;
- c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;
- d) Records of checks for identity and conformity with the packaging instructions, including the results of in-process controls;
- e) Details of the packaging operations carried out, including references to equipment and the packaging lines used;
- f) Whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;
- g) Notes on any special problems or unusual events including details, with signed authorisation for any deviation from the Packaging Instructions;
- h) The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation. Where there are there are robust electronic controls in place during packaging there may be justification for not including this information;
- i) Approval by the person responsible for the packaging operations.

PROCEDURES AND RECORDS

Receipt

- 4.22 There should be written procedures and records for the receipt of each delivery of each starting material, (including bulk, intermediate or finished goods), primary, secondary and printed packaging materials.
- 4.23 The records of the receipts should include:
- a) The name of the material on the delivery note and the containers;
 - b) The "in-house" name and/or code of material (if different from a);
 - c) Date of receipt;
 - d) Supplier's name and manufacturer's name;
 - e) Manufacturer's batch or reference number;
 - f) Total quantity and number of containers received;

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- g) The batch number assigned after receipt;
- h) Any relevant comment.

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

Sampling

4.25 There should be written procedures for sampling, which include 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.

Testing

4.26 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.

Other

4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Authorised Person(s). 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.

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

4.29 There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples:

- a) Validation and qualification of processes, equipment and systems;
 - (i) Equipment assembly and calibration;
 - (ii) Technology transfer;
 - (iii) Maintenance, cleaning and sanitation;
- b) Personnel matters including signature lists, training in GMP and technical matters, clothing and hygiene and verification of the effectiveness of training;

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- c) Environmental monitoring;
- d) Pest control;
- e) Complaints;
- f) Recalls;
- g) Returns;
- h) Change control;
- i) Investigations into deviations and non-conformances;
- j) Internal quality/GMP compliance audits;
- k) Summaries of records where appropriate (e.g. product quality review);
- l) Supplier audits.

4.30 Clear operating procedures should be available for major items of manufacturing and test equipment.

4.31 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 these operations out.

4.32 An inventory of documents within the Quality Management System should be maintained.

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CHAPTER 5 : PRODUCTION

PRINCIPLE

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

GENERAL

- 5.1. Production should be performed and supervised by competent people.
- 5.2. All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.
- 5.3. All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.
- 5.4. Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.
- 5.5. Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.
- 5.6. Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.
- 5.7. All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.
- 5.8. Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
- 5.9. Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.
- 5.10. At every stage of processing, products and materials should be protected

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from microbial and other contamination.

- 5.11. When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitising materials.
- 5.12. At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.
- 5.13. 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, ...).
- 5.14. Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.
- 5.15. Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occur, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.
- 5.16. Access to production premises should be restricted to authorised personnel.
- 5.17. Normally, the production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.

PREVENTION OF CROSS-CONTAMINATION IN PRODUCTION

- 5.18. 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, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly sensitising materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.
- 5.19. Cross-contamination should be avoided by appropriate technical or organisational measures, for example:

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- a) Production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;
- b) Providing appropriate air-locks and air extraction;
- c) Minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
- d) Keeping protective clothing inside areas where products with special risk of cross-contamination are processed;
- e) Using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
- f) Using "closed systems" of production;
- g) Testing for residues and use of cleaning status labels on equipment.

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

VALIDATION

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

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

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

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

STARTING MATERIALS

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

5.26. Starting materials should only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question,

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including handling, labelling and packaging requirements, as well as complaints and rejection procedures are discussed with the manufacturer and the supplier.

- 5.27. For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.
- 5.28. If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.
- 5.29. Starting materials in the storage area should be appropriately labelled (see Chapter 5, Item 13). Labels should bear at least the following information:
- The designated name of the product and the internal code reference where applicable;
 - A batch number given at receipt;
 - Where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);
 - Where appropriate, an expiry date or a date beyond which retesting is necessary.

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

- 5.30. There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified (see Chapter 6, Item 13).
- 5.31. Only starting materials which have been released by the Quality Control Department and which are within their shelf-life should be used.
- 5.32. Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.
- 5.33. Each dispensed material and its weight or volume should be independently checked and the check recorded.
- 5.34. Materials dispensed for each batch should be kept together and conspicuously labelled as such.

PROCESSING OPERATIONS - INTERMEDIATE AND BULK PRODUCTS

- 5.35. Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting

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materials, products, product residues or documents not required for the current operation.

