



**GUIDELINES FOR GOOD MANUFACTURING PRACTICES FOR
FINISHED PHARMACEUTICAL PRODUCTS
PART 1**

APRIL, 2023

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FOREWORD

Rwanda Food and Drugs Authority (Rwanda FDA) is a regulatory body established by the Law N° 003/2018 of 09/02/2018 determining its mission, organization and functioning. One of its main powers is to formulate regulations and guidelines for regulating the manufacture of Pharmaceutical products to ensure that they comply with quality standards required for good manufacturing practices.

Considering the provisions of the regulations N° FDISM/FDIC/TRG/005, governing Good Manufacturing Practices for medical products. The Authority issues the guidelines N° FDISM/FDIC/GDL/001 Good Manufacturing Practice for Finished Pharmaceutical Products - Part 1.

Badly manufactured Pharmaceutical products' effects are one of the public health concerns not only to our country but also all over the world. It is in this context that the Rwanda Food and Drugs Authority intends to put in place guidelines that provide for good manufacturing practices of Pharmaceutical products to ensure that manufactured medicines do not constitute harmful effects to people's health that leads to losses of life.

It is expected that these guidelines will offer a clear understanding to manufacturers and other persons concerned by the guidelines during the evaluation process; they will protect consumers and pharmaceutical manufacturing industry, thus promoting health protection, business as well as the national economy as a whole.

Dr. Emile BIENVENU
Director General



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28/03/2023	4	<ol style="list-style-type: none"> 1. Chapter 2: 2.1 Types of inspection Updated the Types of inspection from “pre-approval” to “Routine” and updated the text 2. added another type referred to as “Any type of Inspection” as deemed necessary by the Authority

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ABBREVIATIONS AND ACRONYMS

API	Active Pharmaceutical Ingredient
CAPA	Corrective Actions and/or Preventive Actions
GMP	Good Manufacturing Practices
HVAC	Heating, Ventilation and Air Conditioning
ICH	International Council for Harmonization
OOS	Out-Of-Specification
PIC/S	Pharmaceutical Inspection Cooperation Scheme
QA	Quality Assurance
QC	Quality Control
SOP	Standard Operating Procedures
VICH	Veterinary International Conference on Harmonization

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DEFINITIONS

“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;

“Authorized person” is an individual recognized 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 before for batch release;

“Batch or lot” defines 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. 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, characterized 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 sterilization 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 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;

“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” is 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

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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;

“Certification” The final review and formal approval of a validation or revalidation, followed by approval of a process for routine use;

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

“Computerized system” A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control;

“Consignment (or delivery)” The quantity of 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;

“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;

“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

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adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control;

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

“Intermediate product” Partly processed material that must undergo further manufacturing steps before it becomes a bulk product;

“Large-volume parenteral” Sterile solutions intended for parenteral application with a volume of 100 ml or more in one container of the finished dosage form;

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

“Manufacturer” A company that carries out at least one step of manufacture;

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

“Marketing authorization” a legal document issued by the competent Authority for the purposes of marketing or free distribution of a product which has been approved after evaluation for safety, efficacy and quality;

“Medicinal plant” Plant the whole or part of which is used for pharmaceutical purpose;

“Medical products”: means medicines, vaccines, and diagnostics and medical devices;

“Medicinal products” means substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action;

“Operational qualification” Documented verification that the system or subsystem performs as intended over all anticipated operating ranges;

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

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“Pharmaceutical product” any substance capable of preventing, treating human or animal diseases and any other substance intended for administration to a human being or an animal in order to diagnose diseases, restore, correct or carry out modification of organic or mental functions. It also means products used in disinfecting premises where food and drugs are manufactured, prepared or stored, cleaning hospitals, equipment and farm houses;

“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;

“Production” All operations involved in the preparation of a medicinal product, 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 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 fulfills 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;

“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

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compliance with established requirements;

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

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

“Starting material” Any substance used in the production of a medicinal product, but excluding packaging materials;

“Sterility” 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 criteria interacting activities and techniques that are united to form an organized whole;

“Validation programme (or plan)” A document describing the activities to be performed in a validation, including the acceptance 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 programme 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).

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CHAPTER ONE: INTRODUCTION

1.0 Background

Rwanda FDA was established by the Law N° 003/2018 of 09/02/2018 determining its mission, organization and functioning. The mandate of Rwanda FDA is to protect public health through regulation of human and veterinary medicines, vaccines and other biological products, processed foods, poisons, medicated cosmetics, medical devices, household chemical substances, tobacco and tobacco products.

1.1 Purpose of these Guidelines

These Guidelines (and the Annexes) are adopted from the Pharmaceutical Inspection Cooperation Scheme (PIC/S), PE 009-13 (Part 1), 1st January 2017. The PIC/S Guidelines are internationally accepted Good Manufacturing Practice Guidelines.

These Guidelines are intended to provide guidance to the pharmaceutical manufacturers of finished pharmaceutical products on how to comply with Good Manufacturing Practice (GMP).

The Guidelines shall form the basis of GMP inspection by Rwanda Food and Drugs Authority (Rwanda FDA) as one of the requirements for registration of pharmaceutical products in Rwanda.

1.2 Legal Framework

Article 9, paragraph 1 of the Law N° 003/2018 of 09/02/2018 establishing Rwanda FDA and determining its mission, organization and functioning mandates states that Rwanda FDA has the power to formulate regulations and guidelines for regulating the manufacture, import and export, distribution, sale and use of regulated products.

One of the means of regulating the manufacture of pharmaceutical products is through compliance with Good Manufacturing Practice (GMP) requirements as laid down in these Guidelines. The Guidelines were also developed in accordance with Regulations N° FDISM/FDIC/TRG/005 governing Good Manufacturing Practices for medical products.

1.3 Scope

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

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CHAPTER 2: GOOD MANUFACTURING PRACTICE INSPECTION

2.1 Types of inspections

2.1.1 There shall be four types of good manufacturing practice inspections which should be divided into the following categories:

- a. Routine inspection;
- b. concise inspection;
- c. follow-up inspection;
- d. special inspection; and
- e. any other types as the Authority may designate.

