



**REGULATIONS GOVERNING GOOD MANUFACTURING  
PRACTICES OF MEDICAL PRODUCTS**

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

**RWANDA FDA**  
Rwanda Food and Drugs Authority

## REGULATION DEVELOPMENT HISTORY

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<b>INTERNAL VALIDATION BY RWANDA FDA</b>	10 <sup>th</sup> September 2021
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<b>ADOPTION OF STAKEHOLDERS' COMMENTS</b>	17 <sup>th</sup> September 2021
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## DOCUMENT REVISION HISTORY

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04/01/2022	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

**RWANDA FDA**  
Rwanda Food and Drugs Authority



**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 the Rwanda FDA and determining its mission, organization and functioning, hereby adopts and issues these Regulations N° CBD/TRG/024 Rev. N° 1, Governing Good Manufacturing Practices of medical Products, made this 14<sup>th</sup> day of February 2022

**Dr. Emile BIENVENU**  
**Director General**

*E. Bienvenu*  
*11/02/2022*



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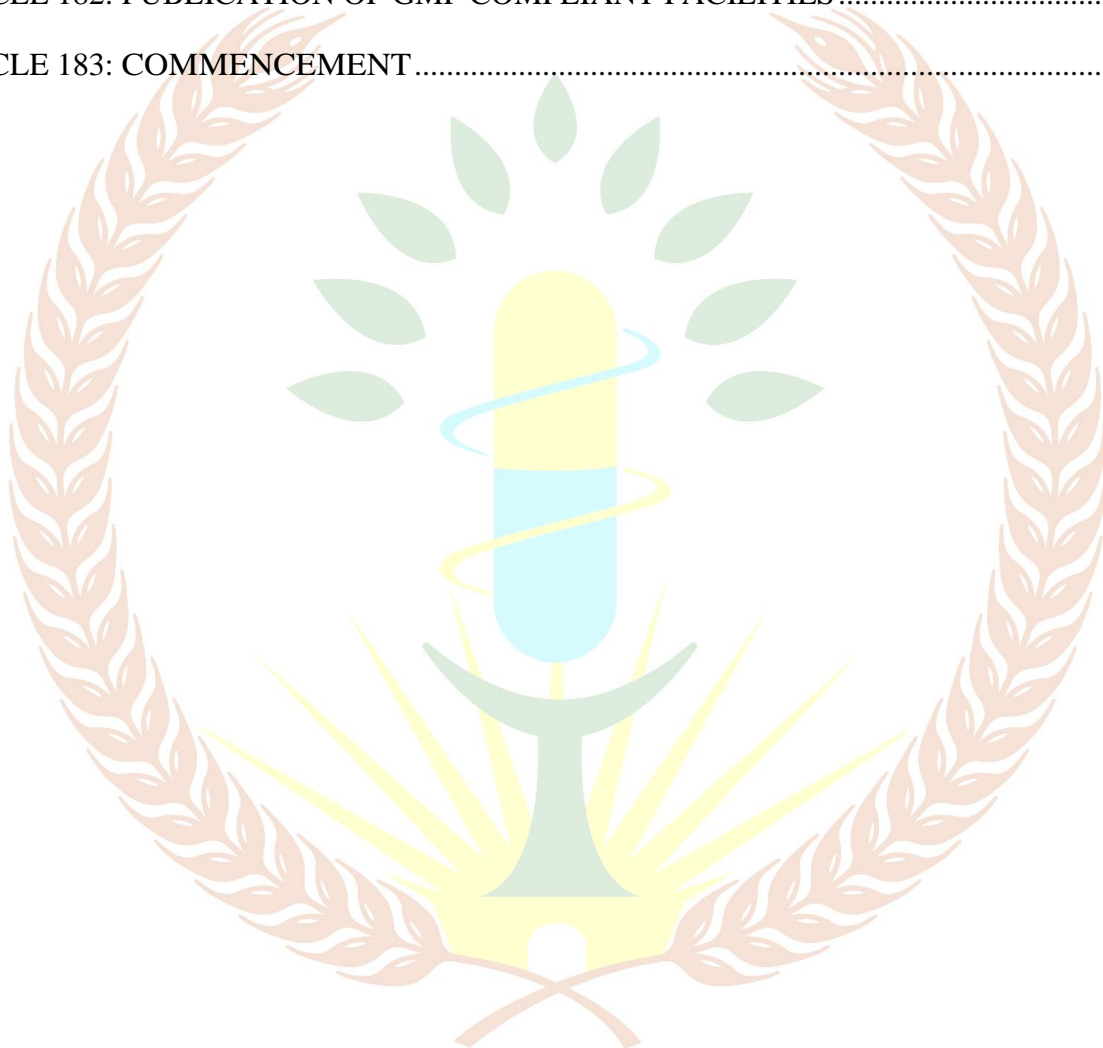
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## **ABBREVIATION AND ACRONYMS**

CAPA	:Corrective and Preventive Actions
HEPA	: High Efficiency Particulate Air
HVAC	: Heating, ventilation, and Air conditioning
GMP	: Good manufacturing Practice
ICH	: International Council for Harmonization
MOU	: Memorandum of Understanding
QA	: Quality Assurance
RWANDA FDA	: Rwanda Food and Drugs Authority
WHO	: World Health Organization



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## CHAPTER I: GENERAL PROVISIONS

### **Article 1: Purpose of these Regulations**

These Regulations govern Good Manufacturing Practices of Medical Products.

### **Article 2: Citation**

These regulations may be cited as the Rwanda FDA Regulations Governing Good Manufacturing Practices of Medical Products.

### **Article 3: Application**

The regulations for human and veterinary manufacturing facilities applies to all types of good manufacturing practice inspections of active pharmaceutical ingredients and finished pharmaceutical products that manufacture, import, export, distribute, store, sell and that are used within and outside Rwanda.

### **Article 4: Definitions**

In these regulations, unless the context otherwise requires, the:

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

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

“**Conflict of interest**” means any interest in any business related to medicines declared 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 an immediate or latent health risk and any observation that involves fraud, misrepresentation or falsification of products or data;

“**Good Manufacturing Practice inspector**” is an inspector appointed by the Rwanda FDA who possesses qualification and experience in pharmaceutical manufacturing, quality control and quality assurance to conduct an inspection or assessment in order 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 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 medicines, vaccines, diagnostics and medical devices.

“**Minister**” means the Minister 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 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;

“**Product quality review**” means regular, periodic or rolling quality reviews of all medicinal products, including export-only products, 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.

“**Recall**” means an action taken by the manufacturer to remove pharmaceutical 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 a specific intended use can be consistently fulfilled;



## CHAPTER II: GOOD MANUFACTURING PRACTICE INSPECTION

### **Article 5: Types of inspections**

There are four types of Good Manufacturing Practice inspections divided into the following categories:

Routine inspection;

- 1<sup>o</sup> Concise inspection;
- 2<sup>o</sup> Follow-up inspection;
- 3<sup>o</sup> Special inspection; and
- 4<sup>o</sup> Any other types as the authority may designate.

Subject to paragraph 1 of this Article, the inspection is conducted as follows:

- 1<sup>o</sup> **Routine GMP inspection** is a full inspection of all applicable components of GMP and licensing provisions. It may be indicated when the manufacturer:
  - a. Newly established,
  - b. Requests for renewal of a manufacturing license,
  - c. Has a history on non-compliance with GMP
  - d. 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,
  - e. Has not been inspected during the last 3 to 5 years.
- 2<sup>o</sup> **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.
- 3<sup>o</sup> **Follow-up GMP inspections** may include reassessment or re-inspections made to monitor the result of corrective measures. They are normally carried out from 6 weeks to 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.

- 4° **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.

#### **Article 6: Application for GMP**

A person who intends to undergo a Good Manufacturing Practice inspection shall apply to the Director General of Rwanda FDA by submitting the following:

- 1° Duly filled application documents as prescribed in the DIS/GDL/002 Guidelines on Good Manufacturing Practice for Finished Pharmaceutical Products - Part 1;
- 2° Inspection fee as prescribed in the CBD/TRG/004 Regulations Regulations related to Regulatory service tariff/Fees and fines.

Notwithstanding the provisions of paragraph 1 of this article, the inspection shall not be conducted at a facility which has not submitted applications for products registration.

#### **Article 7: Desk review**

After receiving the application, the Authority may conduct an assessment of the application by desk documents review or use any other inspection report from a relevant regulatory body to satisfy itself that the application has complied with the conditions for good manufacturing practice.

Dossiers for desk assessments is conducted upon 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 to be used for documents desk review shall be as follows:

- 1° Facilities must be located in countries with Stringent National Medicines Regulatory Agencies; as approved by WHO
- 2° Facilities located in countries which are ICH founding/standing regulatory members;
- 3° Facilities located in countries which are Standing regulatory members; or facilities Inspected and approved under the framework of World Health Organization (WHO) requalification program.

**Article 8: Reliance**

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

**Article 9: Virtual / Remote Inspections**

Upon receipt of a duly filled application, the Authority may conduct a voluntary virtual/remote interactive inspection of facilities where pharmaceutical products are manufactured, processed or packed.

This type of inspection is used when the Authority declares a case of Force majeure on physical inspections.

The assessment of the applicant's dossiers should indicate that the facility has complied with the conditions for good manufacturing practice according to its internal policy as well as that of the country of origin, where applicable, before it can be selected for Virtual/remote interactive inspections.

Facilities for virtual/remote interactive inspections is conducted upon discretion of the Authority. The criteria of selection of applicants for virtual/remote interactive inspections shall be as follows:

- 1<sup>o</sup> Rwanda FDA has declared force majeure on physical inspection. E.g. If there are travel restrictions resulting from a public health emergency.
- 2<sup>o</sup> Facilities must be located in countries with Stringent National Medicines Regulatory Agencies;
- 3<sup>o</sup> Facilities must be located in countries which are Standing regulatory members; or facilities Inspected and approved under the framework of World Health Organization (WHO) requalification program.
- 4<sup>o</sup> When the facilities physical inspection is not considered to be critical to Rwanda FDA missions

**Article 10: 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 foreign sites and a period of twelve (12) months for national manufacturers.



## CHAPTER III : QUALITY MANAGEMENT PRINCIPLES

### **Article 11 : Principle**

A manufacturer shall be responsible for the following:

- 1<sup>o</sup> The quality of medicinal product manufactured is fit for their intended use; the medicinal product complies with the requirements of market authorization;
- 2<sup>o</sup> Medicinal product does not place patients at risk due to inadequate safety, quality or efficacy.

A manufacturer shall implement the quality management systems with the following:

- 1<sup>o</sup> Appropriate structure or quality system encompassing the organizational structure;
- 2<sup>o</sup> Appropriate procedures;
- 3<sup>o</sup> Appropriate processes and resource.

### **Article 12 : Quality Assurance system**

A manufacturing facility shall have comprehensively designed and correctly implemented of quality assurance system.

A Quality Assurance (QA) system appropriate for pharmaceutical product manufacturing. The QA must have the following:

- 1<sup>o</sup> Medicinal products are designed and developed in a way that takes account of the requirements of good manufacturing practice;
- 2<sup>o</sup> Production and control operations are clearly specified in a written form;
- 3<sup>o</sup> Job description for managerial posts is clearly specified;
- 4<sup>o</sup> Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
- 5<sup>o</sup> All necessary controls on starting materials, intermediate products, and bulk products and any other in-process controls, calibrations, and validations are carried out;
- 6<sup>o</sup> The finished product is correctly processed and checked as per the defined procedures;
- 7<sup>o</sup> Medicinal products are not sold or supplied before the authorized persons have certified;
- 8<sup>o</sup> Satisfactory arrangements exist to ensure medicinal products are stored, distributed, and handled to maintain its quality throughout their shelf-life;
- 9<sup>o</sup> There is a procedure for self-inspection and quality audit that regularly appraises the effectiveness and applicability of the quality assurance system;
- 10<sup>o</sup> Deviations are reported, investigated and recorded;
- 11<sup>o</sup> There is a system for approving changes that may have an impact on product quality;



12<sup>o</sup> There is a regular evaluation of the quality of pharmaceutical products to verify the consistency of the process and ensuring its continuous improvement; and there is a system for quality risk management.

**Article 13 : Good Manufacturing Practice**

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.

Good Manufacturing Practice shall consist of the following basic requirements:

- 1<sup>o</sup> The manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality that comply with their specifications;
- 2<sup>o</sup> Critical steps of manufacturing processes and any significant changes made to the processes are validated;
- 3<sup>o</sup> All necessary facilities are provided including:
  - a. Appropriately qualified and trained personnel,
  - b. Adequate premises and space,
  - c. Suitable equipment and services,
  - d. Correct materials, containers and labels,
  - e. Approved procedures and instructions,
  - f. Suitable storage and transport and,
  - g. Adequate personnel, laboratories and equipment for in process controls under the responsibility of the production management.
- 4<sup>o</sup> Instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided,
- 5<sup>o</sup> Operators are trained to carry out procedures correctly,
- 6<sup>o</sup> Records are made manually and by recording instruments during manufacturing process to show that all the steps required by the defined procedures and instructions have been taken and that the quantity and quality of the product are as expected and any significant deviations are fully recorded and investigated,
- 7<sup>o</sup> Records covering manufacture and distribution, which enable the complete history of a batch to be traced are retained in a comprehensible and accessible form,
- 8<sup>o</sup> The proper storage and distribution of the products minimizes any risk to their quality,
- 9<sup>o</sup> A system is available to recall any batch of product from sale or supply,

10<sup>o</sup> Complaints about marketed products are examined and causes of quality defects are investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.

