



RWANDA FDA
Rwanda Food and Drugs Authority

**REGULATIONS GOVERNING MANUFACTURING
PRACTICES OF MEDICAL PRODUCTS**

(Rwanda FDA law N° 003/2018 of 09/02/2018, Article 9)

REGULATION DEVELOPMENT HISTORY

DRAFT ZERO	30th August 2021
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STAKEHOLDERS CONSULTATION	30th August 2022
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Document revision history

Date of revision	Revision number	Changes made and/or reasons for revision
8/ 10/2022	0	First Issue
14/01/2022	1	Addition of three articles; Article 9: Describing Virtual/remote inspections and the criteria for applicants to be considered for these types of inspections Article 177: Describing the establishment of a scientific and advisory Committee Article 182: Describing frequency of publication of GMP compliant facilities

28/08/2022	2	<ol style="list-style-type: none"> 1. Streamlined regulation as per the recommendation from SOP on Document control ODG/QMS/SOP/001 2. Editorial Changes were done 3. Requirements for different articles were removed from the Regulations governing GMP of Medical Products and moved to the various guidelines. 4. Article 10: The article for reliance was renamed reliance/recognition since the criteria for both activities were similar. Also the word Stringent Regulatory Authority was replaced by the new terminology WLA (WHO Listed Authority) 5. Articles 11 and 12: Desk review and Virtual inspection: The criteria for Desk review and Virtual inspections were removed and inserted into the relevant guidelines. 6. Article 14: Certificate and Validity. Here the validity of the GMP certificate for both domestic and foreign sites was aligned. 7. Definition: added definition for Active Pharmaceutical Ingredient. <p>Added Articles;</p> <ol style="list-style-type: none"> 8. Article 5: obligation of manufacturer to get GMP certificate 9. Article 6: Language: This article describes the language of official documents for GMP applications. 10. Article 7: Authenticity of Documents This article describes the responsibility of the applicant to provide reliable documents and the authority of Rwanda FDA to reject documents considered not to be authentic 11. Article 8: Safe custody and confidentiality of information: This article describes the responsibility of the Authority to safeguard applicants' information. 12. Article 9: Assessment of GMP application. This article describes how applicants' dossiers are assessed and how communication is done between the Authority and the applicant
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		<p>13. Article 13: This article describes the criteria for considering applicants for temporary waivers of onsite inspection during emergency states</p> <p>14. Article 145: Warnings, suspensions, and revocations: This article details when the Authority can take these actions against an applicant.</p> <p>15. Article 146: restoration of a suspended or revoked GMP certificate. This article details when the Authority can take such actions against a suspended or revoked GMP certificate.</p> <p>16. Article 89: on Transport and delivery validation was added.</p>
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ADOPTION AND APPROVAL OF THE REGULATIONS

In EXERCISE of the powers conferred upon Rwanda Food and Drugs Authority by Article N° 9 of the Law N° 003/2018 of 09/02/2018 establishing Rwanda FDA and determining its mission, organization, and functioning, hereby ADOPTS and ISSUES these regulations No.: FDISM/FDIC/TRG/005 Rev_2 governing Good Manufacturing Practices of Medical Products on this 23/09/2022.

Dr. Emile BIENVENU
Director General





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CHAPTER ONE: GENERAL PROVISIONS

Article One: Purpose of these Regulations

These regulations govern Good Manufacturing Practices herein after abbreviated as (GMP) of Medical Products.

Article 2: Citation

These regulations may be cited as the “Regulations FDISM/FDIC/TRG/005, Governing Good Manufacturing Practices of Medical Products.”

Article 3: Scope

These regulations shall apply to GMP inspections of active pharmaceutical ingredients and finished pharmaceutical products sites that manufacture, import, export, distribute, store, sell, and that are used within and outside Rwanda for medical products.

Article 4: Definitions

In these regulations, unless the context otherwise requires, the following terms are defined as follows:

“**Authority**” means the Rwanda Food and Drugs Authority or its acronym “Rwanda FDA”, established by Law N° 003/2018 of 09/02/2018.

“**Authorization**” means the license to manufacture medical products

“**Authorized Person**” means an individual; who possesses a recognized academic degree, has extensive knowledge, training and experience, and successfully demonstrated his/her ability to solve or resolve problems relating to the subject matter.

“**Applicant**” means any legal or natural person, established within or outside Rwanda, seeking to obtain or having obtained the license to manufacture medical products;

“**Active substance starting material**” means any substance from which an active substance is manufactured or extracted;

“**Active substance intermediate**” means a substance that is obtained during the production of an active substance and which is intended for further processing;

“**Active Pharmaceutical Ingredient (API or Drug Substance)**” means 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

“Conflict of interest” means any interest in any business related to medicines declared or undeclared by the inspector that may affect or reasonably perceived to affect the quality or the result of his work or remediation;

“Critical observation” means an observation describing a situation that will most likely result in a non-compliant product or a situation that may result in immediate or latent health risk and any observation that involves fraud, misrepresentation, or falsification of products or data;

“Finished pharmaceutical product (FPP)” represents a pharmaceutical product after final release (manufacturing control release, quality control release, packaging control release).

“Good Manufacturing Practice inspector” is an inspector appointed by the Rwanda FDA who possesses qualifications and experience in pharmaceutical manufacturing, quality control, and quality assurance to conduct an inspection or assessment to verify GMP compliance of a manufacturing site on behalf of Rwanda FDA.

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

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

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

“Medical product” includes human and veterinary drug, human and animal vaccines and other biological products used in clinical as drug, herbal medicines and human and veterinary medical devices.

“Minister” means the “Person” a physical or legal entity responsible for health;

“Pharmaceutical product” means any substance capable of preventing, treating human or animal diseases and any other substance intended for administration to a human being or an animal 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 farmhouses;

“Product quality review” means regular, periodic, or rolling quality reviews of all medicinal products, including export-only products, conducted to verify the consistency of the existing process,

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the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements.

“Raw material” means any substance, reagent, or solvent which is intended for use in the production of an active substance and from which the active substance is not directly manufactured or extracted.

“Recall” means an action taken by the manufacturer to remove a medical product from the market or to retrieve any such product from any person to whom it has been supplied, because the product may be hazardous to health; fail to conform to any claim made by its manufacturer relating to its quality, safety or efficacy; or not meet the requirements under these Regulations;

“Validation” means the establishment of documented and objective evidence that the particular requirements for specific intended use can be consistently fulfilled.

“WHO Listed Authority” means a regulatory authority which is:

1. A member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015); or
2. An ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or
3. A regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015).”

CHAPTER II: GOOD MANUFACTURING PRACTICE INSPECTION

Article 5: Obligation to obtain GMP certificate

Any premise related to the manufacture of medical products must possess a valid GMP certificate issued by the Authority

No person or entity shall manufacture medical products without prior authorization from the Authority.

The GMP certificate for premises used for carrying out activities under Paragraph 1 of this article of this Regulation is granted by Authority. The requirements to obtain a GMP certificate are detailed in the relevant guidelines.