- 5.36. Intermediate and bulk products should be kept under appropriate conditions.
- 5.37. Critical processes should be validated (see "VALIDATION" in this Chapter).
- 5.38. Any necessary in-process controls and environmental controls should be carried out and recorded.
- 5.39. Any significant deviation from the expected yield should be recorded and investigated.

PACKAGING MATERIALS

- 5.40. The purchase, handling and control of primary and printed packaging materials should be accorded attention similar to that given to starting materials.
- 5.41. Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorised access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorised personnel following an approved and documented procedure.
- 5.42. Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.
- 5.43. Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

PACKAGING OPERATIONS

- 5.44. When setting up a programme for the packaging operations, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.
- 5.45. Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate check-list.
- 5.46. The name and batch number of the product being handled should be displayed at each packaging station or line.
- 5.47. All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity

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with the Packaging Instructions.

- 5.48. Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.
- 5.49. Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.
- 5.50. The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.
- 5.51. Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.
- 5.52. Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.
- 5.53. Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.
- 5.54. On-line control of the product during packaging should include at least checking the following:
 - a) General appearance of the packages;
 - b) Whether the packages are complete;
 - c) Whether the correct products and packaging materials are used;
 - d) Whether any over-printing is correct;
 - e) Correct functioning of line monitors.

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

- 5.55. Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed record should be kept of this operation.
- 5.56. Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

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

FINISHED PRODUCTS

- 5.58. Finished products should be held in quarantine until their final release under conditions established by the manufacturer.
- 5.59. The evaluation of finished products and documentation which is necessary before release of product for sale are described in Chapter 6 (Quality Control).
- 5.60. After release, finished products should be stored as usable stock under conditions established by the manufacturer.

REJECTED, RECOVERED AND RETURNED MATERIALS

- 5.61. Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorised personnel.
- 5.62. The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Record should be kept of the reprocessing.
- 5.63. 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.
- 5.64. The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.
- 5.65. Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for re-sale, re-labelling or recovery with a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into

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account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical re-processing to recover active ingredients may be possible. Any action taken should be appropriately recorded.

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CHAPTER 6 : QUALITY CONTROL

PRINCIPLE

This chapter should be read in conjunction with all relevant sections of the GMP guide.

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

GENERAL

- 6.1 Each holder of a manufacturing authorisation should have a Quality Control Department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.
- 6.2 The principal duties of the head of Quality Control are summarised in Chapter 2.
The Quality Control Department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, oversee the control of the reference and/or retention samples of materials and products when applicable, ensure the correct labelling of containers of materials and products, ensure the monitoring of the stability of the products, participate in the investigation of complaints related to the quality of the product, etc. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.
- 6.3 Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.
- 6.4 Quality Control personnel should have access to production areas for sampling and investigation as appropriate.

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GOOD QUALITY CONTROL LABORATORY PRACTICE

- 6.5 Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3. Laboratory equipment should not be routinely moved between high risk areas to avoid accidental cross- contamination. In particular, the microbiological laboratory should be arranged so as to minimize risk of cross-contamination.
- 6.6 The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed in Chapter 7, Outsourced Activities, can be accepted for particular reasons, but this should be stated in the Quality Control records.

Documentation

- 6.7 Laboratory documentation should follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department:
- a) Specifications;
 - b) Procedures describing sampling, testing, records (including test worksheets and/or laboratory notebooks), recording and verifying;
 - c) Procedures for and records of the calibration/qualification of instruments and maintenance of equipment;
 - d) A procedure for the investigation of Out of Specification and Out of Trend results;
 - e) Testing reports and/or certificates of analysis;
 - f) Data from environmental (air, water and other utilities) monitoring, where required;
 - g) Validation records of test methods, where applicable.
- 6.8 Any Quality Control documentation relating to a batch record should be retained following the principles given in Chapter 4 on retention of batch documentation.
- 6.9 Some kinds of data (e.g. tests results, yields, environmental controls) should be recorded in a manner permitting trend evaluation. Any Out of Trend or Out of Specification data should be addressed and subject to investigation.
- 6.10 In addition to the information which is part of the batch documentation, other raw data such as laboratory notebooks and/or records should be retained and readily available.

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Sampling

6.11 The sample taking should be done and recorded 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.

6.12 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). The sampling plan used should be appropriately justified and based on a risk management approach.

6.13 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn. They should be managed in a manner to minimize the risk of mix-up and to protect the samples from adverse storage conditions.

6.14 Further guidance on reference and retention samples is given in Annex 19 on Reference and Retention samples.

Testing

6.15 Testing methods should be validated. A laboratory that is using a testing method and which did not perform the original validation, should verify the appropriateness of the testing method. All testing operations described in the Marketing Authorisation or technical dossier should be carried out according to the approved methods. Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routine testing.