**Article 14: Quality control**

Quality control as part of good manufacturing practice shall perform the following activities:

- 1<sup>o</sup> Sampling of raw material, intermediate and finished product,
- 2<sup>o</sup> Develop specification,
- 3<sup>o</sup> Carry out testing,
- 4<sup>o</sup> Documentation,
- 5<sup>o</sup> Develop release procedure,
- 6<sup>o</sup> Release of materials, intermediate and finished product.

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

**Article 15: Quality control Requirements**

Quality control shall meet the following basic requirement:

- 1<sup>o</sup> Adequate facilities, trained personnel and approved procedures;
- 2<sup>o</sup> Conduct sampling, inspecting and testing of starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
- 3<sup>o</sup> Samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department;
- 4<sup>o</sup> Test methods must be well documented and validated;
- 5<sup>o</sup> Records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated;
- 6<sup>o</sup> The finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container, and correctly labelled;
- 7<sup>o</sup> Records must be made of the results of inspecting and testing starting materials, intermediate, bulk, and finished products against specifications; product assessment shall include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;

- 8° No batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of the marketing authorization. Sufficient reference samples of starting materials and products shall be retained to permit future examination of the product if necessary; the retained product shall be kept in its final pack unless the pack is exceptionally large. Other duties performed by quality control shall be;
- a. Establish, validate and implement all quality control procedures;
  - b. Evaluate, maintain and store the reference standards for substances
  - c. Ensure correct labelling of containers of materials and products;
  - d. Ensure that the stability of the active pharmaceutical ingredients and products are monitored;
  - e. Participate in the investigation of complaint related to quality of the product; and
  - f. Participate in environmental monitoring as per written procedure and shall be recorded.
  - g. Personnel shall have access to production areas for sampling and investigation where necessary.

**Article 16: Product quality review**

Manufacturing facility shall carry regular, periodic or rolling quality review of all medicinal products including export only products in order to:

- 1° Verify consistency of existing process;
- 2° Verify appropriateness of current specification for starting material and finished products;
- 3° Establish trends;
- 4° Identify product and process improvements.

The review shall be conducted and documented annually, taking into account previous reviews and shall include at least the following information:

- 1° Review of starting materials and packaging materials used for the product, especially those from new sources;
- 2° A review of critical in-process controls and finished product results;
- 3° A review of all batches that failed to meet established specifications and their investigation;
- 4° A review of all significant deviations or nonconformance's, the related investigations and the effectiveness of resultant corrective and preventive actions taken;
- 5° A review of all changes made to the processes or analytical methods;
- 6° A review of dossier variations submitted, granted or refused,



- 7° A review of the results of the stability monitoring program and any adverse trends;
- 8° A review of all quality-related returns, complaints and recalls and the investigations performed at that time;
- 9° A review of adequacy of any other previous corrective actions on product process or equipment;
- 10° For new dossiers and variations to the dossiers, a review of post-marketing commitments;
- 11° The qualification status of relevant equipment and utilities; and
- 12° A review of technical agreements to ensure that they are up to date.

A manufacturer shall carry out evaluation of results of review and assessment whether corrective and preventive action or any revalidation is needed to be done.

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

Where market authorization holder is different from manufacturer, there shall be technical agreement in place between the various parties with their responsibilities for producing the quality review.

The authorized person responsible for final batch certification, together with the marketing authorization holder, shall ensure that the quality review is performed in a timely manner and is accurate.

#### **Article 17: Quality risk management**

A manufacturer shall have a systematic process for assessment, control, communication and review of risk to the quality of pharmaceutical product.

The system shall ensure evaluation of the risk based on scientific knowledge and experience with the process to protect patient.

The formality and documentation of the quality risk management process shall be based on risk level.

#### **Article 18: Sanitation and Hygiene**

Every aspect of pharmaceutical products manufacturing shall be carried out in a high-level sanitation and hygiene.

Sanitation and hygiene shall cover personnel, premises, equipment and apparatus, production material and containers, products for cleaning; and disinfection and anything that could be source of contamination of the product.

There shall be an integrated comprehensive program of sanitation and hygiene



## CHAPTER IV : PERSONNEL

### **Article 19 : Principles governing staff**

There shall be sufficient qualified personnel to carry out all manufacturing activities and the responsibilities for every individual has to be clearly understood and recorded.

The manufacturer shall have an organization chart.

All responsible staff shall have their duties recorded in written descriptions and adequate Authority to carry out their responsibilities. Duties for responsible personnel may be delegated to designated deputies of satisfactory qualification level.

There are shall be no gaps or unexplained overlaps in responsibilities of personnel concerned with the application of good manufacturing practice.

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

Unauthorized personnel shall not enter production, storage and quality control areas or use them as passage.

### **Article 20: Key personnel**

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

- 1<sup>o</sup> Head of production;
- 2<sup>o</sup> Head of quality unit;
- 3<sup>o</sup> Head of quality assurance;
- 4<sup>o</sup> Head of quality control; and
- 5<sup>o</sup> Authorized person.

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

Key posts shall be occupied by full-time personnel.

A manufacturer shall notify the Authority the name of qualified and authorized person appointed by the manufacturers.

A manufacturer shall notify the Authority of the name of a person to whom functions have been delegated by the responsible person under sub- regulation (1), and the specific functions which have been delegated to such persons.

**Article 21: Academic qualifications of key personnel**

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

The head of production shall, at the minimum be a holder of a bachelor education in Pharmacy but where he or is not available, alternative options shall be for person who holds at least a bachelor education in the following:

- 1<sup>o</sup> Pharmaceutical sciences and technology;
- 2<sup>o</sup> Chemistry (analytical or organic) or biochemistry;
- 3<sup>o</sup> Chemical engineering;
- 4<sup>o</sup> Veterinary medicine.
- 5<sup>o</sup> Any other relevant qualification

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

- 1<sup>o</sup> Pharmacy;
- 2<sup>o</sup> Pharmaceutical sciences and technology;
- 3<sup>o</sup> Chemistry (analytical or organic) or biochemistry.
- 4<sup>o</sup> Any other relevant qualification

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

- 1<sup>o</sup> Pharmacy;
- 2<sup>o</sup> Pharmaceutical sciences and technology;
- 3<sup>o</sup> Chemistry (analytical or organic) or biochemistry;
- 4<sup>o</sup> Microbiology.
- 5<sup>o</sup> Any other relevant qualification

**Article 22: Shared Responsibilities**

The heads of the production and quality control units generally shall have some shared, or jointly exercised responsibilities relating to quality in:

- 1<sup>o</sup> The authorization of written procedures and other documents, including amendments;
- 2<sup>o</sup> The monitoring and control of the manufacturing environment; plant hygiene;
- 3<sup>o</sup> Process validation and calibration of analytical apparatus;
- 4<sup>o</sup> Training including the application and principles of quality assurance;

- 5° The approval and monitoring of suppliers of materials;
- 6° The approval and monitoring of contract manufacturers;
- 7° The designation and monitoring of storage conditions for materials and products;
- 8° The performance and evaluation in process controls;
- 9° The retention of records;
- 10° The monitoring of compliance with good manufacturing practice requirements;
- 11° The inspection, investigation, and taking of samples, in order to monitor factors that may affect product quality.

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

- 1° Ensure products are produced and stored according to the appropriate documentation in order to obtain the required quality;
- 2° To approve the instructions relating to production operations, including the in- process controls and to ensure their strict implementation;
- 3° To ensure that the production records are evaluated and signed by a designated person before they are made available to the quality control department;
- 4° To check the maintenance of the department, premises and equipment;
- 5° To ensure that the appropriate process validations and calibrations of control equipment are performed and recorded, and the reports made available;
- 6° To ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

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

- 1° To approve or reject starting materials, packaging materials, and intermediate, bulk, and finished products;
- 2° To evaluate batch records;
- 3° To ensure that all necessary testing is carried out;
- 4° To approve sampling instructions, specifications, test methods, and other quality control procedures;
- 5° To approve and monitor analysis carried out under contract;
- 6° To check the maintenance of the department, premises and equipment;
- 7° To ensure that, appropriate validations, including those of analytical procedures, and calibrations of control equipment are done;
- 8° To ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need;



- 9° Establish, implement and maintain the quality system;
- 10° Supervision of regular internal audits or self-inspections;
- 11° Participate in external audits; and
- 12° Participate in validation program.

### **Article 23: Training**

A manufacturer shall provide training as per written program for all the personnel whose duties take them into production areas or into control laboratories including the technical, maintenance, and cleaning personnel, and any other personnel whose activities could affect the quality of the product. Recruited personnel shall receive training appropriate to the duties assigned to them in addition to basic training on theory and practice of good manufacturing practice.

All personnel shall receive continuing training, evaluated and records be retrieved as per approved training program.

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

Visitors or untrained personnel shall not enter production and quality control areas, if necessary, they shall be closely supervised and practice personnel hygiene including wearing protective clothing.

Consultants and contract staff shall be qualified for their service and their training records kept.

### **Article 24: Personal hygiene**

A person prior or during employment shall undergo health examination. All personnel conducting visual inspection shall undergo periodic eye examination.

Every person engaged with manufacturing process shall be trained in the practice of personal hygiene including washing hands before entering production areas. Signs and instruction posters for personnel hygiene shall be displayed on respective areas.

A person with an apparent illness or open lesions that may adversely affect the quality of products shall not be allowed to handle starting materials, packaging materials, in-process materials, or drug products until the condition is no longer judged to be a risk.

All employees shall be instructed and encouraged to report to their immediate supervisor a condition relating to plant, equipment, or personnel that they consider may adversely affect the products.

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

Personnel shall wear clear body covering appropriate to the duty they perform including hair covering in order to protect product from contamination.

All reusable clothes, shall be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.

A person shall not be allowed to eat, drink, smoke, chew, store plants, food, drinks, smoking material or personal medicines in production, laboratory, and storage areas or in any other areas where they might adversely influence product quality.



Personal hygiene procedures including the use of protective clothing shall apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees such as contractors' employees, visitors, senior managers and inspectors.

## CHAPTER V: GMP PREMISES

### **Article 25: Layout and design**

Premises shall be located, designed, constructed, adapted, and maintained to suit the operations carried out. Premises for GMP must have the following:

- 1<sup>o</sup> Their layout and design shall aim to minimize the risk of errors and permit effective cleaning and maintenance to avoid cross contamination, build-up of dust or dirt, and any adverse effect on the quality of products.
- 2<sup>o</sup> situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.
- 3<sup>o</sup> Premises used for the manufacture of drug products shall be suitably designed and constructed to facilitate good sanitation.
- 4<sup>o</sup> maintained and ensured that repair and maintenance operations do not present any hazard to the quality of products.
- 5<sup>o</sup> cleaned and where applicable, disinfected as per written procedures and records maintained. Electrical supply, lighting, temperature, humidity, and ventilation shall be appropriate and do not adversely affect, directly or indirectly the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.
- 6<sup>o</sup> designed and equipped to provide maximum protection against the entry of insects, birds or any other animals. There shall be procedure for rodent and pest control and records shall be maintained.

### **Article 26: Production area**

In order to minimize the risk of a serious medical hazard due to cross-contamination, the dedicated, separate and self-contained facilities shall be available for the production of particular pharmaceutical products, such as penicillin, cephalosporin and other highly sensitizing materials and biological preparations like live microorganisms.

The production of certain additional products, such as antibiotics, hormones, cytotoxic substances, highly active medicinal products, and non-medicinal products, shall not be conducted in the same facilities.

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

Premises shall be laid out to allow production to 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.

The adequacy of the working and in-process storage space shall permit the orderly and logical positioning of equipment and materials to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross- contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces such as walls, floors, and ceilings shall be smooth and free from cracks. The open joints, shall not shed particulate matter to permit easy and effective cleaning if necessary. Pipe work, light fittings, ventilation points, and other services shall be designed and sited to avoid the creation of recesses that are difficult to clean and in case of maintenance purposes, they shall be accessible from outside the manufacturing areas.

Drains shall be of adequate size and equipped to prevent back-flow and open channels shall be avoided where possible, but if they are necessary, they shall be shallow to facilitate cleaning and disinfection. Production areas shall be effectively ventilated, with air-control facilities including control of temperature and, where necessary, humidity and filtration appropriate to the products handled, to the operations undertaken, and to the external environment.

These areas shall be regularly monitored during production and non-production periods to ensure compliance with their design specifications.

Where dust is generated during sampling, weighing, mixing, processing operations and packaging of powders, measures shall be taken to avoid cross contamination and facilitate cleaning.

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

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

### **Article 27: Storage area**

Storage areas shall be of sufficient capacity to 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.