2.1.2 The inspection should be conducted as follows:

- a. The routine inspection is a full inspection of all applicable components of GMP and licensing provisions. It shall be conducted at any time when the product has been registered but before expiry of validity of registration of such product. It may be indicated when the manufacturer:
 - i. Requests for renewal of a manufacturing license to operate
 - ii. Has a history on non-compliance with GMP;
 - iii. Has introduced new product lines or new products, or has made significant modifications to manufacturing methods or processes, or has made changes in key personnel, premises, equipment, among others;
 - iv. Has not been inspected during the last 3 to 5 years.
- b. Concise GMP inspections are the evaluation of limited aspects relating to GMP compliance within a facility. The manufacturers with a consistent record of compliance with GMP through previous routine inspections are eligible for concise inspections. The focus of a concise inspection is on a limited number of GMP requirements selected as indicators of overall GMP performance, plus the identification of any significant changes that could have been introduced since the last inspection. Collectively, the information obtained will indicate the overall attitude of the firm towards GMP. Evidence of unsatisfactory GMP performance observed during a concise inspection should trigger a more comprehensive inspection.
- c. Follow-up GMP inspections (reassessment or re-inspection) are made to monitor the result of corrective measures. They are normally carried out from six (6) weeks to six (6) months after the initial inspection, depending on the nature of the defects and the work to be undertaken. They are limited to specific GMP requirements that have not been observed or that have been inadequately implemented.

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- d. Special GMP inspections may be necessary to undertake spot checks following complaints, recalls related to suspected quality defects in products or reports of adverse drug reactions. Such inspections may be focused on one product, a group of related products, or specific operations such as mixing, sterilization, or labeling. Special visits may be also made to establish how a specific product is manufactured as a prerequisite for marketing approval or issuance of an export certificate. A further reason for special visits to gather specific information on or to investigate specific operations and to advise the manufacturer of regulatory documents.
- e. Any other types as the Authority may designate. This may include pre-approval inspection for newly established facility.

2.2 Application for GMP

The manufacturer or applicant who intends to conduct a Good Manufacturing Practice inspection shall submit an application dossier to the Authority on the following address:

Director General
Rwanda Food and Drugs Authority
Nyarutarama Plaza, Rwanda
KG 9 Avenue, Kigali
P.O. Box 1948, Kigali, Rwanda.
E-mail: info@rwandafda.gov.rw

The requirements for application for GMP inspection of finished pharmaceutical products and active pharmaceutical ingredients manufacturing facilities are detailed in the annexes of these guidelines. Notwithstanding the provisions above, the inspection shall not be conducted to facility which has not submitted applications for product registration.

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CHAPTER 3: PHARMACEUTICAL QUALITY SYSTEM

3.1 Principles

The holder of a Manufacturing Authorization must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorization or Clinical Trial Authorization, 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 of staff in different departments at all levels within the company, by the company's suppliers and 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 which 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 also additional legal responsibilities for the holder of the Manufacturing Authorization and for the Authorized 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 emphasize their relationships and their fundamental importance to the production and control of medicinal products.

3.2 Pharmaceutical quality system

3.2.1 Quality Management is a wide-ranging concept covering all matters, which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Management therefore incorporates Good Manufacturing Practices.

3.2.2 GMP applies to the lifecycle stages from the manufacture of investigational medicinal products, technology transfer, commercial manufacturing 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.

3.2.3 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.

3.2.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that:

a. Product realization is achieved by designing, planning, implementing, maintaining and

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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 take 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;
- 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;

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

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taken in response to investigations. The effectiveness of such actions should be monitored and assessed, in line with Quality Risk Management principles;

- n. Medicinal products are not sold or supplied before an Authorized Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorization and any other regulations relevant to the production, control and release of medicinal products;
- o. 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;
- p. There is a process for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Pharmaceutical Quality System.

3.2.5 Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and those roles, responsibilities, and authorities are defined, communicated and implemented throughout the organization. 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 organization to the Pharmaceutical Quality System.

3.2.6 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.

3.2.7 The Pharmaceutical Quality System should be defined and documented. A Quality Manual or equivalent documentation should be established and contain a description of the quality management system including management responsibilities.

3.3 Good manufacturing practice for pharmaceutical products

3.3.1 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 Authorization, Clinical Trial Authorization 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;

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- 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 complete history of a batch to be traced are retained in a comprehensible and accessible form;
- i. The distribution of the products minimizes 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.

3.4 Quality control

- 3.4.1 Quality Control is part of Good Manufacturing Practices, which is concerned with sampling, specifications, testing, documentation and release procedures to 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 satisfactory.

The basic requirements of Quality Control ensure 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

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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 Authorization or Clinical Trial Authorization, are of the purity required, and are enclosed within their proper containers and correctly labelled;
- f. Records are made of inspection report and testing results of materials, intermediate, bulk, and finished products that were formally assessed against specifications. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;
- g. No batch of product is released for sale or supply prior to certification by an Authorized Person in accordance with relevant requirements;
- h. Sufficient reference samples of starting materials and products are retained in accordance with Annex 18 of the Guidelines on Good Manufacturing Practices on Medical Products _ Annexes, reference number: FDISM/FDIC/GDL/002 to permit future examination of the product if necessary and that the sample is retained in the final pack.

3.5 Product quality review

3.5.1 Regular periodic or rolling quality reviews of all authorized 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 Authorization variations submitted, granted or refused, including those for third

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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 Authorizations and variations to Marketing Authorizations, a review of post-marketing commitments;
- j. The qualification status of relevant equipment and utilities, e.g. 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.

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

3.6 Quality risk management

3.6.1 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.

3.6.2 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.

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- c. Examples of the processes and applications of Quality Risk Management can be found inter alia in Annex 19 of the Guidelines on Good Manufacturing Practices on Medical Products _ Annexes, reference number: FDISM/FDIC/GDL/002.

CHAPTER 4: PERSONNEL

4.1 Principles

The 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.

4.2 General

- 4.2.1 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 individual should not be so extensive as to present any risk to quality.
- 4.2.2 The manufacturer must have an organization chart in which the relationships between the heads of Production, Quality Control and where applicable Head of Quality Assurance or Quality Unit and the position of the Authorized Person(s) are clearly shown in the managerial hierarchy.
- 4.2.3 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.
- 4.2.4 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 organization. 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.

4.3 Key personnel

- 4.3.1 A manufacturing facility should have the following key personnel:

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- a. Head of production;
- b. Head of quality unit;
- c. Head of quality assurance;
- d. Head of quality control; and
- e. Authorized person.

4.3.2 Senior Management should appoint Key Management Personnel including 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, an authorized Person(s) shall be designated for the purpose. In large organizations, it may be necessary to delegate some of the functions of key personnel. Additionally, depending on the size and organizational 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 their responsibilities are shared with the Head of Quality Control and Head of Production and the senior management should therefore ensure that roles, responsibilities and authorities are clearly defined.