6.16 The results obtained should be recorded. Results of parameters identified as critical quality attributes should be trended and checked to make sure that they are consistent with each other. Any calculations should be critically

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examined.

6.17 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, 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 approval or rejection (or other status decision) and the dated signature of the designated responsible person;
- i) Reference to the equipment used.

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

6.19 Special attention should be given to the quality of laboratory reagents, solutions, glassware, reference standards and culture media. They should be prepared and controlled in accordance with written procedures. The level of controls should be commensurate to their use and to the available stability data.

6.20 Reference standards should be established as suitable for their intended use. Their qualification and certification, as such, should be clearly stated and documented. Whenever compendial reference standards from an officially recognised source exist, these should preferably be used as primary reference standards unless fully justified (the use of secondary standards is permitted once their traceability to primary standards has been demonstrated and is documented). These compendial materials should be used for the purpose described in the appropriate monograph unless otherwise authorised by the National Competent Authority.

6.21 Laboratory reagents, solutions, reference standards and culture media should be marked with the preparation and opening date and the signature of the person who prepared them. The expiry date of reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardisation and the last

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current factor should be indicated.

- 6.22 Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents, solutions and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.
- 6.23 Culture media should be prepared in accordance with the media manufacturer's requirements unless scientifically justified. The performance of all culture media should be verified prior to use.
- 6.24 Used microbiological media and strains should be decontaminated according to a standard procedure and disposed of in a manner to prevent the cross-contamination and retention of residues. The in-use shelf life of microbiological media should be established, documented and scientifically justified.
- 6.25 Animals used for testing components, materials or products, should, where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.

On-going stability programme

- 6.26 After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile) associated with the formulation in the marketed package.
- 6.27 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.
- 6.28 This mainly applies to the medicinal product in the package in which it is sold, but consideration should also be given to the inclusion in the programme of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.

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- 6.29 The ongoing stability programme should be described in a written protocol following the general rules of Chapter 4 and results formalised as a report. The equipment used for the ongoing stability programme (stability chambers among others) should be qualified and maintained following the general rules of Chapter 3 and Annex 15.
- 6.30 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:
- Number of batch(es) per strength and different batch sizes, if applicable;
 - Relevant physical, chemical, microbiological and biological test methods;
 - Acceptance criteria;
 - Reference to test methods;
 - Description of the container closure system(s);
 - Testing intervals (time points);
 - Description of the conditions of storage (standardised ICH/VICH conditions for long term testing, consistent with the product labelling, should be used);
 - Other applicable parameters specific to the medicinal product.
- 6.31 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 (for example the frequency of testing, or when updating to ICH/VICH recommendations).
- 6.32 The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year). For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.
- 6.33 In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going stability study should be conducted after any significant change or significant deviation to the process

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or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.

- 6.34 Results of on-going stability studies should be made available to key personnel and, in particular, to the Authorised Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned. Results of on-going stability studies should be available at the site of manufacture for review by the competent authority.
- 6.35 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, affecting product batches released on the market should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with Chapter 8 of the GMP Guide and in consultation with the relevant competent authorities.
- 6.36 A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

Technical transfer of testing methods

- 6.37 Prior to transferring a test method, the transferring site should verify that the test method(s) comply with those as described in the Marketing Authorisation or the relevant technical dossier. The original validation of the test method(s) should be reviewed to ensure compliance with current ICH/VICH requirements. A gap analysis should be performed and documented to identify any supplementary validation that should be performed, prior to commencing the technical transfer process.
- 6.38 The transfer of testing methods from one laboratory (transferring laboratory) to another laboratory (receiving laboratory) should be described in a detailed protocol.
- 6.39 The transfer protocol should include, but not be limited to, the following parameters:
- Identification of the testing to be performed and the relevant test method(s) undergoing transfer;
 - Identification of the additional training requirements;
 - Identification of standards and samples to be tested;
 - Identification of any special transport and storage conditions of test items;
 - The acceptance criteria which should be based upon the current validation study of the methodology and with respect to ICH/VICH

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requirements.

- 6.40 Deviations from the protocol should be investigated prior to closure of the technical transfer process. The technical transfer report should document the comparative outcome of the process and should identify areas requiring further test method revalidation, if applicable.
- 6.41 Where appropriate, specific requirements described in other guidelines should be addressed for the transfer of particular testing methods (e.g. Near Infrared Spectroscopy).