The areas shall be designed or adapted to ensure good storage conditions, clean and dry with sufficient lit and maintained within acceptable temperature limits.

If special storage conditions are required such as humidity and temperature these shall be provided and controlled, monitored and their records be maintained.

Receiving and dispatch bays shall be separated and protect materials and products from the weather.

Reception areas shall be designed and equipped to allow containers of incoming materials to be cleaned before storage.

Where quarantine status is ensured by storage in separate areas, these areas shall be clearly marked and their access restricted to authorized personnel and if the system is used to replace the physical quarantine it shall be given equivalent security.

Separate sampling area for starting materials shall be provided. In case sampling is performed in the storage area, it shall prevent contamination or cross-contamination.

Storage of rejected, recalled, or returned materials or products shall be segregated.

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 pharmaceutical product for its labelling, and special attention shall be paid to sampling, safe and secure storage of these materials.

**Article 28: 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 29: 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;

- 1° Suitable for the operations carried out;
- 2° With sufficient space to avoid mix-ups and cross-contamination; and
- 3° With adequate and suitable storage space for samples, reference standards, if necessary, with cooling, and records.

The design of the laboratories shall take into account the suitability of construction materials, prevention of fumes, and ventilation.

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 30: 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.

## CHAPTER VI: EQUIPMENT

### **Article 31: Design and location of equipment**

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

### **Article 32: Manufacturing equipment**

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

Repairs and maintenance operations shall not present any hazard to the quality of the products

Manufacturing equipment shall be designed so that, it can be easily and thoroughly cleaned as per written procedures and stored only in clean and dry condition.

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

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

Equipment shall be installed to minimize any risk of error or contamination.

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.

Wherever appropriate, closed equipment shall be used and in case open equipment is used precautions shall be taken to minimize contamination.

Balances and other measuring equipment of an appropriate range and precision shall be available for production and control operations and shall be calibrated and checked at defined intervals using appropriate methods and adequate records maintained.

Measuring, weighing, recording, control equipment and instruments shall be serviced and calibrated at pre-specified intervals and records maintained.

To ensure satisfactory functioning, instruments shall be checked daily or prior to use for performing analytical tests and the date of calibration, servicing and the date when recalibration is due shall be clearly indicated on the equipment.

Current drawings of critical equipment and support systems shall be maintained.

Fixed pipe work shall be clearly labelled to indicate the contents and, where applicable, the direction of flow.



All service piping's and devices shall be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.

Water for pharmaceutical use and other water pipes shall be sanitized as per written procedures that detail the action limits for microbial contamination and measures to be taken.

Control-laboratory equipment shall be removed from production and quality control areas, or at least be clearly labelled as defective.

## **CHAPTER VII : DOCUMENTATION**

### **Article 33 : Good documentation practice**

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:

- 1<sup>o</sup> Specifications for all materials and methods of manufacture and control;
- 2<sup>o</sup> An audit trail that will permit investigation of the history of any suspected defective batch;  
and
- 3<sup>o</sup> Availability of data needed for validation, review and statistical analysis.

A manufacturer shall design and make use of the documents which are free from errors and available in writing.

### **Article 34: Prepared document**

A manufacturer shall design, prepare, review and distribute documents with care and the prepared documents shall comply with the relevant parts of the manufacturing and marketing authorizations.

A manufacturer shall ensure that the documents:

- 1<sup>o</sup> Are approved, signed, and dated by appropriate authorized persons and a document shall not be changed without authorization;
- 2<sup>o</sup> Have unambiguous contents and the title, nature, and purpose should be clearly stated and laid out in an orderly fashion and easy to check.
- 3<sup>o</sup> Be regularly reviewed and kept up to date.

A manufacturer shall have a system for revising documents to prevent inadvertent use of the superseded version and the superseded documents shall be retained for a specified period of time.

In case of reproduced documents:

- 1<sup>o</sup> They shall be clear and legible;
- 2<sup>o</sup> Working documents from master documents must not allow any error to be introduced through the reproduction process.

Where documents require the entry of data the entries shall be clear, legible, and indelible and sufficient space shall be provided for such entries. In case of any alteration made to a document:

1<sup>o</sup> Manufacturer shall sign and date; the alteration shall permit the reading of the original information.

2<sup>o</sup> Where appropriate, the reason for the alteration shall be recorded.

A manufacturer shall record and keep complete records when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable.

A manufacturer shall retain records and associated standard operating procedures for at least one year after the expiry date of the finished product.

A manufacturer may keep data and record electronically or may have data-processing systems or by photographic or other reliable means.

A manufacturer shall have Master formulae and detailed standard operating procedures relating to the system in use and the accuracy of the records shall be checked.

If a manufacturer is handling documents by electronic data-processing methods:

1<sup>o</sup> Only authorized persons shall be able to enter or modify data in the computer, and there shall be a record of changes and deletions,

2<sup>o</sup> Access shall be restricted by passwords or other means,

3<sup>o</sup> Entry of critical data shall be independently checked,

4<sup>o</sup> Batch records electronically stored shall be protected by back-up transfer on magnetic tape, microfilm, paper printouts, or other means,

5<sup>o</sup> Manufacturer shall ensure all electronically stored data are readily available during the period of retention.

### **Article 35: Labels**

A manufacturer shall ensure labels that applied to containers, equipment, or premises are clear, unambiguous, and in the company's agreed format.

Colour coding to indicate status for quarantined, accepted, rejected, or cleaned shall be used.

All finished drug products shall be identified by labelling, as required by the national legislation, bearing at least the following information;

1<sup>o</sup> The name of the drug product;

2<sup>o</sup> A list of the active ingredients if applicable, with the international non-proprietary names, showing the amount of each present, and a statement of the net contents, such as number of dosage units, weight, or volume;

3<sup>o</sup> The batch number assigned by the manufacturer;

4<sup>o</sup> The expiry date in an un-coded form;

5<sup>o</sup> Any special storage conditions or handling precautions that may be necessary;

- 6° Directions for use, warnings and precautions that may be necessary; and
- 7° The name and address of the manufacturer or the company or the person responsible for placing the product on the market.
- 8° For reference standards, the label or accompanying document shall indicate concentration, date of manufacture, expiry date, date the closure is first opened, and storage conditions where appropriate.

**Article 36: Documents required specifications and testing procedures**

A manufacturer shall have appropriate, approved and dated specifications and testing procedures for identity, content, purity, and quality for:

- 1° Starting materials,
- 2° Packaging materials,
- 3° Finished products,
- 4° Specifications of water, solvents and reagents such as acids and bases used in production shall be included.

A manufacturer shall have documents describing validated testing procedures in the context of available facilities and equipment before they are adopted for routine testing.

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

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

**Article 37: Specifications for starting and packaging materials**

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

- 1° The designated name, the International Non-proprietary Name and internal code reference;
- 2° The reference, if any to a pharmacopoeia! Monograph;
- 3° Qualitative and quantitative requirements with acceptance limits.

Depending on the company's practices the following data may be added to the specifications:

- 1° The approved supplier;
- 2° A specimen of printed materials;
- 3° Directions for sampling and testing, or a reference to procedures;
- 4° Storage conditions and precautions;
- 5° The maximum period of storage before re- examination.



A manufacturer shall ensure all packaging material conform to specifications with emphasis placed on the compatibility of the material with the drug product it contains.

The material shall be examined for defects as well as for the correctness of identity markings.

Documents describing testing procedures shall state the required frequency for re-assaying each starting material, as determined by its stability.

**Article 38: Specifications for intermediate and bulk products**

A manufacturer shall ensure availability of specifications for intermediate and bulk products which shall be similar to specifications for starting materials or for finished products, as appropriate

**Article 39: Specifications for finished products**

Specifications for finished products shall include:

- 1° The designated name of the product and the code reference where applicable;
- 2° The designated name of the active ingredients if applicable and the International Non-proprietary Names;
- 3° The formula or a reference to the formula;
- 4° A description of the dosage form and package details;
- 5° Directions for sampling and testing or a reference to procedures;
- 6° The qualitative and quantitative requirements, with acceptance limits;
- 7° The storage conditions and precautions, where applicable; and
- 8° The shelf-life.

**Article 40: Master Formulae and Processing Instructions**

A manufacturer shall formally approve master formula for each product and batch size to be manufactured.

A manufacturer shall document the processing instructions for each product.

**Article 41: Packaging Instructions**

A manufacturer shall formally approve packaging instructions for each product pack size and type. The approved packaging instructions shall make reference to the following:

- 1° The name of the product;
- 2° Description of its pharmaceutical form, strength, and method of application where applicable;
- 3° The pack size expressed in terms of the number, weight, or volume of the product in the final container;
- 4° A complete list of all the packaging materials required for a standard batch size;



- 5° Where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
- 6° Special precautions to be observed;
- 7° A description of the packaging operation; and
- 8° Details of in-process controls with instructions for sampling and acceptance limits.

**Article 42: Batch Processing Records**

A manufacturer shall keep a batch processing record for each processed batch bearing the number of the batch being manufactured.

Batch processing record documented by manufacturer shall be based on the relevant parts of the currently approved master formula.

Before processing of product begins, the manufacturer shall ensure that all equipment and work stations are clear of previous products, documents, or materials which are not required for the planned process, and the equipment used is suitable for the said process.

A manufacturer shall record during processing, the following information at the time each action is taken, and after completion the record shall be dated and signed by the person responsible for the processing operations:

- 1° The name of the product;
- 2° The number of the batch being manufactured;
- 3° Dates and times of commencement, of significant intermediate stages, and of completion of production
- 4° The name of the person responsible for each stage of production;
- 5° The initials of the operators of different significant steps of production and, where appropriate the persons who checked each operation, such as weighing;
- 6° The batch number, analytical control number and the quantity of each starting material actually weighed including the batch number and amount of any recovered or reprocessed material added;
- 7° Any relevant processing operation or event and the major equipment used;
- 8° The in-process controls performed, the initials of the persons carrying them out, and the results obtained;
- 9° The amount of product obtained at different and pertinent stages of manufacture referred as yield, together with comments or explanations for significant deviations from the expected yield;
- 10° Notes on special problems including details, with signed authorization for any deviation from the master formula.

**Article 43: Batch Packaging Records**

A manufacturer shall keep a batch packaging record for each or a part of batch processed based on the relevant parts of the packaging instructions and the method of preparing of such records shall be designed.

Before any packaging operation begins, the manufacturer shall ensure that, all equipment and work stations are clear of previous products, documents, or materials not required for the planned packaging, and the equipment used is suitable for the operation.

At the time each action is taken and after completing of the said action, the manufacturer shall record all the information and the responsible personnel shall clearly be identified by signature or electronic password; and the information recorded shall be as follows:

- 1<sup>o</sup> The name of the product, the batch number,
- 2<sup>o</sup> The quantity of bulk product packed, as well as the planned quantity of finished product that will be obtained and the reconciliation;
- 3<sup>o</sup> The date and time of the packaging operations;
- 4<sup>o</sup> The name of the responsible person carrying out the packaging operation;
- 5<sup>o</sup> The initials of the operators of the different significant steps;
- 6<sup>o</sup> The checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
- 7<sup>o</sup> Details of the packaging operations carried out, including references to equipment and the packaging lines used, and when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;
- 8<sup>o</sup> Whenever possible, samples of the printed packaging materials used, including specimens bearing approval of the printing, the batch number, expiry date, and any additional overprinting;
- 9<sup>o</sup> Notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
- 10<sup>o</sup> The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed, or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

**Article 44: Records Receipts**

A manufacturer shall have written standard procedures and records for the receipt of each delivery of each starting material, primary and printed packaging material.

The records of the receipts documented by manufacturer shall include:

- 1<sup>o</sup> The name of the material on the delivery note and the containers

- 2° The "in-house" name and/or code of material if different from sub regulation (a) above;
- 3° The date of receipt;
- 4° The supplier's name and, if possible, manufacturer's name;
- 5° The manufacturer's batch or reference number;
- 6° The total quantity, and number of containers received;
- 7° The batch number assigned after receipt; and
- 8° Any relevant comment such as state of the containers.

A manufacturer shall document written standard operating procedures for the internal labelling, quarantine, and storage of starting materials, packaging materials, and other materials, as appropriate.

#### **Article 45: Sampling**

A manufacturer shall have written standard operating procedures for sampling, which specify the persons authorized to take samples.

A manufacturer shall document the sampling instructions which include:

- 1° The method of sampling and the sampling plan;
- 2° The equipment to be used;
- 3° Any precautions to be observed to avoid contamination of the material or any deterioration in its quality.
- 4° The amount of samples to be taken;
- 5° Instructions for any required subdivision of the sample;
- 6° The type of sample containers to be used, and whether they are for aseptic sampling or for normal sampling;
- 7° Any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

#### **Article 46: Testing**

A manufacturer shall document written procedure for testing materials and products at different stages of manufacturing describing the methods and equipment to be used.