The Authority shall conduct inspection for confirmation of the compliance to this Regulation and relevant guidelines. A GMP certificate shall not be granted where the Authority finds the applicant not complying with the requirements prescribed in these regulations and relevant regulatory documents.

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Article 6: Application for GMP

A person who intends to undergo a GMP inspection shall apply to the Director General of Rwanda FDA by submitting a set of required documents: the requirements are detailed in the relevant guidelines.

Notwithstanding the provisions of paragraph one of this article, the inspection shall not be conducted at a facility that has not submitted applications for product registration.

All applications and supporting documents shall be made in English, French, or Kinyarwanda. Where some documents are submitted in a language different from English, French, or Kinyarwanda, the applicant shall submit translated copies from approved translators to expedite the review process.

Any document submitted to the Authority shall be authentic when approved by the applicant or by the authorized person.

The Authority may reject an application for GMP inspection of a medical product if it is satisfied that the submitted documents are not authentic or the integrity of data is questionable.

The Authority ensures safe custody of information related to GMP applications of manufacturing sites submitted by applicants. All information submitted shall be treated confidentially and shall not be disclosed to any third party without the written consent of the applicant.

The Authority shall, upon being satisfied by the application, conduct an assessment to verify the compliance with GMP requirements.

- 1^o The Authority may, during the assessment of the dossier, require the applicant to submit additional documents, information, data, or clarification to support the application for GMP inspection.
- 2^o Where the Authority requires additional documents, information, and data and or clarification pursuant to paragraph 1^o of this Article, the processing of the application shall not proceed until the applicant submits the additional submission.
- 3^o Where the applicant fails to submit requested information according to paragraph 2^o of this Article, within a period of ninety (90) days from the date of request, the application shall be considered withdrawn and a new application shall be required.

- 4° Pursuant to the requirements of paragraph 3° of this Article, the applicant may by giving reasons in writing request for an extension of time for submission of additional documents, information, data and or clarification requested by the Authority.
- 5° If the applicant fails to provide satisfactory responses to the requested information according to paragraph 2° of this Article for the fourth time, the application shall be withdrawn and a new application shall be required.
- 6° An application withdrawn pursuant to paragraph 3° and an application rejected pursuant to paragraph 5° of this Article shall only be considered for GMP inspection upon submission of a new application as per the requirements of these Regulations.

Article 11: Reliance and Recognition

The Authority may rely on regulatory decisions from regional, international, and WHO Listed Authority on decisions with regards to GMP inspection compliance when it deems necessary for facilities prequalified by WHO and those inspected and approved by countries or agencies with mutual recognition or cooperation agreements or partnerships with Rwanda.

The criteria for applicants to be considered for reliance and recognition shall be detailed in the Relevant guidelines.

Article 12: Desk review

After receipt of a duly filled GMP application, the Authority may conduct an assessment of the application through a desk assessment review of the documents. Dossiers for desk assessments are conducted at the discretion of the Authority. GMP applicants to be considered for GMP desk review shall have been subjected to a first inspection before being considered for desk assessment review unless otherwise determined by the Authority.

The criteria for eligibility of sites for desk review are detailed in the relevant guidelines

Article 13: Virtual Inspections

Upon receipt of a duly filled application, the Authority may conduct a voluntary virtual interactive inspection of facilities where medical products are manufactured, processed, or packed. This type of inspection is used when the Authority declares a case of force majeure on physical inspections.

Facilities for virtual interactive inspections are conducted at the discretion of the Authority and the criteria for the selection of applicants shall be described in the relevant guidelines.

Article 14: Temporary waivers of onsite inspection during emergency states

Manufacturers who have applied for new and renewal of GMP inspection but do not meet the criteria for desk review or virtual inspection shall form the short-term basis for decision making in the course of emergency situation.

Criteria for applicants to be considered for temporary waivers will be as described in the relevant guidelines.



Article 15: Certificate and Validity

Upon fulfilling the requirements, the Authority shall issue a Certificate of Good Manufacturing Practice. The certificate shall be valid for a period of three (3) years for both foreign and domestic sites.

Any critical changes to the information contained in the GMP certification circumstances, shall be notified to the Authority within a period of fifteen (15) working days.

CHAPTER III: QUALITY MANAGEMENT PRINCIPLES

Article 16: Quality Assurance System

A manufacturer shall establish, document, and implement an effective system for managing the quality of those substances during the manufacturing operations performed by them. The system shall provide for the active participation of the management and manufacturing personnel.

A manufacturing facility shall have a comprehensively designed and correctly implemented Quality Assurance System. The Quality Assurance (QA) system should be appropriate for medical product manufacturing.

Article 17: Good Manufacturing Practices

Good Manufacturing Practice as part of quality assurance shall ensure that the products are consistently produced and controlled to meet the quality standards appropriate to their intended use and requirements of marketing authorization and product specification.

Good Manufacturing Practice rules shall direct to diminish risks due to cross-contamination or mix-ups that cannot be completely prevented through the testing of final products.

Article 18: Quality control

Every pharmaceutical manufacturing facility shall have a quality control unit which is independent of the production units and any other department. The quality control laboratory shall be under the authority of a person with appropriate qualifications and experience.

Article 19: Quality control Requirements

Manufacturers shall comply with the basic requirements for quality control as detailed in the relevant GMP guidelines.

Article 20: Product quality review

The manufacturing facility shall carry out a regular, periodic, or rolling quality review of all medical products including export-only products. The review shall be conducted and documented annually, taking into account previous reviews, and shall include information in the relevant guidelines.

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A Manufacturer shall evaluate results and assess whether corrective and preventive action or any revalidation is required.

Corrective and preventive action shall be documented and shall be performed in a timely and effective manner.

Where the market authorization holder is different from the manufacturer, there shall be a technical agreement in place between the various parties with their responsibilities for producing the quality review. The authorized person responsible for the final batch certification, together with the marketing authorization holder, shall ensure that the quality review is performed promptly and is accurate.

Article 21: Quality risk management

A manufacturer shall have a systematic process for assessment, control, communication, and review of risk to the quality of a medical product. The system shall ensure evaluation of the risk based on scientific knowledge and experience with the process to protect the patient. The formality and documentation of the quality risk management process shall be based on risk level.

Article 22: Sanitation and Hygiene

Every step of medical product manufacturing shall be carried out with a high-level of sanitation and hygiene. The relevant requirements for manufacturers with regards to sanitation and hygiene are detailed in the relevant guidelines.

CHAPTER IV: PERSONNEL

Article 23: Principles governing personnel

The manufacturer shall have an approved organizational chart and ensure an adequate number of personnel having the necessary qualifications acquired through education, training, or practical experience to carry out and supervise the manufacturing of medical products.

All personnel shall be aware of the principles of good manufacturing practice that affect them and receive initial and continuing training, including hygiene

The responsible staff shall have their duties recorded in written descriptions, well understood, and have adequate authority to carry out their responsibilities.

Article 24: Key Personnel

A manufacturing facility shall at least have the following key personnel:

- 1° Head of production;
- 2° Head of quality assurance;
- 3° Head of quality control; and
- 4° Authorized person.