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CHAPTER 7: OUTSOURCED ACTIVITIES

PRINCIPLE

Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the roles and responsibilities of each party. The Pharmaceutical Quality System of the Contract Giver must clearly state the way that the Authorised Person certifying each batch of product for release exercises his/her full responsibility.

Note: This Chapter deals with the responsibilities of manufacturers towards the Competent Regulatory Authorities with respect to the granting of marketing and manufacturing authorisations. It is not intended in any way to affect the respective liability of Contract Acceptors and Contract Givers to consumers; this is governed by other provisions of national law.

GENERAL

- 7.1 There should be a written contract covering the outsourced activities, the products or operations to which they are related, and any technical arrangements made in connection with it.
- 7.2 All arrangements for the outsourced activities including any proposed changes in technical or other arrangements should be in accordance with regulations in force, and the Marketing Authorisation for the product concerned, where applicable.
- 7.3 Where the Marketing Authorisation holder and the manufacturer are not the same, appropriate arrangements should be in place, taking into account the principles described in this chapter.

THE CONTRACT GIVER

- 7.4 The Pharmaceutical Quality System of the Contract Giver should include the control and review of any outsourced activities. The Contract Giver is ultimately responsible to ensure processes are in place to assure the control of outsourced activities. These processes should incorporate quality risk management principles and notably include:
 - 7.4.1 Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract

Acceptor to carry out successfully the outsourced activities. The Contract Giver is also responsible for ensuring by means of the contract that the principles

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and guidelines of GMP as interpreted in this Guide are followed;

- 7.4.2 The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in accordance with regulations in force, and the Marketing Authorisation for the product concerned. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his/her premises, equipment, personnel, other materials or other products;
- 7.4.3 The Contract Giver should monitor and review the performance of the Contract Acceptor and the identification and implementation of any needed improvement.
- 7.5 The Contract Giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities. He/she should also ensure, either by himself/herself, or based on the confirmation of the Contract Acceptor's Authorised Person, that all products and materials delivered to him/her by the Contract Acceptor have been processed in accordance with GMP and the Marketing Authorisation.

THE CONTRACT ACCEPTOR

- 7.6 The Contract Acceptor must be able to carry out satisfactorily the work ordered by the Contract Giver such as having adequate premises, equipment, knowledge, experience, and competent personnel.
- 7.7 The Contract Acceptor should ensure that all products, materials and knowledge delivered to him/her are suitable for their intended purpose.
- 7.8 The Contract Acceptor should not subcontract to a third party any of the work entrusted to him/her 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 those from assessments of the suitability of the third party, are made available in the same way as between the original Contract Giver and Contract Acceptor.
- 7.9 The Contract Acceptor should not make unauthorised changes, outside the terms of the Contract, which may adversely affect the quality of the outsourced activities for the Contract Giver.
- 7.10 The Contract Acceptor should understand that outsourced activities, including contract analysis, may be subject to inspection by the competent authorities.

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THE CONTRACT

- 7.11 A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must be in accordance with regulations in force and the Marketing Authorisation for the product concerned and agreed by both parties.
- 7.12 The contract should describe clearly which party to the contract has responsibility for conducting each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis).
- 7.13 All records related to the outsourced activities, e.g. manufacturing, analytical and distribution records, and reference samples, should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect or to investigating in the case of a suspected falsified product must be accessible and specified in the relevant procedures of the Contract Giver.
- 7.14 The contract should permit the Contract Giver to audit outsourced activities, performed by the Contract Acceptor or their mutually agreed subcontractors.

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CHAPTER 8: COMPLAINTS AND PRODUCT RECALL

PRINCIPLE

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

COMPLAINTS

- 8.1. A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him. If this person is not the Authorised Person, the latter should be made aware of any complaint, investigation or recall.
- 8.2. There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.
- 8.3. Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control should normally be involved in the study of such problems.
- 8.4. If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch should be investigated.
- 8.5. All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
- 8.6. Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.
- 8.7. Special attention should be given to establishing whether a complaint was caused because of counterfeiting.
- 8.8. The Competent Authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, detection of counterfeiting or any other serious quality problems with a product.

RECALLS

- 8.9. 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

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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.

- 8.10. There should be established written procedures, regularly checked and updated when necessary, in order to organise any recall activity.
- 8.11. Recall operations should be capable of being initiated promptly and at any time.
- 8.12. All Competent Authorities of all countries to which products may have been distributed should be informed promptly if products are intended to be recalled because they are, or are suspected of, being defective.
- 8.13. The distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.
- 8.14. Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.
- 8.15. The progress of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.
- 8.16. The effectiveness of the arrangements for recalls should be evaluated regularly.