A manufacturer shall keep records for all tests performed and the documented analysis records shall include at least the following data:

- 1° The name of the material or product and, where applicable, dosage form;
- 2° The batch number and, where appropriate, the manufacturer or supplier;
- 3° References to the relevant specifications and testing procedures;
- 4° Test results, including observations calculations, and reference to any specifications limits;
- 5° Dates and reference number of testing;



- 6° The initials of the persons who performed the testing;
- 7° The dates and initials of the persons who verified the testing and the calculations, where appropriate; and
- 8° A clear statement of release or rejection or other status decision and the dated signature of the designated responsible person.

**Article 47: Batch Number**

Every manufacturer shall have a documented standard operating procedure describing the details of the batch or lot numbering system, with the objective of ensuring that each batch of intermediate, bulk, or finished product is identified with a specific batch number.

The documented standard operating procedures by manufacturer for batch numbering that are applied to the processing stage and to the respective packaging stage shall be related to each other and shall not be repeated.

Batch-number allocation shall be immediately recorded in a logbook including date of allocation, product identity and size of batch.

Every manufacturer shall ensure availability of a written release and rejection procedures for materials and products, and especially for the release for sale of the finished product by an authorized person.

Every manufacturer shall maintain records for the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.

Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached shall be available for validation, equipment assembly and qualification, analytical apparatus and calibration, maintenance, cleaning, and sanitization, personnel matters including qualification, training, clothing, and hygiene; environmental monitoring, pest control, complaints, recalls, returns. Specifically, the manufacturer shall:

- 1° Keep Logbooks with major and critical equipment as appropriate and any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations.
- 2° Have clear standard operating procedures for major items of manufacturing and test equipment placed in close proximity to the equipment.
- 3° appropriately record in chronological order the use of major and critical equipment and the areas where products have been processed
- 4° have written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities to be cleaned and such written procedures shall be followed.

## CHAPTER VIII: PRODUCTION

### **Article 48: Production Operation**

Every manufacturer shall have production operations which follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

### **Article 49: 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.

In case of existence of any deviation from instructions or procedures, manufacturer shall ensure deviation is done in accordance with an approved procedure.

A person cannot deviate from instruction without being approved in writing by a designated person, with the involvement of the quality control department.

A manufacture shall check on yields and reconciliation of quantities to avoid discrepancies outside acceptable limits.

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 be labelled or otherwise identified with an indication of the product or material being processed, its strength, batch number and indication of the production stage.

A person shall not access a production premises without being authorized.

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

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

### **Article 50: Cross contamination and bacterial contamination in Production**

The manufacturer shall take special pre-cautions 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

The manufacturer shall avoid:

- 1<sup>o</sup> Any contamination of a starting material or of a product due to another material or product.
- 2<sup>o</sup> Any risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays, or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin

- 3° Any risk caused by highly sensitizing materials, like biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials.

Every manufacturer shall avoid cross contamination by taking appropriate technical or organizational measures, such as:

- 1° Production in dedicated and self-contained areas which may be required for products such as penicillin, live vaccines, live bacterial preparations and certain other biologicals,
- 2° Conducting campaign production by dedicating time followed by appropriate cleaning in accordance with a validated cleaning procedure;
- 3° Providing appropriate airlocks, pressure differentials, and air extraction;
- 4° Minimizing the risk of contamination caused by recirculation or re-entry of un treated or insufficiently treated air;
- 5° Wearing protective clothing in areas where products with special risk of cross-contamination are processed;
- 6° Using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
- 7° Using a "closed system" of production;
- 8° Testing for residues;
- 9° Using cleanliness status labels on equipment.

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

Every manufacturer shall ensure all production areas where susceptible products are processed undergo periodic environmental monitoring such as microbiological monitoring and particulate matter where appropriate.

The materials used for operations such as cleaning, lubrication of equipment and pest control, shall not come into direct contact with the product.

Notwithstanding the provision of sub regulation (7) above, all manufacturers shall ensure materials used are of a suitable grade to minimize health risks;

A manufacturer shall ensure that water used in the manufacturing of pharmaceutical products is suitable for its intended use.

### **Article 51: Validation**

Every manufacturer shall conduct validation studies that are reinforcing Good Manufacturing Practices and in accordance with defined procedures.

A manufacturer shall record all validation studies' results and conclusions. Whenever a new manufacturing formula or method of preparation is adopted, manufacturer shall take steps to



demonstrate its suitability for routine processing that consistently yield a product of the required quality.

The manufacturer shall:

- 1<sup>o</sup> Validate all significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and the reproducibility of the process,
- 2<sup>o</sup> Perform periodic,
- 3<sup>o</sup> Critical revalidation for all processes and procedures to ensure that they remain capable of achieving the intended results.

### **Article 52: Starting Materials**

Every manufacturer shall purchase starting materials only from suppliers named in the relevant specification and, where possible, directly from the producer.

A manufacturer shall ensure that specifications established by the manufacturer for the starting materials be discussed and agreed upon with the suppliers and aspects of production and control of the starting material in question, including handling, labelling, and packaging requirements as well as complaints and rejection procedures, are discussed and agreed upon between the manufacturer and the supplier.

A manufacturer shall check each consignment for integrity of package and containers seal and for correspondence between the order, the delivery note, and the supplier's labels.

A manufacturer shall check all incoming materials to ensure that the consignment corresponds to the order and containers are clean.

A person shall not lose the original information wherever additional labels are attached to the containers,

A manufacturer shall record report to the quality control department and investigate any damage to containers and any problem that might adversely affect the quality of a material.

A manufacturer shall consider each batch as separate for sampling, testing, and release. A manufacturer shall store and label starting materials in the storage area.

A manufacturer shall ensure that, labels bear at least the following information:

- 1<sup>o</sup> The designated name of the product and the internal code reference where applicable;
- 2<sup>o</sup> The batch numbers given by the supplier and on receipt by the manufacturer, if any;
- 3<sup>o</sup> Where appropriate, the status of the contents such as on quarantine, on test, released, rejected, returned, recalled;
- 4<sup>o</sup> Where appropriate, an expiry date or a date beyond which retesting is necessary.

In case of fully computerized storage systems are used, not all of the above information shall be needed on the label.

A manufacturer shall have appropriate procedures or measures to ensure the identity of the contents of each container of starting material.

Notwithstanding the provision of paragraph 11 of this Article above; manufacturer shall identify sampled bulk containers from which samples have been drawn.

Quality control department shall release starting materials within their shelf-life.

A person shall not dispense starting materials unless dispensed by designated persons using a written procedure.

Each dispensed material by designated persons shall be:

- 1<sup>o</sup> Independently checked and recorded for its weight or volume;
- 2<sup>o</sup> Dispensed for each batch of the final product; and
- 3<sup>o</sup> Kept together and conspicuously labelled as such.

A manufacturer shall quarantine immediately after receipt of all incoming materials and after processing and finished products, until they are released for use or distribution.

A manufacturer shall store under the appropriate conditions all material and products in an orderly fashion to permit batch segregation and stock rotation by a first-expiry and first-out rule.

#### **Article 53: Processing Operations: Intermediate and Bulk Products**

Every manufacturer shall take steps to ensure that the working area and equipment are clean and free from any starting materials, products, product residues, labels, or documents that are not required for the current operation are destroyed before any processing operation is started

In case of purchased intermediate and bulk products, manufacturers shall:

- 1<sup>o</sup> Keep under appropriate conditions;
- 2<sup>o</sup> Handle on receipt as though they were starting materials.

A manufacturer shall carry out and record all in-process controls and environmental controls.

A manufacturer shall institute means of indicating failures of equipment or of services such as water or gas to equipment and the defective equipment shall be withdrawn from use until the defect has been rectified.

All manufacturers shall:

- 1<sup>o</sup> State based on data, time limits for storage of equipment after cleaning and before use;
- 2<sup>o</sup> Clean containers for filling before filling;
- 3<sup>o</sup> Record and investigate any significant deviation from the expected yield; and
- 4<sup>o</sup> Carry out checks to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected

#### **Article 54: Packaging Materials**

A manufacturer shall purchase, handle, and control primary and printed packaging materials. A manufacturer shall pay particular attention to printed packaging materials and:

- 1<sup>o</sup> Store in secure conditions so as to exclude the possibility of unauthorized access;
- 2<sup>o</sup> Use roll feed labels wherever possible;
- 3<sup>o</sup> Store cut labels and other loose printed materials and transport in separate closed containers.

A person shall not issue packaging materials unless issued by designated personnel by following an approved and documented procedure.

A manufacturer shall give a specific reference number or identification mark for each delivery or batch of printed or primary packaging material.

A manufacturer shall destroy and keep its disposal record for all outdated or obsolete primary packaging material or printed packaging material.

#### **Article 55: Packaging Operations**

Every manufacturer shall give attention wherever the program for packaging operations is being set up, to minimizing the risk of cross-contamination, mix-ups, or substitutions.

A person shall not pack different products in close proximity unless there is physical segregation or the use of electronic surveillance.

A manufacturer shall take steps before packaging operations are begun, to ensure that the working area, packaging lines, printing machines, and other equipment are clean and free from any products, materials, or documents previously used and not required for the current operation.

The manufacturer shall:

- 1<sup>o</sup> Perform line clearance according to an appropriate procedure, checklist and records;
- 2<sup>o</sup> Display at each packaging station or line the name and batch number of the product being handled;
- 3<sup>o</sup> Check on delivery all products and packaging materials to be used to the packaging department for quantity, identity and conformity with the packaging instructions;
- 4<sup>o</sup> Clean all containers for filling before filling and shall give more attention to avoid any contaminants such as glass fragments and metal particles;
- 5<sup>o</sup> Ensure filling is quickly followed by sealing and as possible by labelling and if labelling is delayed, manufacturer shall apply appropriate procedures to ensure that no mix-ups or mislabelling can occur;
- 6<sup>o</sup> Check and record the correct performance of any printing such as code numbers or expiry dates done separately or in the course of the packaging;
- 7<sup>o</sup> Take special care when cut labels are used and when overprinting is carried out offline, and in hand-packaging operations;



- 8<sup>o</sup> Perform online verification of all labels;
- 9<sup>o</sup> Check printed and embossed information on packaging materials to ensure that they are distinct and resistant to fading or erasing.

A manufacturer shall perform on-line control of the product during packaging that include at least checks on:

- 1<sup>o</sup> The general appearance of the packages;
- 2<sup>o</sup> Whether the packages are complete;
- 3<sup>o</sup> Whether the correct products and packaging materials are used;
- 4<sup>o</sup> Whether any overprinting is correct; and
- 5<sup>o</sup> The correct functioning of line monitors.

A person shall not be allowed to return samples taken away from the packaging line.

A person shall not reintroduce into process products that have been involved in any an unusual event during packaging unless after special inspection, investigation, and approval by authorized personnel and record of the operation are kept.

A manufacturer shall investigate any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced and accounted for before release.

A manufacturer shall upon completion of a packaging operation, destroy and keep destruction records of any unused batch-coded packaging materials.

A documented procedure requiring checks shall be followed before returning unused materials.

#### **Article 56: Finished Products**

A manufacture shall hold finished products in quarantine area until their final release and that, after they shall be stored as usable stock.

A manufacturer shall evaluate the finished products and keep records for release and sale of a product as described in these regulations.

#### **Article 57: Rejected, Recovered, Reprocessed and Returned Materials**

A manufacturer shall clearly mark rejected materials and products and store separately in restricted areas.

A manufacturer shall return the rejected materials or products to the supplier and where appropriate destroyed in a timely manner after a written approval by the authorized personnel.

A manufacturer shall not reprocess rejected products unless the quality of the final product is not affected and the process is done in accordance with a defined and authorized procedure after evaluation of the risks involved.

A manufacturer shall authorize beforehand the introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture.

A manufacturer shall carry out the recovery in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life and the recovery should be recorded.

A manufacturer shall consider the quality control department for any additional testing of any finished product that has been reprocessed, or the one which a recovered product has been incorporated.

A manufacturer shall destroy products that returned from the market unless it is certain that their quality is satisfactory after been critically assessed by the quality control department in accordance with a written procedure and whenever there is any doubt arises over the quality of the product, it shall not be considered suitable for re-issue or reuse.

**Article 58: Waste Materials**

Every manufacturer shall make a provision for the proper and safe storage of waste materials awaiting disposal and toxic substances and flammable materials shall be stored in suitably designed, separate, enclosed cupboards, as required.

A manufacturer shall not be allowed to accumulate waste material. The material shall be collected in suitable receptacles for removal and thereafter to collection points outside the buildings for disposal.

**Article 59: Veterinary medicinal products containing penicillin**

Manufactured penicillin and non-penicillin containing veterinary medicinal products may be carried out in the same facility provided that all necessary measures have been taken to avoid cross contamination and any risk to operator safety.

**Article 60: Veterinary premixes for medicated feeding stuffs**

Manufacturing premixes shall be carried in a dedicated area which, do not form part of a main manufacturing plant and alternatively, areas shall be surrounded by a buffer zone in order to minimize the risk of contamination of other manufacturing areas.

**Article 61: Ectoparasiticides**

Ectoparasiticides for external application to animals, which are veterinary medicinal products, and subject to marketing authorisation, may be produced and filled on a campaign basis in pesticide specific areas and however other categories of veterinary medicinal products should not be produced in such areas.