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A manufacturer shall formally notify the Authority of the name of qualified and authorized persons appointed by the manufacturer and the specific functions which have been delegated to such persons. Key posts shall be occupied by full-time personnel.

Article 25: Academic qualifications of key personnel

The necessary qualifications of the key personnel will be detailed in the relevant guidelines by the Authority.

Article 26: Training

A manufacturer shall provide training as per the written program for all the personnel whose duties take them into production areas or into quality control laboratories including the technical, maintenance and cleaning personnel and any other personnel whose activities could affect the quality of the product.

Every staff shall receive initial and continuous training appropriate to the duties assigned to them. Records of these training shall be kept and retrieved as per the approved training program.

Personnel working in areas where contamination is hazardous such as clean areas or areas where highly active, toxic, infectious, or sensitizing materials are handled shall be given specific training.

Article 27: Personal hygiene

Every employee whether temporary or full-time employees or non-employees such as contractors' employees, visitors, senior managers, and inspectors shall practice good sanitation and hygiene in the manufacturing area. The relevant requirements for sanitation and hygiene will be prescribed in the relevant guidelines.

CHAPTER V: PREMISES

Article 28: Layout and design

Premises shall be located, designed, constructed, adapted, and maintained to suit the operations carried out and to facilitate cleaning and maintenance, provide maximum protection against the entry of insects, birds, or any other animals, minimize the risk of errors and contamination having regard to the type and stage of manufacturing which the building and facility are used for.

Article 29: Production area

The production area shall be designed to minimize contamination. Dedicated, separate, and self-contained facilities shall be available for the production of particular products, such as penicillin, cephalosporin, and other highly sensitizing materials and biological preparations like live microorganisms, hormones, cytotoxic substances, highly active medicinal products, and non-medicinal products.

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The manufacture of technical poisons, such as pesticides and herbicides, shall not be allowed on premises used for the manufacture of medical products.

Production shall take place in areas connected in a logical order corresponding to the sequence of the operations, materials flow, personnel movement, and the requisite cleanliness levels.

Article 30: Storage area

Storage areas shall be of sufficient capacity to ensure good storage conditions and allow orderly storage of various categories of materials and products; starting and packaging materials, intermediates, bulk, and finished products, products in quarantine, released, rejected, returned, or recalled products. and that these products are maintained within acceptable temperature limits
Highly active materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire, or explosion shall be stored in safe and secure areas.

Printed packaging materials are critical to the conformity of medical products for their labeling, and special attention shall be paid to sampling and safe and secure storage of these materials.

Article 31: Weighing areas

Weighing of starting materials and the estimation of yield by weighing shall be carried out in separate weighing areas designed for that purpose with provisions for control of contamination.

Article 32: Quality control areas

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

Control laboratories shall be designed suitable for the operations carried out, with sufficient space to avoid mix-ups and cross-contamination; and with adequate and suitable storage space for samples, reference standards, if necessary, with cooling, and records.

Laboratories and production areas shall have a separate air supply. Separate air-handling units and other provisions are needed for biological, microbiological, and radioisotope laboratories.

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

Article 33: Ancillary areas

Rest and refreshment rooms shall be separate from other areas. Facilities for changing, storing clothes, washing, and toilet purposes shall be easily accessible and appropriate for the number of users. Toilets shall not communicate directly with production or storage areas.

Maintenance workshops shall be separated from production areas and in case, parts and tools are stored in the production area they shall be kept in rooms or lockers reserved for that use.

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

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CHAPTER VI: EQUIPMENT

Article 34: Design and location of manufacturing equipment

The layout, design, and location of equipment shall aim to minimize the risk of errors and permit effective cleaning and maintenance and, where appropriate sanitization to avoid cross-contamination, build-up of dust or dirt, and any adverse effect on the quality of products.

Article 35: Manufacturing equipment

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

The manufacturer shall establish written procedures for the cleaning of equipment and the subsequent verification of its suitability for use in the manufacturing process.

Control, weighing, measuring, monitoring, and testing equipment that is critical for assuring the quality of the starting materials, intermediates, and finished product shall be calibrated following written procedures and an established schedule.

Article 36: Good documentation practice

The manufacturer shall establish and maintain a documentation system and written procedures covering the manufacturing process. All documents concerning the manufacturing process shall be prepared, reviewed, approved, and distributed following written procedures.

A manufacturer shall have a good documentation practice as an essential part of the quality assurance system which is related to all aspects of GMP including The requirements of Good Documentation Practice will be detailed in the relevant guidelines

All quality-related activities carried out during the manufacturing process shall be recorded at the time they are performed. Any deviation from the written procedures referred to in Article 7(1) shall be documented and explained. Deviations affecting the quality of the active substance or preventing the active substance from meeting the specifications referred to in Article 12(1) shall be investigated, and the investigation and its conclusions shall be documented.

Article 37: Prepared document

A manufacturer shall design and make use of the documents which are free from errors and available in writing. The issuance, revision, replacement, and withdrawal of documents related to the manufacturing process shall be controlled, and records of their revision, replacement, and withdrawal shall be kept.



Article 38: Labels

A manufacturer shall ensure labels that are applied to containers, equipment, or premises are clear, unambiguous, and in the company's agreed format. Color coding to indicate status for quarantined, accepted, rejected, or cleaned shall be used.

CHAPTER VIII: PRODUCTION

Article 39: Production Operation

Every manufacturer shall have production operations that follow clearly defined procedures following manufacturing and marketing authorizations, to obtain products of the requisite quality. Production operations shall be subject to controls to monitor and adjust the production process or verify that the active substance conforms to the specifications of quality pursuant to Article 12(1). Production operations that are critical to ensure that the active substance or finished medical product meets the quality specifications referred to in Article 12(1) shall be carried out under the visual supervision of qualified personnel or subjected to an equivalent control.

Weighing and measuring of active pharmaceutical ingredients and starting materials shall be accurate and shall be conducted in a manner that does not affect their suitability for use.

Article 40: Handling Products

A manufacturer shall ensure that all productions are performed and supervised by competent people. A manufacturer shall not handle materials and products without following written procedures or instructions. A person shall not carry out operations on different products simultaneously or consecutively in the same room or area unless there is no risk of mix-up or cross-contamination.

A manufacturer shall at all times during processing, ensure all materials, bulk containers, major items of equipment, and where appropriate the rooms and packaging lines used are labelled or otherwise identified with an indication of the product or material being processed, its strength, batch number and an indication of the production stage.

A person shall not access production premises without being authorized.

A person shall not produce non-medicinal products in areas or equipment destined for the production of medical products.

Every manufacturer shall perform in-process controls within the production area without carrying any risk for the quality of the product.

Article 41: Cross contamination and bacterial contamination in Production

The manufacturer shall take special precautions when dry materials and products are used in production to prevent the generation and dissemination of dust.

A manufacturer shall make a provision for proper air control such as supply and extraction of air of suitable quality.