4.3.3 The head of production and quality control should be independent of each other.

4.3.4 Key posts shall be occupied by full-time personnel.

4.3.5 The manufacturer should notify the Authority the name of qualified and authorized person appointed by the manufacturers.

4.3.6 The manufacturer should notify the Authority of the name of a person to whom functions have been delegated by the responsible person and the specific functions which have been delegated to such persons.

4.3.7 Key personnel responsible for supervising the manufacture and quality unit including quality assurance and quality control for manufacture of pharmaceutical products should possess the qualification with scientific education and practical experience.

4.3.8 The head of production should have bachelor education in Pharmacy but if not, available options shall be for person with at least a bachelor education in the following:

- a. pharmaceutical sciences and technology;
- b. chemistry (analytical or organic) or biochemistry;
- c. chemical engineering;
- d. Veterinary medicine.

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- e. Any other relevant qualification

4.3.9 The head of quality unit shall have bachelor education in any of the following:

- a. pharmacy;
- b. pharmaceutical sciences and technology;
- c. chemistry (analytical or organic) or biochemistry.
- d. Any other relevant qualification

4.3.10 The head of quality control shall have bachelor education in any of the following:

- a. pharmacy;
- b. pharmaceutical sciences and technology;
- c. chemistry (analytical or organic) or biochemistry;
- d. microbiology.
- e. Any other relevant qualification

4.3.11 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 authorization of written procedures and other documents, including amendments;
- b. the monitoring and control of the manufacturing environment;
- c. plant hygiene;
- d. process validation and calibration of analytical apparatus;
- e. training including the application and principles of quality assurance;
- f. the approval and monitoring of suppliers of materials;
- g. the approval and monitoring of contract manufacturers;
- h. the designation and monitoring of storage conditions for materials and products;

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- i. the performance and evaluation in process controls;
- j. the retention of records;
- k. the monitoring of compliance with good manufacturing practice requirements;
- l. the inspection, investigation, and taking of samples, in order to monitor factors that may affect product quality.

4.3.12 The head of the production department shall have the following responsibilities:

- a. to ensure products are produced and stored according to the appropriate documentation in order to obtain the required quality;
- b. to approve the instructions relating to production operations, including the in- process controls and to ensure their strict implementation;
- c. to ensure that the production records are evaluated and signed by a designated person before they are made available to the quality control department;
- d. to check the maintenance of the department, premises and equipment.
- e. to ensure that the appropriate process validations and calibrations of control equipment are performed and recorded, and the reports made available;
- f. to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

4.3.13 The head of the quality unit including quality assurance and quality control department generally shall have the following responsibilities:

- a. to approve or reject starting materials, packaging materials, and intermediate, bulk, and finished products;
- b. to evaluate batch records;
- c. to ensure that all necessary testing is carried out;
- d. to approve sampling instructions, specifications, test methods, and other quality control procedures;
- e. to approve and monitor analysis carried out under contract;
- f. to check the maintenance of the department, premises and equipment;

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- g. to ensure that, appropriate validations, including those of analytical procedures, and calibrations of control equipment are done;
- h. to ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need;
- i. establish, implement and maintain the quality system;
- j. supervision of regular internal audits or self-inspections;
- k. participate in external audits; and
- l. participate in validation programme.

4.3.14 The duties of the Authorized Person(s) are described in the guidelines governing Licensing of public and private manufacturers, distributors, wholesalers and retailers of medical products Doc No.: FDISM/FDIC/GDL/005, can be summarized as follows:

- a. An Authorized Person must ensure that each batch of medical products has been manufactured and checked in compliance with the regulatory documents in force and in accordance with the requirements of the Marketing Authorization
- b. The Authorized Person(s) must meet the qualification requirements laid down in the guidelines governing Licensing of public and private manufacturers, distributors, wholesalers and retailers of medical products Doc No.: FDISM/FDIC/GDL/005, they shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorization to carry out their responsibilities;
The responsibilities of an Authorized Person may be delegated, but only to other Authorized Person(s).

4.4 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 to ensure that individuals are assigned appropriate responsibilities. Personnel should be selected based on their scientific and technical understanding, product knowledge, and process knowledge and/or risk assessment abilities to appropriately execute certain quality functions.

4.4.1 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.

4.4.2 Besides the basic training on the theory and practice of Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically

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assessed. Training program should be available and approved by either the head of Production or the head of Quality Control, as appropriate and training records should be kept.

- 4.4.3 Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.
- 4.4.4 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.
- 4.4.5 The concept of Quality assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

4.5 Personnel hygiene

- 4.5.1 Detailed hygiene program 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 program should be promoted by management and widely discussed during training sessions.
- 4.5.2 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.
- 4.5.3 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.
- 4.5.4 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.
- 4.5.5 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.
- 4.5.6 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.
- 4.5.7 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.

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4.5.8 Any specific requirements for the manufacture of special groups of products, for example sterile preparations, are covered in the Guidelines on Good Manufacturing Practices on Medical Products _ Annexes, reference number FDISM/FDIC/GDL/002.

CHAPTER 5: PREMISES AND EQUIPMENT

5.1 Principle

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

5.2 Premises

5.2.1 General

5.2.1.1 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.

5.2.1.2 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.

5.2.1.3 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.

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

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

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5.2.2 Production Area

- 5.2.2.1** In order to minimize the risk of a serious medical hazard due to cross- contamination, dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitizing materials (e.g. Penicillin) or biological preparations (e.g. from live micro-organisms). The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxic, certain highly active drugs and non-medicinal products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.
- 5.2.2.2** 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.
- 5.2.2.3** The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.
- 5.2.2.4** 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.
- 5.2.2.5** 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.
- 5.2.2.6** 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.
- 5.2.2.7** 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.
- 5.2.2.8** Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.
- 5.2.2.9** 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.

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- 5.2.2.10** Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.
- 5.2.2.11** Productions areas should be well lit, particularly where visual on-line controls are carried out.
- 5.2.2.12** In-process controls may be carried out within the production area provided they do not carry any risk for the production.

5.2.3 Storage Areas

- 5.2.3.1** 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.
- 5.2.3.2** 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.
- 5.2.3.3** 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.
- 5.2.3.4** Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.
- 5.2.3.5** 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.
- 5.2.3.6** Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.
- 5.2.3.7** Highly active materials or products should be stored in safe and secure areas.
- 5.2.3.8** 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.