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CHAPTER 9: SELF INSPECTION, QUALITY AUDITS , SUPPLIERS' AUDITS AND APPROVAL

PRINCIPLE

Self inspections should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures.

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

- 9.1. Personnel matters, premises, equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at intervals following a pre-arranged programme in order to verify their conformity with the principles of Quality Assurance.
- 9.2. Self inspections should be conducted in an independent and detailed way by designated competent person(s) from the company. Independent audits by external experts may also be useful.
- 9.3. All self inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.

Items for Self-Inspection

- 9.4 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;

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

Self-Inspection Team

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

Frequency of Self-Inspection

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

Self-Inspection Report

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

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

Follow-Up Action

9.8 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

9.6 It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality

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system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (see section 7, “Contract production and analysis”).

Suppliers’ audits and approval

- 9.7 The person responsible for QC should have responsibility, together with other relevant departments, for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.
- 9.8 Before suppliers are approved and included in the approved suppliers’ list or specifications, they should be evaluated. The evaluation should take into account a supplier’s history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier’s ability to conform with GMP standards

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ANNEXES

Refer to separate document entitled "*Guidelines on Good Manufacturing Practice for Medicinal Products - ANNEXES*" document number INS/GDL/001-(Annexes).

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DOCUMENT REVISION HISTORY

Date of revision	Revision number	Document Number	Author(s)	Changes made and reasons for revision
2006	0	Not on record-	Deus Mubangizi	First issue
5 th April 2013	1	INS/GDL/001	Nasser Mbaziira, Kate Kikule, Peter Ssali	Changed format, changed document numbering system, revised all sections and added Annexes in accordance with the current WHO GMP text 2007; and PIC/S-PE 009-07 parts 1, 2 and the Annexes.
15 th March 2017	2	INS/GDL/001	<p><i>Authors:</i></p> <p style="text-align: center;">Kate Kikule, Denis Mwesigwa, Peter Ssali.</p> <p><i>Reviewers:</i></p> <p style="text-align: center;">Conrad Mark, Michael Mutyaba, Mohammed Lukwago, Amoreen Naluyima, Annette Ssenkindu.</p>	<p>1) Transposed the revised Chapters of the PIC/S GMP Guide (PE 009-13) of 1st January 2017, into the NDA GMP Guidelines. The following Chapters of the NDA GMP Guidelines have been revised to match the revisions in the PIC/S GMP Guide (PE 009-13):</p> <ul style="list-style-type: none"> a) Chapter 1 on “Quality Management” (which has become “Pharmaceutical Quality Systems”); b) Chapter 2 on “Personnel”; c) Chapter 6 on “Quality Control”; d) Chapter 7 on “Contract Manufacture and Analysis” (which has become “Outsourced Activities”). <p>The revised Chapters 1, 2, 6 and 7 of the PIC/S GMP Guide (PE 009-13) are based on the equivalent Chapters of the EU GMP Guide with some minor differences in terms of language.</p> <p>Chapters 1, 2 & 7 have been aligned to ICH Q10 and the principles of “Pharmaceutical Quality System” have been integrated. A section on consultants has been added in Chapter 2.</p> <p>The scope of Chapter 7 has been expanded beyond the scope of “contract manufacture and analysis”. Both Chapters 1 and 7 have been renamed to reflect the changes.</p> <p>In Chapter 6, all sections have been</p>

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				<p>reviewed and amended and a new section on "Technical transfer of testing methods" has been added.</p> <ol style="list-style-type: none"> 2) Incorporated references to the Statutory Instruments No. 35; The National Drug Policy and Authority (Licensing) Regulations, 2014. 3) Changed the title "<i>Executive Secretary/Registrar</i>" to "<i>Secretary to the Drug Authority</i>" 4) Separated the Annexes from the main document, because the Annexes apply to both guidelines for FPP and for APIs. 5) Created guidance document for Active Pharmaceutical ingredients (APIs) as Part 2 of the Guidelines on GMP for medicinal products. 6) added the revised NDA mission and vision statements, and core values. 7) The chapter on self-inspection includes merger of sections from the PIC/S GMP 2017 and WHO GMP 2014. 8) The section on "principle" under training has been elaborated by adding sentences from the WHO GMP to the PIC/S GMP. 9) In the interpretation section, the PIC/S definitions have been adopted except for "record", "quality control" and "quality assurance" which were adopted from ISO 9000:2005 Terms and Vocabulary.
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