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Manufacturing operations shall be conducted in a manner that prevents raw materials, active substance starting materials, active substance intermediates, and active substances from being contaminated by other materials and bacterial

Notwithstanding the provision of (Article 41) above, all manufacturers shall ensure materials used are of a suitable grade to minimize health risks;

CHAPTER IX: GOOD PRACTICES IN QUALITY CONTROL

Article 42: Quality

A manufacturer cannot release materials for use or products for sale or supply until their quality has been judged satisfactory.

Article 43: Department and Laboratory

Every manufacturer shall have a separate Quality Control department separated from production and other departments and shall be under a designated person with appropriate qualifications and experience.

All laboratory operations shall be carried out following written procedures and, where necessary, recorded.

Article 44: Documentation

Quality control documents shall consist of the following important parts: specifications, sampling procedures, testing procedures, and records including analytical worksheets and laboratory notebooks, analytical reports and certificates, data from environmental monitoring, where required, validation records of test methods, where applicable, and procedures and record for calibration of instruments and maintenance of equipment.

Article 45: Sampling

The sample taking shall be done following approved written procedures

Reference samples shall be representative of the batch of materials or products from which they are taken and each batch of finished products shall be retained till one year after the expiry date.

A manufacturer shall keep finished products in their final packaging and stored under the recommended conditions.

Samples of starting materials other than solvents, gases, and water shall be retained for at least one year beyond the expiry date of the product if their stability allows.

Reference samples of materials and products shall be of a size sufficient to permit at least two full examinations.



Article 46: Starting Materials and Intermediate products

All tests shall follow the instructions given in the relevant written test procedure for each material or product and the results shall be checked by the supervisor before the material or product is released or rejected.

Article 47: Test requirements

A person shall not release starting or packaging materials unless ensured by the Head of quality control that the materials have been tested for conformity with specifications for identity, strength, purity, and other quality parameters.

Article 48: In-process control

In-process control records shall be maintained and form a part of the batch records as prescribed in these regulations.

Article 49: Finished products

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

A manufacturer shall reject products failing to meet the established specifications or any other relevant quality criteria.

A manufacturer may perform reprocessing only if the product meets all specifications and other quality criteria before its acceptance and release.

Article 50: Batch record review

Every manufacturer shall review production and control records and any divergence or failure of a batch to meet its specifications shall be thoroughly investigated and recorded.

Article 51: Stability Studies

The manufacturer shall monitor the stability of the medicinal product according to a continuous appropriate program.

A manufacturer shall perform stability studies on reconstituted products during product development and if necessary may be monitored on an ongoing basis.

A manufacturer shall describe the ongoing stability program in a written protocol.

Article 52: Reagents and Culture media

A manufacturer shall record upon receipt or preparation of all reagents and culture media.

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Reagents made up in the laboratory shall be prepared and appropriately labelled according to written procedures.

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

Article 53: Reference Standards

Every manufacturer shall ensure the availability of reference standards in the form of official reference standards such as the recognized Pharmacopeia.

All in-house reference standards shall be standardized against an official reference standard/

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

CHAPTER X: CONTRACT

Article 54: Contractual Arrangements

A manufacturing operation or an operation linked thereto which is to be carried out on behalf of the manufacturer of the medical product by another party 'the contract manufacturer' shall be the subject of a written contract. The written contract shall establish the duties of each party and the contract must clearly state how the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises the full responsibility.

Article 55: Obligation of Parties to contract

The contract shall clearly define the responsibilities of the contract manufacturer concerning Good Manufacturing Practices.

The manufacturer of the products shall control those operations carried out by a contract manufacturer to comply with Good Manufacturing Practices.

Article 56: Essential requirements of the contract

Manufacturing shall be undertaken by a manufacturer who holds a manufacturing authorization. The contract shall describe clearly who is responsible for purchasing, testing, and releasing materials and for undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis.

A contract shall not pass to a third party any of the work entrusted without the prior evaluation and approval of the original parties. The contract shall refrain from any activity that may adversely affect the quality of the product manufactured and analyzed.



CHAPTER XI: COMPLAINTS HANDLING AND PRODUCT RECALL

Article 57: Complaints handling

Every manufacturer shall carefully review according to written procedures all complaints and other information concerning potentially defective products.

A manufacturer shall take immediate corrective actions to address the root cause of the problem, and actions should be taken to prevent it from recurring and shall regularly review complaints records.

The Manufacturer shall inform the Authority if there is an action taken following possibly faulty manufacturing, product deterioration, or any other serious quality problems with a product without delay.

Article 58: Product recall

A manufacturer shall not sell, offer, or expose for sale any product subjected to recall.

Every manufacturer shall appoint a person responsible for the execution and coordination of recalls who shall be also independent of the sales and marketing department.

There shall be established written procedures for the organization of any recall activity.

Every manufacturer shall be capable of initiating promptly recall operations at least down to the level of a hospital or pharmacy or any authorized drug outlet.

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

A manufacturer shall have a documented procedure for self-inspection.

Article 60: Items for self-inspection

There shall be established a program for self-inspection to provide a minimum and uniform standard of Good Manufacturing Practice requirements.

Article 61: Self-inspection team

Management shall appoint a self-inspection team consisting of experts in their respective fields and familiar with Good Manufacturing Practices.

Article 62: Frequency of self-inspection

The frequency at which self-inspections are conducted may depend on company requirements but shall preferably be at least once a year and described in the procedure.



Article 63: Self-inspection report

A report shall be made after a self-inspection with inspection findings, evaluation, conclusion, and recommended corrective actions.

Article 64: Follow-up action

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

Article 65: Audits, and approval

The person responsible for Quality Control together with other relevant departments shall have the responsibility of evaluating, and approving vendors and suppliers that meet established specifications before being included in the approved supplier's list.

CHAPTER XIII: MANUFACTURE OF STERILE MEDICINAL PRODUCTS

Article 66: Sterile medicinal products

A manufacturer of sterile products shall be subjected to special requirements to minimize risks of microbiological contamination, and particulate and pyrogenic contamination detailed in the relevant guidelines.

A manufacturer shall strictly follow carefully established and validated methods of preparation and procedure.

Only a minimum number of personnel required shall be present in clean areas and this is particularly important during aseptic processing.

The manufacturing of sterile products shall be carried out in clean areas Clean areas for the manufacture of sterile products shall be classified into four clean grades according to the required characteristics of the environment as follows: Grade A, Grade B, Grade C, and D.

The areas for operations such as blow, fill and sealing technologies, terminally sterilized products, and aseptic preparation shall be monitored during operation in to control the particulate cleanliness of the various grades.

Article 67: Isolator technology

Isolators shall be introduced only after appropriate validation and take into account all critical factors of isolator technology. Monitoring shall be carried out routinely.

Article 68: Personnel

Only a minimum number of personnel required shall be present in clean areas and this is particularly important during aseptic processing.

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Article 69: Premises

In clean areas, sinks and drains should be prohibited in grade A and B areas used for aseptic manufacture, and in other areas, air brakes should be fitted between the machine or sink and the drains.

Both airlock doors should not be opened simultaneously and an interlocking system or a visual or audible warning system should be operated to prevent the opening of more than one door at a time.