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5.2.4 Quality Control Areas

- 5.2.4.1** Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, micro-biologicals and radioisotopes, which should be separated from each other.
- 5.2.4.2** 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.
- 5.2.4.3** Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, among others.
- 5.2.4.4** Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

5.2.5 Ancillary Areas

- 5.2.5.1** Rest and refreshment rooms should be separate from other areas.
- 5.2.5.2** 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.
- 5.2.5.3** 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.
- 5.2.5.4** Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

5.3 Equipment

- 5.3.1** Manufacturing equipment should be designed, located, qualified and maintained to suit its intended purpose.
- 5.3.2** Repair and maintenance operations should not present any hazard to the quality of the products.
- 5.3.3** Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.
- 5.3.4** Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.

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- 5.3.5 Equipment should be installed in such a way as to prevent any risk of error or of contamination.
- 5.3.6 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.
- 5.3.7 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.
- 5.3.8 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.
- 5.3.9 Fixed pipe work should be clearly labelled to indicate the contents and, where applicable, the direction of flow.
- 5.3.10 Distilled, deionized and, where appropriate, other water pipes should be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.
- 5.3.11 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

CHAPTER 6: DOCUMENTATION

6.1 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 utilized must be to establish, control, monitor and record all activities, which directly or indirectly affect 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

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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.

6.2 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 details of all the starting materials, equipment and computerized systems (if any) to be used and specify all processing, packaging, sampling and testing instructions. In-process controls and process analytical technologies to be employed should be specified where relevant, together with acceptance criteria.

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

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

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 materials together with the evaluation for compliance to a stated specification.

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 Authorization dossier.

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

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6.3 Generation and control of documentation

- 6.3.1** All types of documents 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.
- 6.3.2** Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of Product Specification Files, Manufacturing and Marketing Authorization dossiers, as appropriate. The reproduction of working documents from master documents should not allow any error to be introduced through the reproduction process.
- 6.3.3** Documents containing instructions should be approved, signed and dated by appropriate and authorized persons. Documents should have unambiguous contents and be uniquely identifiable. The effective date should be defined.
- 6.3.4** 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.
- 6.3.5** 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.
- 6.3.6** Documents should not be hand-written; although, where documents require the entry of data, sufficient space should be provided for such entries.

6.4 Good documentation practices

- 6.4.1** Handwritten entries should be made in clear, legible, indelible way.
- 6.4.2** 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.
- 6.4.3** 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.

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6.5 Retention of documents

- 6.5.1** 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.
- 6.5.2** Specific requirements apply to batch documentation which must be kept for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the Authorized Person, whichever is the longer. 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.
- 6.5.3** 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 Authorization should be retained whilst the authorization remains in force. It may be considered acceptable to retire certain documentation (e.g. raw data supporting validation reports or stability reports) where the data has been superseded by a full set of new data. Justification for this should be documented and should take into account the requirements for retention of batch documentation; for example, in the case of process validation data, the accompanying raw data should be retained for a period at least as long as the records for all batches whose release has been supported on the basis of that validation exercise.

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.

6.6 Specifications

There should be appropriately authorized and dated specifications for starting and packaging materials, and finished products.

6.6.1 Specifications for starting and packaging materials

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 pharmacopeial monograph;
 - iii. The approved suppliers and, if reasonable, the original producer of the material;

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- 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.

6.6.2 Specifications for intermediate and bulk products

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.

6.6.3 Specifications for finished products

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 pharmacopeial monograph;

6.7 Manufacturing formula and processing instructions

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

6.7.1 The Manufacturing Formula should include:

- a. The name of the product, with a product reference code relating to its specification;

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- 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.

6.7.2 The Processing Instructions should include:

- a. A statement of the processing location and the principal equipment to be used;
- b. The methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilizing);
- c. Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use;
- d. Detailed stepwise processing instructions [e.g. checks on materials, pre-treatments, sequence for adding materials, critical process parameters (time, temperature etc)];
- e. The instructions for any in-process controls with their limits;
- f. Where necessary, the requirements for bulk storage of the products; including the container, labeling and special storage conditions where applicable
- g. Any special precautions to be observed.

6.8 Packaging instructions

Approved Packaging Instructions for each product, pack size and type should exist. These should include, or have a reference to, the following:

- 6.8.1** Name of the product; including the batch number of bulk and finished product;
- 6.8.2** Description of its pharmaceutical form, and strength where applicable;
- 6.8.3** The pack size expressed in terms of the number, weight or volume of the product in the final container;
- 6.8.4** 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;
- 6.8.5** 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

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product;

- 6.8.6** 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;
- 6.8.7** Special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
- 6.8.8** A description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- 6.8.9** Details of in-process controls with instructions for sampling and acceptance limits.

6.9 Batch processing record

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:

- 6.9.1** The name and batch number of the product;
- 6.9.2** Dates and times of commencement, of significant intermediate stages and of completion of production;
- 6.9.3** 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;
- 6.9.4** 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);
- 6.9.5** Any relevant processing operation or event and major equipment used;
- 6.9.6** A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
- 6.9.7** The product yield obtained at different and pertinent stages of manufacture;
- 6.9.8** Notes on special problems including details, with signed authorization for any deviation from the Manufacturing Formula and Processing Instructions;

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6.9.9 Approval by the person responsible for the processing operations. 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.

6.10 Batch packaging record

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;
- 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 authorization 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 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.

6.11 Procedures and records

6.11.1 Receipt

6.11.1.1 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.

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6.11.1.2 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;
- g. The batch number assigned after receipt;
- h. Any relevant comment.

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

6.11.2 Sampling

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.

6.11.3 Testing

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.

6.11.4 Other

6.11.4.1 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 qualified Person(s). All records should be available to the qualified Person. A system should be in place to indicate special observations and any changes to critical data.

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

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

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- a. Validation and qualification of processes, equipment and systems;
- b. Equipment assembly and calibration;
- c. Technology transfer;
- d. Maintenance, cleaning and sanitation;
- e. Personnel matters including signature lists, training in GMP and technical matters, clothing and hygiene and verification of the effectiveness of training;
- f. Environmental monitoring;
- g. Pest control;
- h. Complaints;
- i. Recalls;
- j. Returns;
- k. Change control;
- l. Investigations into deviations and non-conformances;
- m. Internal quality/GMP compliance audits;
- n. Summaries of records where appropriate (e.g. product quality review);
- o. Supplier audits.

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

6.11.4.5 Logbooks should be kept for major or critical analytical testing, production equipment and areas where product has been processed. They should be used to record in chronological order, as appropriate, any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried out these operations.

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

CHAPTER 7: PRODUCTION

7.1 Principle

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

7.2 General

7.2.1 Production should be performed and supervised by competent people.

7.2.2 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.

7.2.3 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.