**Article 62: Miscellaneous**

The use of rodenticides, insecticides, fumigating agents, and sanitizing materials shall not contaminate equipment, starting materials, packaging materials, in-process materials, or finished products.

## CHAPTER IX: GOOD PRACTICES IN QUALITY CONTROL

### **Article 63: Quality**

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

### **Article 64: Department and Laboratory**

Every manufacturer shall have a separate Quality Control department separated from production and other departments.

Each quality control laboratory shall be under designated person with appropriate qualifications and experience, who has one or several control laboratories at disposal.

All laboratories shall have adequate resources to ensure that all the Quality Control arrangements are effectively and reliably carried out.

All laboratory operations shall be carried out in accordance with written procedures and, where necessary, recorded.

### **Article 65: Documentation**

Laboratory documentation shall follow the principles prescribed under these regulations. Notwithstanding the provisions of paragraph 1, quality control documents shall consist of the following important parts:

- 1<sup>o</sup> Specifications;
- 2<sup>o</sup> Sampling procedures;
- 3<sup>o</sup> Testing procedures and records including analytical worksheets and laboratory notebooks
- 4<sup>o</sup> Analytical reports and certificates;
- 5<sup>o</sup> Data from environmental monitoring, where required;
- 6<sup>o</sup> Validation records of test methods, where applicable and
- 7<sup>o</sup> Procedures and record for calibration of instruments and maintenance of equipment.

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

A manufacturer shall keep records for some kind of data such as analytical test results, yields and environmental controls in a manner that permit trend evaluation.

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

### **Article 66: Sampling**

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



- 1° The method of sampling;
- 2° The equipment to be used;
- 3° The quantity of sample to be taken;
- 4° Instructions for any required sub-division of the sample;
- 5° The type and condition of the sample container to be used;
- 6° The identification of containers sampled;
- 7° Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
- 8° The storage conditions; and
- 9° Instructions for the cleaning and storage of sampling equipment.

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 67: 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.

Samples shall be representative of the batches of material from which they are taken and other samples may also be taken to monitor the most stressed part of a process such as beginning or end of a process. Sampling shall be carried out so as to avoid contamination or other adverse effects on quality and the containers that have been sampled shall be marked accordingly and carefully resealed after sampling. Care shall be taken during sampling to guard against contamination or mix-up of, or by, the material being sampled and all sampling equipment that comes into contact with the material should be clean and some particularly hazardous or potent materials may require special precautions.

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

Each sample container shall bear a label indicating:

- 1° The name of the sampled material;
- 2° The batch or lot number;
- 3° The number of the container from which the sample has been taken;
- 4° The number of the sample

- 5° The signature of the person who has taken the sample; and
- 6° The date of sampling.

**Article 68: Test requirements**

A person shall not release a 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.

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

Each batch of printed packaging materials shall be examined following receipt.

**Article 69: In-process control**

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

**Article 70: Finished Products**

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

**Article 71: 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.

A written record of the investigation shall be made and shall include the conclusion and follow-up action.

Out-of-specification results obtained during testing of materials or products shall be investigated in accordance with an approved procedure and records maintained.

**Article 72: Stability Studies**

After marketing the manufacturer shall monitor stability of the medicinal product according to a continuous appropriate program that will permit the detection of any stability issue such as changes in levels of impurities, or dissolution profile associated with the formulation in the marketed package.

Stability shall also be considered to the intermediates and or bulk product such as when the bulk product is stored for a long period before being packaged or shipped from a manufacturing site to a packaging site.

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

A manufacturer shall describe the on-going stability program in a written protocol as prescribed in these regulations.

The equipment used to perform stability studies such as stability chambers among others shall be qualified and maintained.

The number of batches and frequency of testing shall provide a sufficient amount of data to allow trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type shall be included in the stability program and the frequency of testing may take into account a risk-benefit approach.

The manufacturer may apply the principle of bracketing and matrixing designs if scientifically justified in the protocol. In certain situations, additional batches shall be included in the on-going stability program such as an on-going stability study when conducted after a significant change or significant deviation to the process or package.

A manufacturer shall ensure availability of all results of on-going stability studies to key personnel in particular, and the authorized person.

Where ongoing stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there shall be a written agreement between the parties concerned and results of on-going stability studies shall be available at the site of manufacture for review by the competent Authority.

Out of specification or significant typical trends shall be investigated and confirmed out of specification result, or significant negative trend, shall be reported to the relevant competent authorities. The possible impact on batches on the market shall be considered in accordance with these regulations.

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

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

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

A written program for ongoing stability determination shall be developed and implemented to include elements such as:

- 1<sup>o</sup> A complete description of the drug involved in the study;
- 2<sup>o</sup> The complete testing parameters and methods describing all tests for potency, purity, and physical characteristics and documented evidence that indicate stability;
- 3<sup>o</sup> Provision for the inclusion of a sufficient number of batches;
- 4<sup>o</sup> The testing schedule for each drug;
- 5<sup>o</sup> Provision for special storage conditions;
- 6<sup>o</sup> Provision for adequate sample retention; and



- 7<sup>o</sup> A summary of all the data generated, including the evaluation and the conclusions of the study.

Stability shall be determined prior to marketing and following any significant changes in processes, equipment and or packaging materials.

**Article 73: Reagents and Culture media**

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

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

A manufacturer shall indicate on the label the concentration, standardization factor, shelf-life, the date when re-standardization is due, and the storage conditions and the label shall be signed and dated by the person preparing the reagent.

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 74: Reference Standards**

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

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.

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

- 1<sup>o</sup> Name of the material;
- 2<sup>o</sup> Batch or lot number and control number;
- 3<sup>o</sup> Date of preparation;
- 4<sup>o</sup> Shelf-life;
- 5<sup>o</sup> Potency;
- 6<sup>o</sup> Storage conditions.

Official reference standards shall be used only for the purpose described in the appropriate monograph. Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization.

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

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

**CHAPTER X: CONTRACT, PRODUCTION AND ANALYSIS**

**Article 75: Contractual Arrangements**

A manufacturer shall correctly define, agree, and control production and analysis in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality.

There shall be a written contract which clearly establishes the duties of each party and the contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises the full responsibility.

All arrangements for manufacturing and analysis, including any proposed changes in technical or other arrangements, shall be in accordance with the marketing authorization for the product concerned.

A manufacturer shall have a written contract covering the manufacturing and analysis arranged and any technical arrangements made in connection with it. The contract shall permit the audit of the facilities.

In the case of analysis, the final approval for release must be given by the authorized person.

**Article 76: Obligation of Parties to contract**

Parties to the contract shall make sure that:

- 1<sup>o</sup> They assess the competence in carrying out the work or tests required successfully and ensure that the principles of good manufacturing practice described in these regulations are followed;
- 2<sup>o</sup> They provide all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements;
- 3<sup>o</sup> They are fully aware of any problems associated with the product, work, or tests that might pose a hazard to premises, equipment, personnel, other materials, or other products;
- 4<sup>o</sup> They ensure that, all processed products and materials delivered comply with their specifications or that the product has been released by the authorized person;
- 5<sup>o</sup> They have adequate premises, equipment, knowledge, and experience and competent personnel to carry out satisfactorily the work ordered by the contract giver.

**Article 77: Essential requirements of the contract**

Manufacturing shall not be undertaken unless by a manufacturer who holds a manufacturing authorization.

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 analysed.

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

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

In the case of contract analysis, the contract shall state whether or not the samples will be taken at the premises of the manufacturer.

A manufacturing, analytical, and distribution records and reference samples shall have kept available and any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect procedures.

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

The technical aspects of the contract shall be drawn up by competent persons with suitably knowledgeable in pharmaceutical technology, analysis and good manufacturing practice.

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

## **CHAPTER XI: COMPLAINTS HANDLING AND PRODUCT RECALL**

### **Article 78: Defective products**

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

A system shall be designed to recall promptly and effectively products known or suspected to be defective from the market complaints.

A person responsible for handling the complaints and deciding the measures to be taken shall be designated, together with sufficient supporting staff.

Manufacturer shall have 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.

Any complaint concerning a product defect shall be recorded with all the original details and thoroughly investigated and the person responsible for quality control shall be involved in the study of such problems.

If product defect is discovered or suspected in a batch, considerations shall be given to whether other batches should be checked in order to determine whether they are also affected.

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.

There shall be active follow-up of the implementation of corrective actions. Where necessary, manufacturers shall take appropriate follow-up action, possibly including product recall, after investigation and evaluation of the complaint.

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



The manufacturers shall regularly review complaints records for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.

Manufacturer shall inform the Authority there is an action taken following possibly faulty manufacturing, product deterioration, or any other serious quality problems with a product.

**Article 79: Product recall**

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

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

There shall be established written procedures regularly checked and updated 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.

A manufacturer shall ensure that:

- 1<sup>o</sup> All distribution records are readily available to a person responsible for recalls;
- 2<sup>o</sup> The progress of the recall process is monitored and recorded;
- 3<sup>o</sup> Records are including the disposition of the product;
- 4<sup>o</sup> Issuance of a final report which include reconciliation between the delivered and recovered quantities of the products;
- 5<sup>o</sup> The effectiveness of the arrangements for recalls are tested and evaluated from time to time; and
- 6<sup>o</sup> Recalled products are identified and stored separately in a secure area until a decision is taken on their fate.

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

**Article 80: Inspection**

Self-inspection shall:

- 1<sup>o</sup> Evaluate the manufacturer's compliance with good manufacturing practice in all aspects of production and quality control.
- 2<sup>o</sup> Be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions.
- 3<sup>o</sup> Be performed routinely and on special occasions such as product recalls or repeated rejections, or when an inspection by the health authorities is announced.

The team responsible for self-inspection shall consist of personnel who can evaluate the implementation of Good Manufacturing Practice objectively.

All recommendations for corrective action should be implemented and the procedure for self-inspection shall be documented.

**Article 81: Items for self-inspection**

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

**Article 82: Self-inspection team**

Management shall appoint a self-inspection team consisting of experts in their respective fields and familiar with Good Manufacturing Practice and the members of the team may be appointed from inside or outside the company.

**Article 83: 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 84: Self-inspection report**

A report shall be made at the completion of a self-inspection with inspection findings, evaluation, conclusion and recommended corrective actions.

**Article 85: 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 86: Audits and approval**

The person responsible for Quality Control shall, have responsibility together with other relevant departments for approving vendor and suppliers who can reliably supply starting and packaging materials that meet established specifications.

Before suppliers are approved and included in the approved supplier's list or specifications, shall be evaluated and the evaluation shall take into account a vendor's and supplier's history and the nature of the materials to be supplied.

If an audit is required, it shall determine the supplier's ability to conform to Good Manufacturing Practice standards.

**CHAPTER XIII: MANUFACTURE OF STERILE MEDICINAL PRODUCTS**

**Article 87: Sterile medicinal products**

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

Production shall depend on the skill, training and attitudes of the personnel involved and Quality Assurance shall be followed.

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

Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.

The manufacturing of sterile products shall be carried out in clean areas with through airlocks for personnel equipment and materials.

Clean areas shall be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.

The various operations of component preparation, product preparation and filling shall be carried out in separate areas within the clean area.

Manufacturing operations shall be divided into products that are, terminally sterilized and those which are conducted aseptically at some or all stages.

Clean areas for the manufacture of sterile products shall be classified according to the required characteristics of the environment.

Each manufacturing operation shall require an appropriate environmental cleanliness level in the operational state in order to minimize the risks of particulate or microbial contamination of the product or materials being handled.

The manufacture of sterile medicinal products shall distinguish four clean grades as follows:

- 1<sup>o</sup> **Grade A:** The local zone for high risk operations such as filling zone, stopper bowls, open ampoules and vials, making aseptic connections and normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36-0.54 mis (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated. A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.
- 2<sup>o</sup> **Grade B:** Applicable for aseptic preparation and filling, this is the background environment for grade A zone.
- 3<sup>o</sup> **Grade C and D:** Clean areas for carrying out less critical stages in the manufacture of sterile products.

The areas shall be monitored during operation in order to control the particulate cleanliness of the various grades.



Where aseptic operations are performed monitoring shall be frequent using methods and sampling methods used in operation shall not interfere with zone protection.

Results from monitoring shall be considered when reviewing batch documentation for finished product release and surfaces and personnel shall be monitored after critical operations.

Additional microbiological monitoring is also required outside production operations, after validation of systems, cleaning and sanitization.

**Article 88: 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 and include frequent leak testing of the isolator and sleeve system.

**Article 89: Blow, fill, seal and technology**

Blow, fill, seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A or B clothing is used. The environment should comply with the viable and non-viable limits "at rest" and the viable limit only when in operation.

Blow, fill or seal equipment used for the production of products for terminal sterilization should be installed in at least a grade D environment.

**Article 90: Terminally sterilized products**

Preparation of components for most products shall be done in at least a grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilization.

Where there is unusual risk because the product actively supports microbial growth or must be held for a long period before sterilization or is necessarily processed not mainly in closed vessels, preparation shall be done in a grade C environment.

Filling of products for terminal sterilization shall be done in at least a grade C environment.

Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a grade A zone with at least a grade C background.

Preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a grade C environment before terminal sterilization.

**Article 91: Aseptic preparation**

Components after washing shall be handled in at least a grade D environment. Handling of sterile starting materials and components, unless subjected to sterilization or filtration through a micro-

organism-retaining filter later in the process, should be done in a grade A environment with grade B background.

Preparation of solutions which are to be sterile filtered during the process shall be done in a grade C environment and if not filtered, the preparation of materials and products shall be done in a grade A environment with a grade B background.

Handling and filling of aseptically prepared products shall be done in a grade A environment with a grade B background.

Transfer of partially closed containers, as used in freeze drying, shall, prior to the completion of stoppering, be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment.

Preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment, with a grade B background, when the product is exposed and is not subsequently filtered.

### **Article 92: Personnel**

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

Inspections and controls shall be conducted outside the clean areas as far as possible.

All personnel including those concerned with cleaning and maintenance employed in such areas shall receive regular training in disciplines relevant to the correct manufacture of sterile products, in reference to hygiene and the basic elements of microbiology.

Staff who have been engaged in the processing of animal tissue materials or cultures of micro-organisms other than those used in the current manufacturing process shall not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed.

High standards of personnel hygiene and cleanliness are essential and personnel involved in the manufacture of sterile preparations shall be instructed to report any condition which may cause the shedding of abnormal numbers or types of contaminants and periodic health checks for such conditions are desirable.

Actions to be taken about personnel who could be introducing undue microbiological hazard shall be decided by a designated competent person.

Changing and washing shall follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.

The clothing and its quality shall be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination. Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms.

For every worker in a grade A/B area, clean sterile (sterilized or adequately sanitized) protective garments should be provided at each work session.

Gloves shall be regularly disinfected during operations. Masks and gloves shall be changed at least at every working session.

Clean area clothing shall be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.

These operations should follow written procedures.

**Article 93: Premises**

In clean areas, all exposed surfaces shall be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and permit the repeated application of cleaning agents, and disinfectants are used.

To reduce accumulation of dust and facilitate cleaning there shall be no unclean able recesses and a minimum of projecting ledges.

Shelves, cupboards and equipment and doors shall be designed to avoid those unclean able recesses. False ceilings shall be sealed to prevent contamination from the space above them.

Pipes and ducts and other utilities shall be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.

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.

Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent back-flow.

Changing rooms shall be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing and they should be flushed effectively with filtered air.

The final stage of the changing room shall, in the "at rest" state, be the same grade as the area into which it leads and the use of separate changing rooms for entering and leaving clean areas is sometimes desirable.

Hand washing facilities should be provided only in the first stage of the changing rooms.

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 a positive pressure and an 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 pascals guidance values and particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed.

It shall be demonstrated that air-flow patterns do not present a contamination risk and care shall be taken to ensure that air flows do not distribute particles from a particle-generating person, operation or machine to a zone of higher product risk.



Indicators of pressure differences shall be fitted between areas where these differences are important and these pressure differences shall be recorded regularly or otherwise documented.

#### **Article 94: Equipment**

A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilized in a sterilizing tunnel.

Equipment, fittings and services shall be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area and if sterilization is required, it shall be carried out after complete reassembly wherever possible.

When equipment maintenance has been carried out within the clean area, the area shall be cleaned, disinfected and sterilized where appropriate, before processing recommences and if the required standards of cleanliness and asepsis have not been maintained during the work.

Water treatment plants and distribution systems shall be designed, constructed and maintained so as to ensure are liable source of water of an appropriate quality. They should not be operated beyond their designed capacity.

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

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.

#### **Article 95: Sanitation**

The sanitation of clean areas is particularly important and they should be cleaned thoroughly in accordance with a written programme and where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.

Disinfectants and detergents shall be monitored for microbial contamination and dilutions should be kept in previously cleaned containers and stored only for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.

Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

#### **Article 96: Processing**

Precautions to minimize contamination shall be taken during all processing stages including the stages before sterilization.

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

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

Selection of the nutrient medium for validation of aseptic processing should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium.

The process simulation test shall imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps.

Process simulation tests shall be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification the Heating, ventilation, and Air conditioning (HVAC) system, equipment, process and number of shifts. Process simulation tests shall be repeated at least twice a year per shift and process.

The number of containers used for media fills shall be sufficient to enable a valid evaluation and for small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth however a contamination rate of less than 0.1% with 95% confidence limit is acceptable.

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 of any action taken.

Activities in clean areas and especially when aseptic operations are in progress shall be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. Containers and materials liable to generate fibers shall be minimized in clean areas.

The interval between the washing, drying and the sterilization of components, containers and equipment as well as between their sterilization and use shall be minimized and subject to a time-limit appropriate to the storage conditions.

The time between the start of the preparation of a solution and its sterilization or filtration through a micro-organism-retaining filter shall be minimized and there shall be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.

The bioburden shall be monitored before sterilization and there shall be working limits on contamination immediately before sterilization which are related to the efficiency of the method to be used. Where appropriate the absence of pyrogens shall be monitored and all solutions, in particular large volume infusion fluids, should be passed through a micro-organism-retaining filter, if possible sited immediately before filling.

Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilized and passed into the area through double-ended sterilizers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination.

Non-combustible gases shall be passed through micro-organism 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 97: Processing Sterilization**

All sterilization processes shall be validated.

Before any sterilization process is adopted its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed shall be demonstrated by physical measurements and by biological indicators where appropriate.

The validity of the process shall be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment, records should be kept of the results. Validated loading patterns should be established for all sterilization processes.

Biological indicators shall be considered as an additional method for monitoring the sterilization and they should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls.

There shall be a clear means of differentiating products which have not been sterilized from those which have and each basket, tray or other carrier of products or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilized.

Sterilization records shall be available for each sterilization run and they should be approved as part of the batch release procedure.

**Article 98: Sterilization by heat**

Each heat sterilization cycle shall be recorded on a time temperature chart with a suitably large scale or by other appropriate equipment with suitable accuracy and precision.

The position of the temperature probes used for controlling and recording should have been determined during the validation and, where applicable, also checked against a second independent temperature probe located at the same position.

Chemical or biological indicators may also be used, but shall not take the place of physical measurements.

Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time-period is commenced and this time must be determined for each type of load to be processed.

After the high temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling and any cooling fluid or gas in contact with the product should be sterilized, unless it can be shown that any leaking container would not be approved for use.

**Article 99: Sterilization by moist heat**

Both temperature and pressure shall be used to monitor the process.

Control instrumentation shall normally be independent of monitoring instrumentation and recording charts.



Where automated control and monitoring systems are used for these applications, they shall be validated to ensure that critical process requirements are met.

The reading of the independent temperature indicator should be routinely checked against the chart recorder during the sterilization period.

For Sterilizers fitted with a drain at the bottom of the chamber, it may be necessary to record the temperature at this position, throughout the sterilization period.

There should be frequent leak tests on the chamber when a vacuum phase is part of the cycle.

**Article 100: Sterilization by Dry heat**

The process used shall include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air.

Any air admitted should be passed through a High Efficiency Particulate Air (HEPA) filter and this process is also intended to remove pyrogens, challenge tests using endotoxins shall be used as part of the validation.

**Article 101: Filtration of medicinal products**

If the product cannot be sterilized in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron or less, or with at least equivalent micro-organism retaining properties, into a previously sterilized container.

Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilized microorganism retaining filter, immediately prior to filling may be done.

The integrity of the sterilized filter shall be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test.

The same filter shall not be used for more than one working day unless such use has been validated.

**Article 102: Sterile products**

Container shall be closed by appropriately validated methods.

Containers closed by fusion such as glass or plastic ampoules shall be subject to 100% integrity testing.

Containers sealed under vacuum shall be tested for maintenance of that vacuum after an appropriate, pre-determined period.

Filled containers of parenteral products shall be inspected individually for extraneous contamination or other defects and when inspection is done visually, it should be done under suitable and controlled conditions of illumination and background.

Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection.

**Article 103: Sterility testing**

Samples taken for sterility testing should be representative of the whole of the batch, but should in particular include samples taken from parts of the batch considered to be most at risk of contamination. Products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant intervention;

Products which have been heat sterilized in their final containers, consideration shall be given to taking samples from the potentially coolest part of the load.

**CHAPTER XIV: BIOLOGICAL MEDICINAL PRODUCTS FOR HUMAN USE**

**Article 104: Biological medicinal products**

The manufacture of medicinal products shall involve certain specific considerations arising from the nature of the products and the processes.

The ways in which biological medicinal products are produced, controlled and administered shall make some particular precautions necessary.

Control of biological medicinal products shall involve biological analytical techniques which have a greater variability than physico-chemical determinations.

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

**Article 105: 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 substance and who possesses the scientific knowledge upon which the manufacture of these products is based.

The personnel shall include specialists with training appropriate to the products made in the establishment.

**Article 106: Premises and Equipment**

Animals shall be accommodated in separate buildings with self-contained ventilation systems.

The buildings' design 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 107: Animal Quarters and Care Production**

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

Laboratories, operating rooms and all other rooms and buildings used for the manufacture of biological products shall be designed and constructed of materials of the highest standard so that cleanliness, especially freedom from dust, insects and vermin, can be maintained.

**Article 108: Production**

Standard operating procedures shall be available and maintained up to date for all manufacturing operations.

The source, origin and suitability of starting materials shall be clearly defined.

Where necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available. In such cases, release of a finished product is conditional on satisfactory results of these tests.

Where sterilisation of starting materials is required, it shall be carried out where possible by heat. Other appropriate methods may also be used for inactivation of biological materials such as irradiation.

**Article 109: Labeling**

All products shall be clearly identified by labels and the labels used shall remain permanently attached to the containers under all storage conditions and an area of the container shall be left uncovered to allow inspection of the contents.

If the final container is not suitable for labelling such as a capillary tube, it shall be in a labelled package.

The information given on the label on the container and the label on the package shall be approved by the Authority.

**Article 110: Quality Control**

The quality-assurance and quality control department shall have the following principal duties:

- 1<sup>o</sup> To prepare detailed instructions for each test and analysis;
- 2<sup>o</sup> To ensure adequate identification and its segregation of test samples to avoid mix-up and cross contamination;
- 3<sup>o</sup> To ensure that environmental monitoring and equipment validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;
- 4<sup>o</sup> To release or reject raw materials and intermediate products, if necessary;
- 5<sup>o</sup> To release or reject packaging and labelling materials and the final containers in which drugs are to be placed;
- 6<sup>o</sup> To release or reject each lot of finished preparation;
- 7<sup>o</sup> To evaluate the adequacy of the conditions under which raw materials, intermediate products and finished biological preparations are stored;
- 8<sup>o</sup> To evaluate the quality and stability of finished products and, when necessary, of raw materials and intermediate products;



- 9° To establish expiry dates on the basis of the validity period related to specified storage conditions.

## CHAPTER XV: QUALIFICATION AND VALIDATION

### **Article 111: Validation**

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

Furthermore, he or she shall ensure that significant changes to the facilities, equipment and processes, which may affect the quality of the product, are validated.

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

### **Article 112: Validation activities**

Every manufacturer shall plan all validation activities.

They shall also define and document key elements of a validation programme in a validation master plan or equivalent document. The validation master plan shall be a summary document which is brief, concise and clear.

The validation master plan shall contain data on at least the following:

- 1° Validation policy;
- 2° Organizational structure of validation activities;
- 3° Summary of facilities, systems, equipment and processes to be validated;
- 4° Documentation format and the format to be used for protocols and reports;
- 5° Planning and scheduling;
- 6° Change control;
- 7° Reference to existing documents; and
- 8° In case of large-scale manufacturing, it may be necessary to create separate validation master plans.

### **Article 113: Documentation**

A written protocol shall be established to specify how qualification and validation will be conducted. The protocol shall be reviewed and approved and specify critical steps and acceptance criteria.

A report that cross-references the qualification and validation protocol shall be prepared, summarizing the results obtained, commenting on any deviations observed and drawing the necessary conclusions including recommending changes necessary to correct deficiencies.

Any changes to the plan as defined in the protocol 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 a written authorization.

**Article 114: 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 115: Installation Qualification**

Installation qualification shall be performed on new or modified facilities, systems and equipment, they shall include, but not limited to the following:

- 1<sup>o</sup> Installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;
- 2<sup>o</sup> Collection and collation of supplier operating and working instructions and maintenance requirements;
- 3<sup>o</sup> Calibration requirements; and
- 4<sup>o</sup> Verification of materials of construction.

**Article 116: Operational Qualification**

Operational qualifications shall follow installation qualification. They include, but not be limited to the following:

- 1<sup>o</sup> Tests that have been developed from knowledge of processes, systems and equipment;
- 2<sup>o</sup> Tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as " worst case" conditions.

The completion of a successful operational qualification shall allow for the finalization of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. Operating equipment shall permit for a formal "release" of the systems and equipment.