A filtered air supply shall maintain positive pressure and airflow relative to surrounding areas of a lower grade under all operational conditions and shall flush the area effectively.

Adjacent rooms of different grades shall have a pressure differential of 10-15 Pascal guidance values.

Article 70: Equipment

All equipment such as sterilizers, air handling, and filtration systems, air vent and gas filters, water treatment, generation, storage, and distribution systems shall be subject to validation, and planned maintenance, and their return to use should be approved.

Water for injections shall be produced, stored, and distributed in a manner that prevents microbial growth, for example by constant circulation at a temperature above 70°C.

Article 71: Sanitation

The sanitation of clean areas shall be done following a written program and where disinfectants are used, more than one type should be employed. Monitoring must be undertaken regularly to detect the development of resistant strains.

Article 72: Processing

Preparations of microbiological origin shall not be made or filled in areas used for the processing of other medicinal products.

Vaccines of dead organisms or bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products.

Process simulation tests shall be performed at least twice a year per shift and process.

The manufacturer should establish alert and action limits and any contamination should be investigated.

Water sources, water treatment equipment, and treated water shall be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins and records shall be maintained of the results of the monitoring and any action taken.

Non-combustible gases shall be passed through microorganism retentive filters.

The efficacy of any new procedure shall be validated and the validation verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.



Article 73: Processing Sterilization

All sterilization processes shall be validated and records should be kept and they should be approved as part of the batch release procedure. The requirements for each method of sterilization and sterility testing are detailed in the relevant guidelines.

CHAPTER XIV: BIOLOGICAL MEDICINAL PRODUCTS FOR HUMAN USE

Article 74: Biological medicinal products

The manufacture of biological medicinal products shall involve certain specific considerations arising from the nature of the products and the processes. Control of biological medicinal products shall involve biological analytical techniques which have greater variability than physical-chemical determinations.

In-process controls shall take great importance in the manufacture of biological Medicinal products.

Article 75: Personnel

The manufacturing establishment and its personnel shall be under the authority of a person who has been trained in the techniques used in manufacturing biological substances and who possesses the scientific knowledge upon which the manufacture of these products is based.

Article 76: Premises and Equipment

The design building and construction materials shall permit maintenance in a clean and sanitary condition free from insects and vermin.

Facilities for animal care shall include isolation units for quarantine of incoming animals and provision for vermin-free food storage.

Article 77: Animal Quarters and Care Production

The building shall be located, designed constructed, adapted, and maintained to suit the operations to be carried out therein.

CHAPTER XV: VALIDATION AND QUALIFICATION

Article 78: Validation

A manufacturer shall identify validation work needed to prove control of the critical aspects of their operations.

Manufacturers shall use a risk assessment approach to determine the scope and extent of validation.

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Article 79: Validation activities

Every manufacturer shall plan all validation activities a validation master plan or equivalent document.

Article 80: Documentation

A written protocol shall be established to specify how qualification and validation will be conducted. Any changes to the plan as defined in the protocol shall be documented with appropriate justification. After completion of a satisfactory qualification, a formal release for the next step in qualification and validation shall be made as written authorization.

Article 81: Design Qualification

The first element of the validation of new facilities, systems, or equipment shall be design qualification. The compliance of the document with Good Manufacturing Practice shall be demonstrated and documented by the manufacturer.

Article 82: Installation Qualification

Installation qualification shall be performed on new or modified facilities, systems, and equipment.

Article 83: Operational Qualification

Operational qualifications shall follow installation qualification.

Article 84: Performance Qualification

Performance qualification shall follow successful completion of installation qualification and operating equipment.

Article 85: Qualification of established facilities, systems, and equipment

Evidence shall be available to support and verify the operating parameters and limits for the critical variables of the operating equipment. Calibration, cleaning, preventative maintenance, operating procedures, and operator training procedures and records shall be documented.

Article 86: Process validation

Process validation shall be categorized as prospective validation, concurrent validation; and retrospective validation.

Facilities, systems, and equipment to be used shall have been qualified and analytical testing methods shall be validated. Staff taking part in the validation work shall have been appropriately trained.

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Facilities, systems, equipment and processes shall be periodically evaluated to verify that they are still operating validly.

Article 87: Cleaning validation

Cleaning validation shall be performed to confirm the effectiveness of a cleaning procedure.

Article 88: Transport and delivery validation

The manufacturer shall be responsible for qualification of all transportation or vehicles used in the transportation of medical products to ensure medical product safety and quality. The requirements for transport and delivery qualification are described in the relevant guidelines.

Article 89: Change control

Written procedures shall be in place to describe the actions to be taken if a change is proposed. All changes that may affect product quality or reproducibility of the process shall be formally requested, documented, and accepted.

The likely impact of the change of facilities, systems, and equipment on the product shall be evaluated, including risk analysis. The need for, and the extent of, requalification and revalidation shall be determined.

Article 90: Revalidation

Facilities, systems, equipment, and processes, including cleaning, shall be periodically evaluated to confirm that they remain valid, updated and maintained.

CHAPTER XVI: DIGITALIZED SYSTEM

Article 91: Computerized systems

In case computerized systems are used, there shall be no resultant decrease in product quality or quality assurance.

Article 92: Validation

Before a system using a computer is brought into use, the computer system shall be validated.

Article 93: Handling of system

A written detailed description of the system shall be produced including diagrams as appropriate and kept up to date.

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The user of computerized software shall take all reasonable steps to ensure that it has been produced following a system of quality assurance.

Data shall only be entered or amended by authorized persons. There shall be a defined procedure for the issue, cancellation, and alteration of authorization to enter and amend data, including the changing of personal passwords.

Data shall be secured by physical or electronic means against willful or accidental damage. Stored data shall be checked for accessibility, durability, and accuracy.

CHAPTER XVII: WATER FOR PHARMACEUTICAL USE

Article 94: Pharmaceutical water system

Pharmaceutical water production, storage, and distribution systems shall be designed, installed, commissioned, validated, and maintained to ensure the reliable production of water of appropriate quality. The system shall not be operated beyond its designed capacity.

Article 95: Water quality specifications

Companies wishing to supply multiple markets shall set specifications that meet the strictest requirements from each of the relevant pharmacopeias.

Article 96: Drinking water

Drinking water shall be supplied under continuous positive pressure in a plumbing system free of any defects that could lead to contamination of any product.

Article 97: Purified water

Purified water shall be prepared from a potable water source as a minimum quality feed-water, should meet the pharmacopoeia specifications for chemical and microbiological purity, and should be protected from re-contamination and microbial proliferation.

Article 98: Highly purified water

Highly purified water shall be prepared from portable water as minimum quality feed water. This grade of water shall meet the same quality standard as water for injections including the limit for endotoxins.

Article 99: Water for injections

Water for injections shall be prepared from potable water as minimum-quality feed water.



Article 100: Other grades of water

When a specific process requires a special non-pharmacopeia grade of water, they shall be specified and at least satisfy the pharmacopeia requirements of the grade of pharmaceutical water for the use required for the type of dosage form or process step.