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- 7.2.4 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.
- 7.2.5 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.
- 7.2.6 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.
- 7.2.7 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.
- 7.2.8 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
- 7.2.9 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.
- 7.2.10 At every stage of processing, products and materials should be protected from microbial and other contamination.
- 7.2.11 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 sensitive materials.
- 7.2.12 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.
- 7.2.13 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 colors to indicate status (for example, quarantined, accepted, rejected, clean, ...).
- 7.2.14 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.
- 7.2.15 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.
- 7.2.16 Access to production premises should be restricted to authorized personnel.

7.2.17 Normally, the production of non-medicinal products should be avoided in areas and with the

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equipment destined for the production of medicinal products.

7.3 Prevention of cross-contamination in production

- 7.3.1 Contamination of a starting material or a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapors, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations containing living organisms, certain hormones, cytotoxic, 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.
- 7.3.2 Cross-contamination should be avoided by appropriate technical or organizational measures, for example:
- a. Production in segregated areas (required for products such as penicillin, 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. Minimizing 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.
- 7.3.3 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.

7.4 Validation

- 7.4.1 Validation studies should reinforce GMP and be conducted in accordance with defined procedures. Results and conclusions should be recorded.
- 7.4.2 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

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materials and equipment specified, should be shown to yield a product consistently of the required quality.

7.4.3 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.

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

7.5 Starting materials

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

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

7.5.3 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.

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

7.5.5 Starting materials in the storage area should be appropriately labelled (see Chapter 9). Labels should bear at least the following information:

- a. The designated name of the product and the internal code reference where applicable;
- b. A batch number given at receipt;
- c. Where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);
- d. Where appropriate, an expiry date or a date beyond which retesting is necessary.

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

7.5.6 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 8).

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

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- 7.5.8 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.
- 7.5.9 Each dispensed material and its weight or volume should be independently checked and the check recorded.
- 7.5.10 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

7.6 Processing operations: intermediate and bulk products

- 7.6.1 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.
- 7.6.2 Intermediate and bulk products should be kept under appropriate conditions.
- 7.6.3 Critical processes should be validated (see "VALIDATION" in this Chapter).
- 7.6.4 Any necessary in-process controls and environmental controls should be carried out and recorded.
- 7.6.5 Any significant deviation from the expected yield should be recorded and investigated.

7.7 Packaging materials

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

7.8 Packaging operations

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

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- 7.8.2 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.
- 7.8.3 The name and batch number of the product being handled should be displayed at each packaging station or line.
- 7.8.4 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.
- 7.8.5 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.
- 7.8.6 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 mislabeling can occur.
- 7.8.7 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.
- 7.8.8 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.
- 7.8.9 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.
- 7.8.10 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.
- 7.8.11 On-line control of the product during packaging should include at least checking the following:
- General appearance of the packages;
 - Whether the packages are complete;
 - Whether the correct products and packaging materials are used;
 - Whether any over-printing is correct;
 - Correct functioning of line monitors.

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

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

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7.8.13 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.

7.8.14 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.

7.9 Finished products

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

7.9.2. The evaluation of finished products and documentation which is necessary before release of product for sale are described in Chapter 8 (Quality Control).

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

7.10 Rejected, recovered and returned materials

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

7.10.2. The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected; if the specifications are met and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. Record of the reprocessing should be kept.

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

7.10.4. 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.

7.10.5. Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt that 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 unit of the facility in charge in accordance with a

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written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical re-processing to recover active ingredients may be possible. Any action taken should be appropriately recorded.

CHAPTER 8: QUALITY CONTROL

8.1 Principle

Quality Control is concerned with sampling, specifications and testing as well as the organization, documentation and release procedures, which ensure that the necessary and relevant tests are carried out, and 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.

8.2 General

8.2.1 Each holder of a manufacturing authorization should have a Quality Control unit. This department or unit 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 or her disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.

8.2.2 The principal duties of the head of Quality Control are summarized in Chapter 4. The Quality Control department/unit as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, keep the reference samples of materials and products, ensure the correct 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.

8.2.3 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.

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

8.3 Good quality control laboratory practices

8.3.1 Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 5. Laboratory equipment should not be routinely moved between high risk areas to avoid accidental cross- contamination. In particular, the

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microbiological laboratory should be arranged so as to minimize risk of cross-contamination.

8.3.2 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.

8.4 Documentation

8.4.1 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/unit:

- a. Specifications;
- b. Sampling procedures,
- c. Testing procedures and records (including analytical worksheets and/or laboratory notebooks).
- d. Procedures for and records of the calibration/qualification of instruments and maintenance of equipment;
- e. A procedure for the investigation of Out of Specification and Out of Trend results;
- f. Analytical reports and/or certificates
- g. Data from environmental (air, water and other utilities) monitoring, where required;
- h. Validation records of test methods, where applicable.

8.4.2 Any Quality Control documentation relating to a batch record should be retained following the principles given in Chapter 4 on retention of batch documentation.

8.4.3 For Some kinds of data (e.g. tests result, yields, and environmental controls) it recommended that records are kept in a manner permitting trend evaluation. Any Out of Trend or Out of Specification data should be addressed and subject to investigation.

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

8.5 Sampling

8.5.1 The sample taking should be done and recorded in accordance with approved written procedures that describe:

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- 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 noxious materials;
- h. The storage conditions;
- i. Instructions for the cleaning and storage of sampling equipment.

8.5.2 Reference samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process). The sampling plan used should be appropriately justified and based on a risk management approach.

8.5.3 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.

8.5.4 Further guidance on reference and retention samples is provided for under Annex 18 on Reference and Retention samples of the Guidelines on Good Manufacturing Practices on Medical Products _ Annexes, reference number: FDISM/FDIC/GDL/002.

8.6 Testing

8.6.1 Analytical methods should be validated. All testing operations described in the Marketing Authorization should be carried out according to the approved methods.

8.6.2 The results obtained should be recorded and 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 examined.

8.6.3 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;

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- 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;

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

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

8.6.6 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 recognized 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 compendia materials should be used for the purpose described in the appropriate monograph unless otherwise authorized by the National Competent Authority of the concerned entity.

8.6.7 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 unstable reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardization and the last current factor should be indicated.

8.6.8 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.

8.6.9 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

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use.

- 8.6.10 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.
- 8.6.11 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.