**Article 117: Performance Qualification**

Performance qualification shall follow successful completion of installation qualification and operating equipment. Performance qualification shall include, but not be limited to the following:

- 1<sup>o</sup> Tests, using production materials, qualified substitutes or simulated products, that have been developed from knowledge of the process and the facilities, systems or equipment; and
- 2<sup>o</sup> Tests to include a condition or set of conditions encompassing upper and lower operating limits.

Albeit performance qualification is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with operating equipment.

**Article 118: 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 119: Process validation**

Process validation shall be categorized as follows:

- 1<sup>o</sup> Prospective validation;
- 2<sup>o</sup> Concurrent validation; and
- 3<sup>o</sup> Retrospective validation.

Subject to in the provisions of the paragraph 1 (1<sup>o</sup>), prospective validation shall normally be completed prior to the distribution and sale of the medicinal product.

Prospective validation shall include, but not be limited to the following:

- 1<sup>o</sup> Short description of the process;
- 2<sup>o</sup> Summary of the critical processing steps to be investigated;
- 3<sup>o</sup> List of the equipment or facilities to be used including measuring, monitoring and recording equipment together with its calibration status;
- 4<sup>o</sup> Finished product specifications for release;
- 5<sup>o</sup> List of analytical methods, as appropriate;
- 6<sup>o</sup> Proposed in-process controls with acceptance criteria;
- 7<sup>o</sup> Additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
- 8<sup>o</sup> Sampling plan;
- 9<sup>o</sup> Methods for recording and evaluating results;
- 10<sup>o</sup> Functions and responsibilities; and
- 11<sup>o</sup> Proposed timetable.

Using prospective validation process including specified components, a series of batches of the final product may be produced under routine conditions.

In theory the number of process runs carried out and observations made shall be sufficient to allow for the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches or runs within the finally agreed parameters would constitute a validation of the process.

Batches made for process validation shall be the same size as the intended industrial scale batches.



If it is intended that validation batches be sold or supplied, the conditions under which they are produced shall comply fully with the requirements of good manufacturing practice, including the satisfactory outcome of the validation exercise, and where applicable, the marketing authorization.

Subject to provisions of the paragraph 1(2<sup>o</sup>) of this Article, in exceptional circumstances, where prospective validation is not possible, it may be necessary to validate processes during routine production, to be referred as concurrent validation.

The decision to carry out concurrent validation must be justified, documented and approved by authorized personnel.

Documentation requirements for concurrent validation are the same as those specified under provisions of the paragraph 3, to 8 of this Article.

Processes in use for some time shall also be validated, to be referred as retrospective validation.

Retrospective validation shall be acceptable only for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.

Validation of such processes shall be based on historical data. The source of data for retrospective validation shall include, but not limited to:

- 1<sup>o</sup> batch processing and packaging records
- 2<sup>o</sup> process control charts,
- 3<sup>o</sup> maintenance log books,
- 4<sup>o</sup> records of personnel changes,
- 5<sup>o</sup> process capability studies,
- 6<sup>o</sup> finished product data, including trend cards and storage stability results.

Batches selected for retrospective validation shall be representative of all batches made during the review period, including any batches that failed to meet specifications, and shall be sufficient in number to demonstrate process consistency.

Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.

For retrospective validation, generally data from ten to thirty consecutive batches shall be examined to assess process consistency, but fewer batches may be examined if justified.

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.

Facilities, systems, equipment and processes shall be periodically evaluated to verify that they are still operating in a valid manner.

**Article 120: Cleaning validation**

Cleaning validation shall be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carry-over of product residues, cleaning agents and microbial contamination shall be logically based on the materials involved.

The limits shall be achievable and verifiable.

Validated analytical methods having sensitivity to detect residues or contaminants shall be used.

The detection limit for each analytical method shall be sufficiently sensitive to detect the established acceptable level of the residue or contaminant.

Cleaning procedures for product contact surfaces of the equipment shall be validated. Consideration may be given to non-contact parts and the intervals between use and cleaning as well as cleaning and re-use shall be validated. Cleaning intervals and methods shall be determined.

For cleaning procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes.

A single validation study utilizing a "worst case" approach may be carried out which takes account of the critical issues.

Three consecutive applications of the cleaning procedure shall be performed and shown to be successful in order to prove that the method is validated.

"Test until clean" shall not be considered as an appropriate alternative to cleaning validation.

Products which simulate the physico-chemical properties of the substances to be removed may exceptionally be used instead of the substances themselves, where such substances are either toxic or hazardous.

**Article 121 Change control**

Written procedures shall be in place to describe the actions to be taken if a change is proposed to a starting material, product component, process equipment, process environment or site, method of production or testing or any other change that may affect product quality or reproducibility of the process.

Change control procedures shall ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of desired quality and consistent with the approved specifications.

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 122: Revalidation**

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

Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation under these regulations.

## **CHAPTER XVI: DIGITALIZED SYSTEM**

### **Article 123: Computerized systems**

A manufacturer may use digitalized systems to replace manual operations.

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

Subject to provisions of the paragraph 1 of this Article, consideration shall be given to the risk of losing aspects of the previous system by reducing the involvement of operators.

When computerized systems are used, there shall be close co-operation between key personnel and those involved with computer systems.

Persons in responsible positions shall have the appropriate training for the management and use of systems within their field of responsibility which utilizes computers.

Appropriate expertise shall be available and used to provide advice on aspects of design, validation, installation and operation of computerized systems.

### **Article 124: Validation**

The extent of validation necessary for computerized systems, shall depend on a number of factors including the use to which the system is to be put, whether it is prospective or retrospective and whether or not novel elements are incorporated.

Validation shall be considered as part of the complete life cycle of a computer system.

Subject to provisions of the paragraph 2 of this Article, the cycle shall include stages of planning, specification, programming, testing, commissioning, documentation, operation, monitoring and changing.

### **Article 125: Handling of system**

Attention shall be paid to the siting of equipment in suitable conditions where extraneous factors cannot interfere with the system.

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

The system shall describe the principles, objectives, security measures and scope and the main features of the way in which the computer is used and how it interacts with other systems and procedures.

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

The system shall include, where appropriate, built-in checks of the correct entry and processing of data.



Before a system using a computer is brought into use, it shall be thoroughly tested and confirmed as being capable of achieving the desired results.

If a manual system is being replaced, the two shall run in a parallel for a time, as part of the testing validation

Data shall only be entered or amended by persons authorized to do so. Suitable methods of deterring unauthorized entry of data include the use of keys, pass cards, personal codes and restricted access to computer terminals.

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.

Consideration shall be given to systems allowing for recording of attempts to access by unauthorized persons.

When critical data are being entered manually there shall be an additional check on the accuracy of the record which is made. The check may be done by a second operator or by validated electronic means.

The system shall record the identity of operators entering or confirming critical data.

Authority to amend entered data shall be restricted to nominated persons.

Any alteration to an entry of critical data shall be authorized and recorded with the reason for the change.

Consideration shall be given to the system creating a complete record of all entries and amendments to be referred as an "audit trail".

Alterations to a system or to a computer programme shall only be made in accordance with a defined procedure which shall include provision for validating, checking, approving and implementing the change.

An alteration shall only be implemented with the agreement of the person responsible for the part of the system concerned, and the alteration shall be recorded.

Every significant modification shall be validated.

For quality auditing purposes, it shall be possible to obtain meaningful printed copies of electronically stored data.

Data shall be secured by physical or electronic means against wilful or accidental damage.

Stored data shall be checked for accessibility, durability and accuracy.

If changes are proposed to the computer equipment or its programs, the checks referred to in precedent paragraph, shall be performed at a frequency appropriate to the storage medium being used.

Data shall be protected by backing-up at regular intervals and stored as long as necessary at a separate and secure location.

There shall be available adequate alternative arrangements for systems which need to be operated in the event of a breakdown. The time required to bring the alternative arrangements into use shall be related to the possible urgency of the need to use them. For example, information required to effect a recall must be available at short notice.

The procedures to be followed if the system fails or breaks down shall be defined and validated.

Any failures and remedial action taken shall be recorded.

A procedure shall be established to record and analyse errors and to enable corrective action to be taken.

When outside agencies are used to provide a computer service, there shall be a formal agreement including a clear statement of the responsibilities of that outside agency.

When the release of batches for sale or supply is carried out using a computerized system, the system shall recognize that only an authorized person can release the batches and it shall clearly identify and record the person releasing the batches.

## **CHAPTER XVII: WATER FOR PHARMACEUTICAL USE**

### **Article 126: Water requirements and uses**

Water is the most widely used substance, raw material or starting material in the production, processing and formulation of pharmaceutical products and it has unique chemical properties due to its polarity and hydrogen bonds which is able to dissolve, absorb, adsorb or suspend in many different compounds.

### **Article 127: 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 an appropriate quality.

The system shall not be operated beyond their designed capacity.

Water shall be produced, stored and distributed in a manner that prevents unacceptable microbial, chemical or physical contamination such as dust and dirt.

### **Article 128: Water quality specifications**

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

### **Article 129: 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 130: 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 recontamination and microbial proliferation.

**Article 131: Highly purified water**

Highly purified water shall be prepared from potable water as minimum quality feed-water which is a unique specification for water found only in the European Pharmacopoeia.

This grade of water shall meet the same quality standard as water for injections including the limit for endotoxins, but the water-treatment methods are not considered to be as reliable as distillation.

Highly purified water may be prepared by combinations of methods such as reverse osmosis, ultra-filtration and deionization.

**Article 132 Water for injections**

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

Water for injection is not sterile water and is not a final dosage form and it is an intermediate bulk product.

Water for injections is the highest quality of pharmacopoeia water for pharmaceutical use.

**Article 133: Other grades of water**

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

**Article 134: Application of specific waters to processes and dosage forms**

The Authority shall define the requirement to use the specific grades of pharmaceutical water for use for different dosage forms or for different stages in washing, preparation, synthesis, manufacturing or formulation.

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 135: Water purification methods**

The chosen water purification method, or sequence of purification steps, shall be appropriate to the application in question and the following shall be considered when selecting the water treatment method:

- 1<sup>o</sup> The water quality specification;
- 2<sup>o</sup> The yield or efficiency of the purification system;
- 3<sup>o</sup> Feed-water quality and the variation over time (seasonal changes);
- 4<sup>o</sup> The reliability and robustness of the water- treatment equipment in operation;
- 5<sup>o</sup> The availability of water-treatment equipment on the market;
- 6<sup>o</sup> The ability to adequately support and maintain the water purification equipment; and the operation costs.



**Article 136: Production of drinking-water**

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

- 1° Filtration;
- 2° Softening;
- 3° Disinfection or sanitization such as by sodium hypochlorite (chlorine)
- 4° Injection;
- 5° Iron (ferrous) removal;
- 6° Precipitation; and
- 7° Reduction of specific inorganic /organic materials.

**Article 137 Production of purified water**

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

Typically, iron exchange, ultra-filtration and reverse osmosis processes shall be used and distillation can also be used.

**Article 138: Production of highly purified water**

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

Typically iron exchange, ultrafiltration and reverse osmosis processes shall be used.

**Article 139: 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:

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

**Article 140: 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 as a key part of the whole system, and shall be designed to be fully integrated with the water purification components of the system.

**Article 141: Materials that come into contact with systems**

The materials that come into contact with water for pharmaceutical use, including pipe work, valves and fittings, seals, diaphragms and instruments, shall be selected to satisfy the following objectives:

- 1° Compatibility; All materials used shall be compatible with the temperature and chemicals used by or in the system
- 2° Prevention of leaching; All materials that come into contact with water for pharmaceutical use shall be non-leaching at the range of working temperatures.
- 3° Corrosion resistance; Purified water, highly purified water and water for injection are highly corrosive; to prevent failure of the system and contamination of the water, the materials selected shall be appropriate
- 4° The method of jointing shall be carefully controlled, and all fittings and components shall be compatible with the pipe work used.

**Article 142: 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 143: Storage vessel requirements**

The design and size of the vessel shall take into consideration the following elements:

- 1° Capacity; and
- 2° Contamination control considerations.

**Article 144: Water distribution pipework**

The distribution of purified water, highly purified water and water for injection shall be accomplished using a continuously circulating pipework loop.

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 145: 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 146: Qualification of water system**

Purified water, highly purified water and water for injection systems are all considered to be direct impact, quality critical systems that 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 147: 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 148: 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 149: 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<sup>o</sup> Demonstrate extended reliable performance;
- 2<sup>o</sup> Ensure that seasonal variations are evaluated; and
- 3<sup>o</sup> 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 150: 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.

Monitoring shall include a combination of online instrument monitoring of parameters such as flow, pressure, temperature, conductivity and total organic carbon, and offline sample testing for physical, chemical and microbiological attributes.

Offline samples shall be taken from points of use and specific sample points.

Samples from points of use shall be taken in a similar way to that adopted when the water is being used in service.



**Article 151: Maintenance of water systems**

Water for Pharmaceutical use systems shall be maintained in accordance with a controlled, documented maintenance program that takes into account the following:

- 1° Defined frequency for system elements;
- 2° The calibration program
- 3° Standard operating procedures for specific tasks;
- 4° Control of approved spares;
- 5° Issue of clear maintenance plan and instructions;
- 6° Review and approval of systems for use upon completion of work; and
- 7° Record and review of problems and faults during maintenance.