Article 101: Application of specific waters to processes and dosage forms

The grade of water used shall take into account the nature and intended use of the intermediate or finished product and the stage in the manufacturing process at which the water is used.

Article 102: Water purification methods

The chosen water purification method, or sequence of purification steps, shall be appropriate to the application in question. Factors to consider when selecting the water treatment methods will be detailed in the relevant guideline.

Article 103: Production of drinking-water

Typical processes employed at a user plant or by a water supply authority shall include:

- 1^o Filtration;
- 2^o Softening;
- 3^o Disinfection or sanitization such as bi-sodium hypochlorite (chlorine) Injection;
- 4^o Iron (ferrous) removal;
- 5^o Precipitation; and
- 6^o Reduction of specific inorganic /organic materials.

Article 104: Production of purified water

Any appropriately qualified purification technique or sequence of techniques shall be used to prepare purified water.

Article 105: Production of highly purified water

Any appropriately qualified purification technique or sequence of techniques shall be used to prepare highly purified water where needed.

Article 106: Production of water for injections

Distillation shall be the preferred technique and it is considered a more robust technique based on phase change, and in some cases, high-temperature operation of the process equipment.

The following shall be considered when designing a water purification system:

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- 1^o The feed-water quality;
- 2^o The required water quality specification;
- 3^o The optimum generator size to avoid the over-frequent start/stop cycling;
- 4^o Blow-down and dump functions; and
- 5^o Cool-down venting to avoid contamination ingress.

Article 107: Water purification, storage and distribution systems

The water storage, and distribution shall work in conjunction with the purification plant to ensure consistent delivery of water to the user points, and to ensure optimum operation of the water purification equipment. The storage and distribution system shall be considered a key part of the whole system, and shall be designed to be fully integrated with the water purification components of the system.

Article 108: Materials that come into contact with systems

The materials that come into contact with water for pharmaceutical use, including pipework, valves, fittings, seals, diaphragms, and instruments, shall be selected as per relevant requirements as detailed in the guidelines.

Article 109: System sanitization and bioburden control

Water treatment equipment, storage and distribution systems used for purified water, highly purified water, and water for injection shall be provided with features to control the proliferation of microbiological organisms during normal use, as well as techniques for sanitizing or sterilizing the system after intervention for maintenance.

Article 110: Storage vessel requirements

The design and size of the vessel shall take into consideration the following elements; Capacity; and contamination control considerations.

Article 111: Water distribution pipework

The distribution of purified water, highly purified water, and water for injection shall be accomplished using a continuously circulating pipework loop. The proliferation of contaminants within the storage tank and distribution loop shall be controlled. Filtration shall not be used in distribution loops or at take-off user points to control bio-contamination.

Article 112: Start-up and commissioning of water systems

The commissioning work shall include setting to work, system setup, and controls loop tuning and recording of all system performance parameters. If it is intended to use or refer to commissioning

data within the validation work, then the quality of the commissioning work and associated data and documentation shall be commensurate with the validation plan requirements.

Article 113: Qualification of a water system

Purified water, highly purified water, and water for injection systems are all considered to have a direct impact on quality critical systems and shall be qualified. The qualification shall follow the validation convention of design review or design qualification, installation qualification, operational qualification, and performance qualification.

A three-phase approach shall be used to satisfy the objective of proving the reliability and robustness of the system in service over an extended period.

Article 114: Performance Qualification: Phase I

A test period of 2 to 4 weeks shall be spent monitoring the system intensively. During this period the system shall be operated continuously without failure or performance deviation.

Article 115: Performance Qualification: Phase 2

A further test period of 2 to 4 weeks shall be spent carrying out further intensive monitoring while deploying all the refined SOPs after the satisfactory completion of phase I. The sampling scheme shall be generally the same as in phase I; water can be used for manufacturing purposes during this phase.

Article 116: Performance Qualification: Phase 3

Phase 3 typically shall run for 1 year after the satisfactory completion of phase 2.

Water can be used for manufacturing purposes during this phase which has the following objectives and features:

- 1^o Demonstrate extended reliable performance;
- 2^o Ensure that seasonal variations are evaluated; and
- 3^o The sample locations, sampling frequencies, and tests shall be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2.

Article 117: Continuous system monitoring

After completion of phase 3 of the qualification program for the water for pharmaceutical use system, a system review shall be undertaken. A routine monitoring plan shall be established based on the results of phase 3.



Article 118: Maintenance of water systems

Water for Pharmaceutical use systems shall be maintained following a controlled, documented maintenance program

Article 119: System reviews

Water for Pharmaceutical use systems shall be reviewed at appropriate regular intervals. The review team shall comprise representatives from engineering, Quality Assurance, operations, and maintenance.

CHAPTER XVIII: HEATING, VENTILATION, AND AIR-CONDITIONING SYSTEMS FOR NON-STERILE PHARMACEUTICAL DOSAGE FORMS

Article 120: Heating, ventilation, and air-conditioning system

Every pharmaceutical dosage form shall be manufactured under an installed and retained heating, ventilation, and air-conditioning system to ensure that the quality of medical products is not compromised

The system shall be well-designed to provide comfortable conditions for operators.

Article 121: Prevention of contamination and cross-contamination

There shall be prevention of contamination and cross-contamination as an essential design to be inspected by the Authority within the system of heating, ventilation and air-conditioning of the Manufacturing site.

The design of the heating, ventilation and air-conditioning system shall be shown in the drawings of the pharmaceutical manufacturing plant.

Article 122: Temperature, relative humidity and ventilation

The system temperature, relative humidity, and ventilation shall not adversely affect the quality of medical products during their manufacture and storage or the accurate functioning of equipment.

CHAPTER XIX: QUALITY RISK MANAGEMENT

Article 123: Quality Risk Management

The Quality Risk Management methodology shall:

- 1^o Be dynamic, iterative, and responsive to change; and
- 2^o Systematically analyze products and processes to ensure the best scientific rationale is in place to improve the ability to succeed;

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3^o Identify important knowledge gaps associated with processes that need to be understood to properly identify risks and provide a communication process that will best interface with all relevant parties involved;

Facilitate the transfer of process knowledge and product development history to ease product progression along the life-cycle and to supplement already available knowledge about the product;

Article 124: Duties and ability of the personnel

A manufacturer shall keep personnel with specific knowledge and expertise available at the manufacturing site to ensure effective planning and completion of Quality Risk Management activities:

Article 125: Risk assessment of the product

At any time when the risk assessment of the product is conducted, the manufacturer shall need to determine the safety and efficacy of the product in addition to its quality concerns and where applicable; all the risks that may be reasonably expected to occur in the activity under evaluation shall be listed for verification by inspectors.

Article 126: Assessment of products

Where risk assessments and controls are made to the product for an ongoing activity, it shall:

- 1^o Be subject to periodic and frequency of review;
- 2^o Be appropriate for the nature of the activity.

Specific corrective actions shall be developed to prevent the recurrence of instances where there have been deviations from established risk control measures, especially for high risks.