8.7 On-going stability program

- 8.7.1 After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate program that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile) associated with the formulation in the marketed package.
- 8.7.2 The purpose of the on-going stability program is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.
- 8.7.3 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 program of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.
- 8.7.4 The ongoing stability program should be described in a written protocol following the general rules of Chapter 6 and results formalized as a report. The equipment used for the on-going stability program (stability chambers among others) should be qualified and maintained following the general rules of Chapter 5 and Annex 21 of Guidelines on Good Manufacturing Practices on Medical Products _ Annexes, reference number: FDISM/FDIC/GDL/002.
- 8.7.5 The protocol for an on-going stability program should extend to the end of the shelf life period and should include, but not be limited to, the following parameters:
- a) Number of batch(es) per strength and different batch sizes, if applicable;
 - b) Relevant physical, chemical, microbiological and biological test methods;
 - c) Acceptance criteria;

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- d) Reference to test methods;
- e) Description of the container closure system(s);
- f) Testing intervals (time points);
- g) Description of the conditions of storage (standardized ICH/VICH conditions for long term testing, consistent with the product labelling, should be used);
- h) Other applicable parameters specific to the medicinal product.

8.7.6 The protocol for the on-going stability program can be different from that of the initial long term stability study as submitted in the Marketing Authorization dossier provided that this is justified and documented in the protocol (for example the frequency of testing, or when updating to ICH/VICH recommendations).

8.7.7 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 program (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 matrix designs may be applied if scientifically justified in the protocol.

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

8.7.9 Results of on-going stability studies should be made available to key personnel and, in particular, to the qualified 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.

8.7.10 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 10 of the GMP Guide and in consultation with the relevant competent authorities.

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

8.8 Technical transfer of testing methods

8.8.1 Prior to transferring a test method, the transferring site should verify that the test method(s) comply with those as described in the Marketing Authorization or the relevant technical dossier. The original validation of the test method(s) should be reviewed to ensure compliance

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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.

8.8.2 The transfer of testing methods from one laboratory (transferring laboratory) to another laboratory (receiving laboratory) should be described in a detailed protocol.

8.8.3 The transfer protocol should include, but not be limited to, the following parameters:

- a) Identification of the testing to be performed and the relevant test method(s) undergoing transfer;
- b) Identification of the additional training requirements;
- c) Identification of standards and samples to be tested;
- d) Identification of any special transport and storage conditions of test items;
- e) The acceptance criteria which should be based upon the current validation study of the methodology and with respect to ICH/VICH requirements.

8.8.4 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.

8.8.5 Where appropriate, specific requirements described in other guidelines should be addressed for the transfer of particular testing methods (e.g. Near Infrared Spectroscopy).

CHAPTER 9: OUTSOURCED SERVICES

9.1 Principles

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 that clearly establishes the roles and responsibilities of each party. The Quality Management System of the Contract Giver must clearly state the way that the Qualified 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 authorizations. 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 community and national law.

9.2 General

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- 9.2.1 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.
- 9.2.2 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 Authorization for the product concerned, where applicable.
- 9.2.3 Where the Marketing Authorization holder and the manufacturer are not the same, appropriate arrangements should be in place, taking into account the principles described in this chapter.

9.3 The Contract Giver

- 9.3.1 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:
- 9.3.2 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 and guidelines of GMP as interpreted in this Guide are followed;
- 9.3.3 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 Authorization 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;
- 9.3.4 The Contract Giver should monitor and review the performance of the Contract Acceptor and the identification and implementation of any needed improvement.
- 9.3.5 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 Authorized Person, that all products and materials delivered to him/her by the Contract Acceptor have been processed in accordance with GMP and the Marketing Authorization.

9.4 The contract acceptor

- 9.4.1 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.
- 9.4.2 The Contract Acceptor should ensure that all products, materials and knowledge delivered to him/her are suitable for their intended purpose.

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- 9.4.3 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.
- 9.4.4 The Contract Acceptor should not make unauthorized changes, outside the terms of the Contract, which may adversely affect the quality of the outsourced activities for the Contract Giver.
- 9.4.5 The Contract Acceptor should understand that outsourced activities, including contract analysis, may be subject to inspection by the competent authorities.

9.5 The contract

- 9.5.1 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 Authorization for the product concerned and agreed by both parties.
- 9.5.2 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).
- 9.5.3 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.
- 9.5.4 The contract should permit the Contract Giver to audit outsourced activities, performed by the Contract Acceptor or their mutually agreed subcontractors.

CHAPTER 10: COMPLAINTS AND PRODUCT RECALL

10.1 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

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be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

10.2 Complaints

- 10.2.1. 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 Qualified Person, the latter should be made aware of any complaint, investigation or recall.
- 10.2.2. 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.
- 10.2.3. 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.
- 10.2.4. 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.
- 10.2.5. All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
- 10.2.6 Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.
- 10.2.7 Special attention should be given to establishing whether a complaint was caused because of counterfeiting.
- 10.2.8 The Competent Authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, and detection of counterfeiting or any other serious quality problems with a product.

10.3 Recalls

- 10.3.1. A person should be designated as responsible for execution and co-ordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organization. If this person is not the Qualified Person, the latter should be made aware of any recall operation.
- 10.3.2 There should be established written procedures, regularly checked and updated when necessary, in order to organize any recall activity.

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

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- 10.3.4. 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.
- 10.3.5 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.
- 10.3.6. Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.
- 10.3.7. 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.
- 10.3.8. The effectiveness of the arrangements for recalls should be evaluated regularly.

CHAPTER 11: SELF-INSPECTION, QUALITY AUDITS, SUPPLIERS' AUDITS AND APPROVAL

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

- 11.1.1 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 program in order to verify their conformity with the principles of Quality Assurance.
- 11.1.2 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.
- 11.1.3 All self-inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements

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on the actions subsequently taken should also be recorded.

11.2 Items for self-inspection

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

- a. personnel;
- b. premises including personnel facilities;
- c. maintenance of buildings and equipment;
- d. storage of starting materials and finished products;
- e. equipment;
- f. production and in-process controls;
- g. QC;
- h. documentation;
- i. sanitation and hygiene;
- j. validation and revalidation program;
- 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.

11.3 Self-inspection team

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.

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11.4 Frequency of self-inspection

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.

11.5 Self-inspection report

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

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

11.6 Follow-up action

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

11.7 Quality audit

It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (see section 9, “Contract production and analysis”).

11.8 Suppliers’ audits and approval

11.8.1 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.

11.8.2 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.