**Article 152: 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 153: Heating, ventilation and air-conditionings system**

Every pharmaceutical dosage forms shall be manufactured under installed and retained heating, ventilation and air-conditioning system to ensure that the quality of pharmaceutical products is not compromise.

The system shall be well-designed to provide comfortable conditions for operators of the manufacturing including architectural layouts with regard to the airlock positions, doorways and lobbies.

**Article 154: 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 pharmaceutical manufacturing plant.

**Article 155: Temperature, relative humidity and ventilation**

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

**Article 156: Production of sterile pharmaceutical products**

The inspectors shall use the production of sterile pharmaceutical products as the basic part of good manufacturing practice manufacturing of pharmaceutical dosage forms.

**CHAPTER XIX: QUALITY RISK MANAGEMENT**

**Article 157: Quality Risk Management**

All manufacturers shall maintain two primary principles of Quality Risk Management to be considered by the Authority for quality assurance of pharmaceutical products as provided hereunder:

- 1<sup>o</sup> Evaluation of the risk to quality which shall be based on scientific knowledge and linked to the protection of the patient; and
- 2<sup>o</sup> The level of effort, formality and documentation of the quality risk management process shall be commensurate with the level of risk.

Beside the principles provided under sub regulation (1) the Quality Risk Management methodology shall:

- 1<sup>o</sup> When applied, processes using Quality Risk Management methodologies be dynamic, iterative and responsive to change; and
- 2<sup>o</sup> Systematically analyse products and processes to ensure the best scientific rationale is in place to improve the ability of success;
- 3<sup>o</sup> Identify important knowledge gaps associated with processes that need to be understood to properly identify risks provide a communication process that will best interface with all relevant parties involved;
- 4<sup>o</sup> 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; and
- 5<sup>o</sup> Enable the pharmaceutical industry to adopt a risk-based approach to development as circumstances of applicable guidelines by the Authority may allow.

**Article 158: 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:

- 1<sup>o</sup> Conduct a risk analysis;
- 2<sup>o</sup> Identify and analyse potential risks;
- 3<sup>o</sup> Identify, evaluate risks and determine which risks should be controlled and which ones

- can be accepted;
- 4<sup>o</sup> Recommend and implement adequate risk control measures; and
  - 5<sup>o</sup> Devise procedures for risk review monitoring and verification.

**Article 159: Risk assessment of the product**

At any time when the risk assessment to the product is conducted, the manufacturer shall need to determine the safety and efficacy of product in addition to the 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.

Subject to the provision of the paragraph 1 of this Article potential risks to be considered shall include:

- 1<sup>o</sup> Materials and ingredients;
- 2<sup>o</sup> Physical characteristics and composition of the product; processing procedures;
- 3<sup>o</sup> Microbial limits, where applicable
- 4<sup>o</sup> Premises;
- 5<sup>o</sup> Equipment;
- 6<sup>o</sup> Packaging;
- 7<sup>o</sup> Sanitation and hygiene;
- 8<sup>o</sup> Personnel - human error;
- 9<sup>o</sup> Utilities; and
- 10<sup>o</sup> Supply chain.

**Article 160: Assessment of products**

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

- 1<sup>o</sup> Be subject to periodic and the frequency of review; and
- 2<sup>o</sup> Be appropriate for the nature of the activity.

Specific corrective actions shall be developed to prevent 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 161: 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 on the original Decision; and

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 162: Verification of Quality Risk Management process and methodologies**

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

- 1° Review of the Quality Risk Management process and its records;
- 2° 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 163: 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 the 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 industry's quality unit and management. The information shall be communicated to stakeholders for their support.

**Article 164: Mitigation Plans**

A manufacturer shall have a 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 risk.

**Article 165: Training and education**

Every industry or factory shall:

- 1° Train employees to understand Quality Risk Management is,
- 2° Possess the skills necessary to apply it properly, and be appropriately resourced to enable the effective practice of the Quality Risk Management principles;
- 3° Develop training programme 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<sup>o</sup> 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 166: Responsibilities of Pharmaceutical manufacturer**

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

In case of external experts, a technical agreement or other equivalent document with the experts may be made where a GMP responsibility is assumed or in the alternative a contract staff may be involved to lead or participate in risk assessments.

The extent of involvement and responsibility accountability shall be documented in a technical agreement or other equivalent document between the individual and the pharmaceutical Industry.

In 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 across various functions and departments of their organization and ensuring that the respective activities are adequately defined, planned, resourced, deployed and reviewed.

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 167: Complaint handling and investigation**

Handling and investigation of quality complaints shall be done in accordance with 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 risk assessment made.

**Article 168: 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 to include, but not limited to:

- 1<sup>o</sup> General approach to both planned and unplanned risk assessment and include scope, responsibilities, controls, approvals, management systems, applicability and exclusions;
- 2<sup>o</sup> Personnel with appropriate qualifications, experience and training including their responsibilities with regard to quality risk management being clearly defined;

- 3<sup>o</sup> Senior management should be involved in the identification and implementation of quality risk management principles within the company;
- 4<sup>o</sup> The risk management procedures for each area of application should be clearly defined;
- 5<sup>o</sup> 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 169 : Active pharmaceutical ingredients**

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

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

Starting material and be incorporated as a significant structural fragment into the structure of the Active pharmaceutical ingredients starting;

An active pharmaceutical ingredient starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. The manufacturer shall designate and document the rationale for the point at which production of the active pharmaceutical ingredients Starting begins.

## **CHAPTER XXI: WASTE MANAGEMENT FOR MEDICINAL PRODUCT MANUFACTURERS AND INSPECTION**

### **Article 170: Hazardous Waste**

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

### **Article 171 : Non-hazardous Pharmaceutical waste**

Non-Hazardous Pharmaceutical Waste comprised of all other pharmaceutical waste that are not stated above shall be controlled.

Subject to any environmental regulation on force, waste disposal must be done primarily by land filling or closure of existing dump sites; or

Modern sanitary landfills that are not dumped engineered facilities used for disposing of solid wastes on land without creating hazards to public health or safety.

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 172: Inspections**

The Authority shall conduct inspection for the purpose of ensuring that:

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

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 in accordance with paragraph 2 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 in accordance with this regulation as he shall consider appropriate.

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, will provide a CAPA report within an identified period and will pay re-inspection fees to the Authority before being re-inspected.

### **Article 173: Appointment of inspectors**

The Authority shall appoint inspectors to inspect domestic and overseas manufacturing facilities where medicines used in Rwanda are manufactured.

The inspectors shall have the relevant qualification in terms of academic education, training and experience in order to effectively take part in inspection of pharmaceutical manufacturing facilities.

### **Article 174: Conflict of Interest**

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

### **Article 175: Powers of inspectors**

For the purposes of enforcing compliance for conducting inspections, an inspector appointed in accordance with these regulations shall, upon production of evidence that he is so authorized, have the right:

- 1<sup>o</sup> At any reasonable time to enter any premises, other than premises used only as a private dwelling house, which he has reason to believe it is necessary for him to visit, including any premises of any person who carries out any of the activities referred to

- in these Regulations;
- 2<sup>o</sup> To carry out at those premises during that visit inspections, examinations, tests and analyses as he considers necessary;
  - 3<sup>o</sup> To require the production of, and inspect any article or substance at, the premises;
  - 4<sup>o</sup> To require the production of inspect and take copies of, or 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;
  - 5<sup>o</sup> To take possession of any samples for examination and analysis and any other article, substance, book, document, data, record in whatever form they are held at, or in the case of computer data or records accessible at, the premises;
  - 6<sup>o</sup> To question any person whom, he finds at the premises and whom he has reasonable cause to believe is able to give him relevant information;
  - 7<sup>o</sup> To require any person to afford him such assistance as he considers necessary with respect to any matter within that person's control, or in relation to which that person has responsibilities; and
  - 8<sup>o</sup> To require, as he considers necessary, any person to afford him such facilities as he may reasonably require that person to afford him; but nothing in this paragraph shall be taken to compel the production by any person of a document of which he would on grounds of legal professional privilege be entitled to withhold production on an order for disclosure in an action in the court or, as the case may be, on an order for production of documents in an action in the court.

An inspector will enter the premise that are closed or unoccupied, the inspector is required to collaborate with the local administration and a representative of the public investigation body of the area.

Together they shall provide written proof of the premises to be inspected before 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 prior to physical inspection. The written proof shall be part of the report that must be submitted to the Authority.

An inspector entering premises by virtue of provisions of paragraph 1 of this Article, of a warrant under the provisions of paragraph 1 of this Article, may take with him when he enters those premises such equipment as may appear to him necessary and any person who is authorized by the Director General to accompany him on that visit.

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

Where, pursuant to provisions of paragraph 1 (5<sup>o</sup>), an inspector takes possession of any article, substance, book, document, data or record, he or 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 statement giving particulars of the article, substance, book, document, data or record sufficient to identify and acknowledging that he or she has taken possession of the document.

Where, pursuant to Paragraph 1 (5<sup>o</sup>) of this Article, an inspector takes a sample for analysis, the Director General may make such arrangements for analysis of that sample as he considers appropriate.

#### **Article 176: Inspections**

Upon arrival to the inspection site, the inspectors shall convene a pre-inspection meeting with the inspected and the leading inspector shall preside 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 GMP Aide-memoir, 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 177: Establishment of a scientific and advisory Committee**

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

#### **Article 178: Joint Inspection**

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

### **CHAPTER XXIII: FINAL PROVISIONS**

#### **Article 179: Suspensions and revocations**

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

- 1<sup>o</sup> Objects to any suspension or revocation of authorization, or to any notice served;
- 2<sup>o</sup> Objects to the refusal of authorization or the imposition of any condition, may notify the director general of its desire to make written representations to, or be or appear before and be heard by, a person appointed by the director general for that purpose.

Any notification of an objection pursuant to provisions of paragraph 1 of this Article, shall be made within fourteen days of service on the notice to which the notification pursuant to paragraph 1 of this Article, relates.

Where the Authority receives a notification pursuant to provisions of paragraph 1 of this Article, he or she shall appoint a person to consider the matter.



The person appointed shall determine the procedure to be followed with respect to the consideration of any objection

The person appointed pursuant to provisions of paragraph 3 of this Article, 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 made pursuant to provisions of paragraph 5 of this Article, 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 pursuant to provisions of paragraph 5 of this Article,

Within fourteen days of receipt of any recommendation made pursuant to provisions of paragraph 5 of this Article, the Director General shall inform the complainant whether he accepts the recommendation and, if he does not accept it, of the reasons for his decision.

Where the Director General is notified of an objection pursuant to provisions of paragraph 1 (1<sup>o</sup>) of this Article, before the date upon which the suspension or revocation or the notice is due to take effect, the suspension or revocation of a notice in respect of which the objection is made shall not take effect until:

- 1<sup>o</sup> The person appointed pursuant to provisions of paragraph 3 of this Article, has considered the matter in accordance with the provisions of this regulation and made a recommendation; and
- 2<sup>o</sup> The director general has informed the complainant concerned of his decision with regard to the recommendation pursuant to provisions of paragraph 9 of this Article.

Subject to the provisions of paragraph 10 of this Article), where the Director General is notified of an objection pursuant to Subject to the provisions of paragraph 1 (1<sup>o</sup>) of this Article, within the period specified provisions of paragraph 2 of this Article, to a suspension, revocation or other notice which has already taken effect on the date the notification was made, the suspension, revocation or notice in respect of which the objection is made shall cease to have effect until;

- 1<sup>o</sup> The person appointed pursuant to provisions of paragraph 3 of this Article has considered the matter in accordance with the provisions of paragraph (11) shall not apply;
- 2<sup>o</sup> In relation to a suspension or revocation, ora notice served, which takes immediate effect in accordance with these regulations; or
- 3<sup>o</sup> In any other case, where the director general determines that it is necessary in the interests of public safety for the suspension, revocation or notice to take effect on the date originally specified, and serves a notice in writing to that effect on the

establishment concerned.

### **Article 180: Appeals**

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 notice.

The Authority shall within 30 working days from the date of appeal application review, vary or reject its own 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 having Health in his or her attributions whose decision shall be final.

### **Article 181: Administrative sanctions**

Any person who contravenes the provisions of these Regulations, shall be liable to the penalties prescribed in Rwanda FDA regulations 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<sup>o</sup> Minor non-compliances
  - a. Corrective action within a given timeframe
  - b. Request for compliance report
- 2<sup>o</sup> Major non-compliances
  - a. issue warning letter
  - b. request for corrective action within a given timeframe
  - c. temporary withdrawal or suspension of marketing authorization
  - d. Request for comprehensive compliance report
  - e. Follow-up inspection to verify implementation of corrective action within a given timeframe
- 3<sup>o</sup> Critical non-compliances include
  - a. Permanent withdrawal of marketing authorization in case of registered products.
  - b. Suspension of marketing authorization in case of registered products
  - c. Not to grant marketing authorization for new application.

### **Article 182: 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 Rwanda FDA website, and on any other media, as the Rwanda FDA may decide from time to time

**Article 183: Commencement**

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

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End of Document

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