The actions shall ensure that the risk is brought under control as soon as possible in compliance with the established deviation handling procedures; and specific corrective actions shall be developed in advance for each identified risk including what is to be done when a deviation occurs, who is responsible for implementing the corrective actions, and that a record will be kept and maintained of the actions taken.

Article 127: Manufacturer to conduct Risk review and keep records

Every manufacturer shall have appropriate systems in place to ensure that the output of the Quality Risk Management process is periodically monitored and reviewed, as appropriate, to assess new information that may impact the original decision.

Records and documents associated with risk review shall be signed and dated by the person carrying out the review and by a responsible official of the quality unit of the company.

Article 128: Verification of Quality Risk Management process and methodologies

A manufacturer shall carry on frequency verification to confirm the proper functioning of the Quality Risk Management process including:

- 1^o Review of the Quality Risk Management process and its records;
- 2^o Confirmation that identified risks is kept under control.

Initial verification of the planned Quality Risk Management activities shall be considered necessary to determine whether the system is scientifically and technically sound to effectively control identified risks.

Article 129: Risk communication and documentation

Communication of the Quality Risk Management process shall be made to stakeholders engaged in both the data collection process for the risk assessment and the decision-making for risk control to ensure commitment and support for Quality Risk Management.

The output of the Quality Risk Management process and associated risk analysis justifying the approach shall be documented and endorsed by the company's quality unit and management. The information shall be communicated to stakeholders for their support.

Article 130: Mitigation Plans

A manufacturer shall have risk mitigation plans in place to apply where any risk to patient safety is posed or where multiple failures in systems occur, the mitigation plans shall be sufficiently robust to cover posed risks.

Article 131: Training and education

Every company or factory shall:

- 1^o Train employees to understand Quality Risk Management,
- 2^o Possess the skills necessary to apply it properly, and be appropriately resourced to enable the effective practice of the Quality Risk Management principles;
- 3^o Develop a training program to support Quality Risk Management activities, working instructions and procedures drawn up to clarify the strategy and define the tasks of all involved in these activities; and
- 4^o Provide specific training as required to enhance awareness to staff responsible for managing and reviewing risks who shall also receive formal training in the relevant procedures.

Article 132: Responsibilities of Pharmaceutical manufacturer

A pharmaceutical manufacturer shall form teams for conducting a Quality Risk Management process which shall involve experts in the appropriate areas in addition to individuals who are knowledgeable on the subject.



The extent of involvement and responsibility accountability shall be documented in a technical agreement or other equivalent documents between the individual and the pharmaceutical company. In the case of authorized person, it shall be important that a company's internal procedures are clear on where the responsibility lies for final approval of risk acceptance documents. All effective matrix team leadership shall be required to take responsibility for coordinating Quality Risk Management. The head and team shall need to identify critical resources to progress the Quality Risk Management activities, and also specify a timeline, deliverables, and appropriate levels of decision-making for the Quality Risk Management process.

Article 133: Complaint handling and investigation

Handling and investigation of quality complaints shall be done following written Standard Operating Procedures available at the site. The scope and depth of the investigation including whether a desk review or on-site inspection will be done shall be based on a risk assessment made.

Article 134: Duty of Inspectors

Inspectors shall assess whether a manufacturer has appropriate skills, scientific knowledge as well as product and process knowledge for the Quality Risk Management procedure being inspected. This shall include, but is not limited to:

- 1^o A general approach to both planned and unplanned risk assessment and includes scope, responsibilities, controls, approvals, management systems, applicability, and exclusions;
- 2^o Personnel with appropriate qualifications, experience, and training including their responsibilities concerning quality risk management being clearly defined;
- 3^o Senior management should be involved in the identification and implementation of quality risk management principles within the company;
- 4^o The risk management procedures for each area of application should be clearly defined;
- 5^o Quality assurance principles shall be applied to quality risk management-related documentation such as review, approval, implementation, and archiving.

CHAPTER XX: ACTIVE PHARMACEUTICAL INGREDIENTS

Article 135: Active pharmaceutical ingredients

Every manufacturer shall design Active Pharmaceutical Ingredients referred to as "Active pharmaceutical ingredients".

Starting Material" as raw material, intermediate, can be used in the production of active pharmaceutical ingredients

The manufacturer shall designate and document the rationale for the point at which production of the active pharmaceutical ingredients starting begins.

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CHAPTER XXI: WASTE MANAGEMENT FOR MEDICINAL PRODUCT MANUFACTURERS AND INSPECTION

Article 136: Hazardous Waste

A manufacturer shall ensure that hazardous waste pharmaceuticals involving antineoplastic agents, radioactive agents, hormonal products, penicillin, and solvents from the laboratory shall be segregated and managed.

Article 137: Non-hazardous Pharmaceutical waste

Non-Hazardous Pharmaceutical Waste comprised of all other pharmaceutical waste that is not stated above shall be controlled subject to any environmental regulation on the force.

In case of liquid effluent which poses a safety or contamination risk, the effluent shall be treated in Effluent Treatment Plant before being discharged to any municipal drain.

CHAPTER XXII: CONDUCTING INSPECTIONS

Article 138: Application for GMP Inspections

The Authority shall inspect to ensure that:

- 1^o Manufacturers comply with the requirements of these Regulations; and
- 2^o Non-conformances against these Regulations are identified.

The Authority upon receipt of duly filled application dossiers and appropriate proof of payment of GMP inspection fees from the applicant will schedule an inspection date for the premises as determined.

All applicants that were found to be non-compliant during GMP inspection, shall provide a CAPA report within an identified period. The applicant will pay re-inspection fees to the Authority before being re-inspected when CAPA has been submitted three times and was found unsatisfactory by the Authority.

The Authority may serve a notice to manufacturers requiring them to furnish it with such information concerning their compliance with these Regulations as shall be specified in the notice.

Any manufacturer that receives an order or information following paragraph 3 of this article shall provide the information requested within the period specified in the notice.

In the event of any serious adverse event or any serious adverse reaction or suspicion thereof, of the product manufactured by the manufacturer, the Authority shall request such information or conduct such inspections following this regulation as shall be considered appropriate.



Article 139: Appointment of inspectors

The Authority shall appoint inspectors to inspect domestic and overseas manufacturing facilities where medical products used in Rwanda are manufactured. The inspectors shall have the relevant qualification in terms of academic education, training, and experience to effectively take part in the inspection of medical products manufacturing facilities.

Article 140: Conflict of Interest

To avoid any conflict of interest, all inspectors will declare any conflict of interest upon appointment.