CHAPTER 12: CLASSIFICATION OF INSPECTION FINDINGS

Non compliances found during inspections are classified in the following three categories:

12.1. Critical non-compliance: A non-compliance which has produced, or leads to a significant risk of producing either product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

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12.2. Major non-compliance

A non-critical deficiency:





- a. which has produced or may produce a product, which does not comply with its marketing authorization; or,
- b. which indicates a major deviation from Rwanda FDA Good Manufacturing Practice; or,
- c. which indicates a major deviation from the terms of the manufacturing authorization; or,
- d. which indicates a failure to carry out satisfactory procedures for release of batches or a failure of the authorized person to fulfil his/her required duties; or
- e. a combination of several “other” deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

12.3. Other non-compliance:

A deficiency which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice. A non-conformance may be “other” either because it is judged as minor, or because there is insufficient information to classify it as critical or major. The categorization of GMP inspection findings will be as described in PIC/S guidance on classification of GMP deficiencies, PI 040-1,3 Appendices, 1 January 2019.

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ENDORSEMENT OF THE GUIDELINES


	Author	Checked by		Approved by
Title	DM/Food and Drugs Inspection and Compliance	HoD/ Food and Drugs Inspection and Safety Monitoring	Quality Assurance Analyst	Director General
Names	Dr. Marilyn M. MURINDAHABI	Dr. Eric NYIRIMIGABO	Théogène NDAYAMBAJE	Dr. Emile BIENVENU
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Date	01/04/2023	01/04/2023	03/04/2023	06 / 04 / 2023

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ANNEX 1: Application form for GMP inspection for Finished Pharmaceutical Products Manufacturing Facilities

Format: QMS/FMT/002 Revision No: 1 Effective Date: 20 June 2022	Department/Division/Office/Unit	Food and Drugs Inspection and Compliance Division
Document Type: Form		Doc. No :FDISM/FDIC/FOM/001
 <p>RWANDA FDA Rwanda Food and Drugs Authority</p>	Title: Application form for Good Manufacturing Practice Inspection for Finished Pharmaceutical Products Manufacturing Facilities	Revision Number : 1
		Revision Date: : 29/08/2022
		Effective Date : 30/09/2023
		Review Due Date : 29/09/2025
		Ref Doc. : FDISM/FDIC/GDL/001

Applicant to fill the following sections

1. Particulars of the Applicant

Name_____

Physical Address_____

Country_____Telephone_____

E-mail_____

2. Particulars of Manufacturing Site to be Inspected

Name of site_____

Physical Address (if different from 1. above)_____

Country_____Tel_____

E-mail:_____

Note: Separate application to be filled in for each individual site

3. Contact Person on Site

Name of contact person_____

Tel: _____Fax:_____

E-mail:_____

4. Authorized Representative/Agent in Rwanda

Name of Local Technical Representative_____

Tel: _____E-mail: _____

5. Type of Medicines/ Active Pharmaceutical Ingredients

Type of medicines manufactured (*double click to check applicable box*)

Human ☐ Veterinary ☐ Human & Veterinary ☐ Herbal ☐

6. Registration of Products in Rwanda

Have you registered any products in Rwanda YES ☐ NO ☐

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Have you submitted product dossier for registration from the production line(s) applied for inspection? YES ☐ NO ☐ (If "YES", list of the products in the table below)

Trade Name (if any)	Generic Name	Dosage Form	Strength	Primary Packaging

7. Inspection Applied for (Double click to check applicable box)

- ☐ First Inspection
☐ Routine Inspection (state previous inspection datesDD/MM/YYYY)
☐ Re-inspection (after failure)
☐ Other (please specify)

8. Major Site Changes Since Last Inspection

Provide summary of changes to personnel, equipment, buildings, specifications, computer systems, products (type, range or category), suppliers and contractors since last inspection, below or as an Attachment to this form.

.....

Production Lines to be Inspected (Please tick or fill in the applicable boxes)

	Yes	No	Building Block name/ number	Number of production lines	Non β -lactam	β -lactam							
						Penicillin	Cephalosporin	Cytotomic	Homone	Human	Veterinary		

1. MANUFACTURING OPERATIONS

1.1 Sterile products

a	Aseptically prepared (list of dosage forms)												
	Large volume liquids												
	Lyophilisates												
	Semi-solids												
	Small volume liquids												
	Solids and implants												

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	Yes	No	Building Block name/ number	Number of production lines	Non β -lactam	β -lactam							
						Penicillin	Cephalexin	Cytotax	Hydrocortisone	Human	Veterinary		
f) Other aseptically prepared products (e.g. eye drops, prefilled syringes)													
g) Terminally sterilized (list of dosage forms)													
Large volume liquids													
Semi-solids													
Small volume liquids													
Solids and implants													
Other terminally sterilised prepared products													
1.2 Non-sterile products (list of dosage forms)													
a) Capsules, hard shell													
Capsules, soft shell													
Impregnated matrices													
Liquids for external use													
Liquids for internal use													
Dry powders for oral suspension													
Medicated lozenges													
Powders/granules in sachets													
Medicinal gases													
j) Other solid dosage forms (please specify)													
k) Pressurised preparations													
Radionuclide generators													
Semi-solids													
Suppositories													
Tablets													
Transdermal patches													
a) Intraruminal devices													
Veterinary premixes													

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	Yes	No	Building Block name/ number	Number of production lines	Non β -lactam	β -lactam							
						Penicillin	Cephalosporin	Cytotoxics	hormones	Human	Veterinary		
Other non-sterile medicinal products													
1.3 Biological medicinal products													
Blood products													
Immunological products													
Vaccines													
Sera													
Other immunological products													
c) Cell therapy products													
Gene therapy products													
Biotechnology products													
Human or animal extracted products													
Biosimilar products													
Other													
1.4 Other products or manufacturing activity													
Manufacture of:													
a) Herbal products													
Homoeopathic products													
Biological active starting materials													
Active pharmaceutical ingredients (chemical)													
Other													
2.0 Sterilisation of active substance/excipients/finished product:													
a) Filtration													
b) Dry heat													
Moist heat (steam, superheated water)													

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	Yes	No	Building Block name/ number	Number of production lines	Non β-lactam	β-lactam							
						Penicillin	Cephalexin	Cytosine	Hormones	Human	Veterinary		
Chemical (ethylene oxide, ozone)													
Gamma irradiation													
Electric beam													
Other													
3.0 Quality control testing													
a) Microbiological: sterility													
Microbiological: non-sterility													
c) Chemical/Physical													
Biological													
Animal													
Stability													

9. Declaration

I hereby certify that the above information is correct and apply for Good Manufacturing Practice inspection of the above-named site(s). I also commit to welcome the Rwanda FDA GMP inspectors for the inspection.

Signature of applicant..... Date.....

Name..... Designation.....

Notes:

1. Please submit a copy of the current Site Master File together with this application (refer to Guideline on preparation of a Site Master File)
2. Submit the completed application together with proof of payment of the appropriate fees, to the Director General Rwanda Food and Drugs Authority.