Article 141: Powers of inspectors

To enforce compliance for conducting inspections, an inspector appointed following these regulations shall, upon production of evidence that he/she is so authorized, have the right:

- 1^o During working hours to enter any premises, other than premises used only as a private dwelling house, where he/she has reason to believe it is necessary to visit, including any premises of any person who carries out any of the activities referred to in these Regulations;
- 2^o To carry out at those premises during the visit, inspections, examinations, tests, and analyses as he/she considers necessary;
- 3^o To require the production of; to inspect and take copies of; extracts from, any book, document, data or record in whatever form it is held at, or in the case of computer data or records accessible at the premises;
- 4^o To take possession of any samples for examination and analysis and any other article, substance, book, document, data or record in whatever form they are held at, or in the case of computer data or records accessible at, the premises;
- 5^o To question any person whom, he/she finds at the premises and has reasonable cause to believe can give relevant information;
- 6^o To require any person to afford he/she such assistance as considered necessary concerning any matter within that person's control, to which that person has responsibilities; and
- 7^o To require, as considered necessary, any person to afford he/she such facilities as may reasonably require that person to afford. Nothing in this paragraph shall be taken to compel the production by any person of a document of which he/she would on grounds of legal professional privilege be entitled to withhold production.
- 8^o To perform his or her duties with respect, confidentiality, humility and with integrity.

The inspector is required to collaborate with the local administration and a representative of the public investigation body of the area to enter premises that are closed or unoccupied. Together they shall provide written proof of the premises to be inspected before the inspection. The written proof stated under this paragraph shall be signed and where necessary photos of the premises must be added to prove the premises were closed or unoccupied before physical inspection. The written proof shall be part of the report that must be submitted to the Authority.

Cover



An inspector entering premises under provisions of paragraph 1 of this Article, may take with him/her when entering those premises such equipment as may appear to be necessary and any person who is authorized by the Authority to accompany him/her on that visit.

Upon exiting any premises which an inspector is authorized to enter by a warrant under paragraph 2 of this Article, he/she shall, if the premises are unoccupied, or the occupier is temporarily absent, leave the premises as effectively secured against trespassers as he/she found them.

Where, pursuant to provisions of point 4⁰ of this article, when an inspector takes possession of any article, substance, book, document, data, or record, he/she shall leave at the premises with a responsible person, or if there is no such person present on the premises, leave in the premises in a prominent

position, a detailed statement giving particulars of what was taken.

Where, pursuant to provisions of point 4⁰ of this article, an inspector takes a sample for analysis, the Authority may make such arrangements for analysis of that sample as considered appropriate.

Article 142: Inspections

Upon arrival at the inspection site, the inspectors shall convene a pre-inspection meeting with the inspected and the leading inspector shall preside over the meeting.

The inspectors shall walk through every section of the plant, ask questions and carefully review records and areas of the manufacturing sites, and may take photographs to support their observations. The inspectors shall list down all non-compliance findings in a document such as the Memorandum of Findings that conforms to the Authority's standards.

After inspection, the inspectors shall convene a closing meeting highlighting issues observed during inspection and sign a memorandum form with the inspected.

Article 143: Establishment of a scientific and advisory committee

The Authority may establish a scientific and advisory committee comprising internal and/or external experts from different fields and scientific research to advise the Authority on Good Manufacturing Practices inspection matters.

Article 144: Joint Inspection

The Authority may participate in joint inspection with regulatory Authorities from other countries such as the East African Partner States and unless notified, these regulations shall apply.

CHAPTER XXIII: FINAL PROVISIONS

Article 145: Warnings, Suspensions, and revocations

A warning letter, suspension, or revocation of the manufacturing authorization shall be granted to the applicant where the Authority finds the applicant not complying with any of the requirements or conditions in these Regulations; or has ceased to be fit to carry on the regulated activities.

Cover

The Authority shall suspend or revoke a GMP certificate of a facility if the facility contravenes the following GMP requirements:

Conditions for suspension

- 1^o Any of the conditions under which the GMP certificate was issued no longer exist
- 2^o The circumstances under which the approval was given no longer exist

Conditions for issuing of warning letter

- 3^o The information on which the approval was given is later found to be false,

Conditions for revocation

- 4^o Repeated violation of the regulatory administrative sanction or decision.

Where the GMP certificate is suspended or revoked, the Authority shall issue a notice to the management of the facility.

The Authority shall take steps including suspension of registered medicinal product or closure to ensure that the manufacturing activity is stopped until otherwise decided by the Authority.

Measures towards enforcing this article may include the publication of the Rwanda FDA's action on its website and other relevant media.

Where the GMP certificate is revoked, the applicant must wait a determined period specified in the relevant guidelines before he/she is eligible to reapply for possible GMP certification, The GMP certification shall be re-instated only if the applicant meets the relevant requirements.

Article 146: Restoration of a suspended or revoked GMP certificate

Pursuant to article 146, the Authority may, upon satisfaction that the reasons for suspension or revocation of GMP certificate have been corrected or if such reason for suspension/ revocation was unfounded.

Article 147: Appeals

An authorization holder or applicant may notify the Authority of his or her grounds when he/she:

- 1^o Objects to any suspension or revocation of the authorization, or any notice served;
- 2^o Objects to the refusal of authorization or the imposition of any condition may notify the Authority of his desire to make written representations to, or be or appear before and be heard by, a person appointed by the Authority for that purpose.

Any person aggrieved by a decision of the Authority may appeal to the Authority for review of a decision within 30 working days from the date of the notice. The Authority shall within 30 working days from the date of appeal review the appeal and make its own decision whether to vary, reject or keep its own decision.

Where the Authority receives notification pursuant to provisions of paragraph 1 of this Article, the Authority shall appoint a person to consider the matter. The person appointed shall determine the procedure to be followed concerning the consideration of any objection.

The person appointed by the Authority, shall consider any written or oral objections made by the objector or complainant in support of its objection, and shall make a recommendation to the Authority.

A recommendation shall be made in writing to the Authority, and a copy of it shall be sent to the complainant concerned, or to its nominated representative. The Authority shall take into account any recommendation made within fourteen days of receipt of such recommendation.

The Authority shall inform the complainant whether it accepts the recommendation and, if not, the reasons for its decision.

If a person is dissatisfied with a decision after review, he/she may appeal to the supervising Authority of Rwanda FDA or the Minister of Health whose decision shall be final.

Article 148: Administrative sanctions

Any person who contravenes the provisions of these Regulations shall be liable to the penalties prescribed in the Authority's regulation related to regulatory service tariff/fee and other applicable sanctions.

The Authority shall take the following regulatory actions as recommended by the inspectors when making decisions on the outcome of inspections.

1^o Minor non-compliances

- a) Corrective action within a given timeframe
- b) Request for compliance report

2^o Major non-compliances

- c) issue warning letter
- d) request for corrective action within a given timeframe
- e) temporary withdrawal or suspension of marketing authorization
- f) Request for comprehensive compliance report
- g) Follow-up inspection to verify the implementation of corrective action within a given timeframe

3^o Critical non-compliances include

- h) Permanent withdrawal of marketing authorization in case of registered products.
- i) Suspension of marketing authorization in case of registered products
- j) Refusal to grant marketing authorization for a new application.



Article 149: Publication of GMP-compliant facilities

A pharmaceutical manufacturing facility that is granted with a certificate of compliance to GMP shall be published on monthly basis on the Rwanda FDA website, and on any other media, as the Authority may decide from time to time

Article 150: Commencement

These Regulations shall enter into force upon their approval and publication on the Authority's website.

End of Document