This box is to be completed by Rwanda FDA official only

Inspection Reference Number:		
Assigned to:	Lead GMP Inspector	Team GMP Inspector(s)

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Guidelines on Good Manufacturing Practice for Finished Pharmaceutical Products - Part 1

<i>Name</i>		
<i>Assigned by :</i> <i>Name</i>	<i>Date:</i>	<i>Title:</i> <i>signature:</i>

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ANNEX 2: Requirements for GMP Inspection Application for Finished Pharmaceutical Products & Active Pharmaceutical Ingredients Manufacturing Facilities

- a. Application letter addressed to DG of Rwanda FDA
- b. Filled and signed application form
- c. Proof of payment of prescribed fees
- d. Site master file (Annex 14, WHO Technical Report Series, No. 961) that is not older than one year from its approval date and any forecasted modifications, including legible colored printouts of water treatment, air-handling systems, including pipeline and instrumentation drawings (P&IDs) in A3 or A2 format
- e. Current manufacturing license for foreign facilities and for domestic facilities to attach application form and proof of payment of manufacturing license.
- f. Current GMP Certificate (GLP, ISO/IEC 17025 accreditation Certificate or WHO prequalification for outsourced laboratory)
- g. List of all the products (medicinal or other) manufactured on site and List of products intended for supply in Rwanda. The lists should include proprietary names and international non-proprietary names (INN).

The following additional documents may be required for GMP desk assessment, virtual inspection and temporary waiver:

- h. Copy of the recent GMP inspection report done by Local medicine regulatory authority and recent GMP inspection report from PIC/S SRA/WLAs or EAC NMRA's if available with a certified translated copy where this is not in English or French or Kinyarwanda.
- i. A copy of any warning letter or equivalent regulatory action issued by any authority to which the site provides or has applied to provide the product.
- j. Corrective and preventive action (CAPA) and proof of CAPA implementation related to the inspection report observations/deficiencies.
- k. The most recent product quality review(s) (PQR)(s) of the concerned product(s)
- l. A confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the product(s) has been performed and all matters dealt with
- m. Quality Manual/Laboratory Manual or equivalent
- n. The completed batch manufacturing/packaging record(s) including the analytical part for the most recently released batch of relevant product(s).
- o. A list of any recalls or any Market complaints registered in the last three years.
- p. Aseptic validation report (Required for products applied for that are not terminally sterilized).
- q. Contract or agreement between the FPP or API manufacturer and the outsourced testing laboratory or sterilization institution (for Outsourced testing laboratory; and Outsourced sterilization).
- r. Validation master plan.
- s. Process validation for one of the products marketed or to be registered in the country of import.

NB: The documents submitted should be sent in searchable pdf format.

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ANNEX 3: GMP Inspection Report**Rwanda Food and Drugs Authority**

Nyarutarama Plaza, KG 9 Avenue

P.O. Box: 1948 Kigali - Rwanda

Email: info@rwandafda.gov.rwwebsite: www.rwandafda.gov.rw

QMS N°: FDISM/FDIC/FMT/019

Revision No: 1

Effective Date: 30/09/2022

GMP INSPECTION REPORT

Inspection dates:	Report date:
1.0 General Information	
1.1 Inspected Site(s)	
a) Name:	
b) Physical address:	
c) City:	
d) Country:	
e) Telephone:	
f) Email address :	
g) Manufacturing license number:	
h) Contact person(s) of the inspected site or facility:	
1.2 Activities carried out by the company at the inspected site	
1.3 GMP Inspectors	
Name of Rwanda FDA Lead Inspector:	
Names of Rwanda FDA GMP Inspectors that carried out the inspection:	
1.5 Name of expert if applicable:	
1.6 Foreign National Regulatory Authority Participation:	
1.7 Type of inspection:	
1.8 Purpose of Inspection:	
1.9 Introduction	
1.10 Other manufacturing activities carried out on the site:	
1.11 Use of outside scientific, analytical, or other technical assistance in manufacture and quality control	
1.12 Previous inspections conducted by:	
1.13 Other Regulatory Authorities	
1.14 Major changes since the previous inspection	
1.15 Samples taken and results obtained (if applicable)	
2.0 Brief Report of the Inspection activities undertaken	
2.1 Scope of Inspection	
2.2 Observations and Findings	

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2.2.1 Pharmaceutical Quality System
2.2.2 Personnel
2.2.3 Premises
2.2.4 Utilities
2.2.5 Equipment
2.2.6 Documentation
2.2.7 Good practices in production
2.2.8 Good practices in quality control
2.2.9 Outsourced Activities
2.2.10 Complaints and Product Recalls
2.2.11 Self-Inspection, Quality Audits, Supplier's Audits
3.0 Summary of non-conformances to GMP
4.0 Recommendations and Conclusion
4.1 Recommendations
4.2 Conclusion – inspection outcome

Definition of Non-conformances

NAMES OF THE INSPECTORS AND SIGNATURES

End of Report

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ANNEX 4: FORMAT OF CERTIFICATE OF COMPLIANCE WITH GOOD MANUFACTURING PRACTICE



Rwanda Food and Drugs Authority

Nyarutarama Plaza, KG 9 Avenue

P.O. Box: 1948 Kigali - Rwanda

Email: info@rwandafda.gov.rw

website: www.rwandafda.gov.rw

QMS N°: FDISM/FDIC/FMT/001
Revision No: 2
Effective Date: 01/03/2023

CERTIFICATE OF COMPLIANCE WITH GOOD MANUFACTURING PRACTICE

Certificate N°:

Issue Date: DD/MM/YYYY

Valid up to: DD/MM/YYYY

This is to certify that the pharmaceutical manufacturing facility with following details:

Name of facility:

Physical address:

License number:

Country:

E-mail:

Telephone:

Has been **inspected/Assessed** by the Rwanda Food and Drugs Authority for compliance with the Good Manufacturing Practice Guidelines.

Based on the **Physical Inspection/Virtual Inspection/Desk Assessment/Reliance Pathway** carried out on DD/MM/YYYY, DD/MM/YYYY, and DD/MM/YYYY it certifies that the pharmaceutical manufacturing facility indicated on this certificate complies with Good Manufacturing Practice for dosage forms, categories and activities listed in Table below:

N°	Dosage form	Category	Activities
1.			

The responsibility for the quality of the individual batches of pharmaceutical products manufactured through this process lies with the manufacturer.

This certificate becomes invalid if the activities or the categories certified change or if the facility is no longer rated to be in compliance with Good Manufacturing Practice.

Name of the Director General

Director General

End of document

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