Format: Revision No: 0 Effective Date: 16 Jul 2021	Department/Division	Food and Drugs Inspection and Safety Monitoring Department
Document Type: **Standard Operating Procedure**		Doc. Number : DIS/SOP/132 Revision Number : 0 Revision Date : 09 Jul 2021 Effective Date : 16 Jul 2021 Review Due Date : 16 Jul 2024
RWANDA FDA Rwanda Food and Drugs Authority	Title: **SOP FOR FOLLOW UP OF NON-COMPLIANCES AFTER GMP INSPECTION OF PHARMACEUTICAL MANUFACTURING FACILITY**	

	Author	Checked by		Approved by
Title	GML&GLP Analyst	Quality Assurance Analyst	DM/FDIC	HoD/FDISM
Names	Fiona MURENZI PADUA	Dr. Vedaste HABYALIMANA	Dr. MURINDAHABI M. Marilyn	Alex GISAGARA
Date	16/07/2021	16/07/2021	16/07/2021	16/07/2021
Signature				

1.0 Purpose

This Standard Operating Procedure is to ensure that:

1.1 Procedures are outlined for Rwanda FDA to follow up on non-compliances observed after GMP inspections of manufacturing facilities and implement administrative actions where necessary.

2.0 Scope

This Standard Operating Procedure:

2.1 Applies to Rwanda FDA GMP inspections of manufacturers of Finished Pharmaceutical Products (FFPs) and of Active Pharmaceutical Ingredients (APIs).

2.0 Scope

This Standard Operating Procedure:

2.1 Applies to Rwanda FDA GMP inspections of manufacturers of Finished Pharmaceutical Products (FFPs) and of Active Pharmaceutical Ingredients (APIs).

3.0 Policy

3.1 GMP Guide – PE 009-13 (Part I), Pharmaceutical Inspection Cooperation Scheme, 1 January 2017, PIC/S Secretariat, Geneva.

3.2 Law No. 003/2018 of 09/02/2018 establishing Rwanda FDA, determining its mission, organization, and functioning states in:
Article 8 (2) ...” regulate compliance with quality standards relating to the manufacture”; and Article 9 (2) …” grant or withdraw authorization relating to matters regulated under this law”.

3.3 Regulations No DIS/TRG/001 Rev. No 0 governing authorization to operate as a manufacturer or wholesaler or small scale manufacturing / compounding or retail seller of pharmaceutical products, 2019, Rwanda Food and Drugs Authority, Kigali, Rwanda.

4.0 Definitions and Abbreviations

4.1 “Critical” non-compliance

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

4.2 “Major” non-compliance

A non-critical deficiency which has produced or may produce a product, which does not comply with its marketing authorization.
Or
Which indicates a major deviation from PIC/s Good Manufacturing Practice;
Or
(within PIC/S) which indicates a major deviation from the terms of manufacturing authorization;
Or
Which indicates a failure to carry out satisfactory procedures for release batches or (within PIC/S) a failure of the authorized person to fulfil his/her required duties
Or

A combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

4.3 "Other" non-compliance

A deficiency which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice

(A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as major or critical)

Note: "Adopted from PIC/S SOP for inspection format, PI 013-3-1 Annex 25 Sep 2007

4.4 "**Author**" The Author shall be the person(s) who created a document or any subsequent revision of the controlled document.

4.5 "**Approved by**" Endorsement providing authority for a document to become officially valid and to be put into formal use.

4.6 "**Checked by/ Authorized by**" Endorsement signifying that the internal document is ready for approval

4.7 "**Controlled Copy**" A document which is distributed to pre-determined persons or staff and if any change or revision is made on the document, the Quality Management Systems Specialist shall submit the revised document and make sure that the previous (superseded) document is retrieved,

4.8 "**Document**"

a) "Document" means readable information and its supporting medium.

b) A "document" describes any policy, procedure, work instruction or form that is to be controlled.

c) A "document" can be a Law, Regulation, standard, policy statement, manual, guideline, protocol, process flow outlines, standard operating procedure, work instruction, drawing, specification, form, record, chart, report, certificate, checklist, aide memoir, register, worksheet, textbook, poster, notice, memorandum, software, photograph, drawing, or plan.

d) A "document" may be on various media e.g. paper, magnetic, electronic or optical computer disc, and may be digital, analog, photographic or written.

4.9 "**Effective Date**" A date after the concerned staff or persons have been formally trained or notified or oriented on the use of the document and records maintained, but shall not be later than 15 working days from the revision date.

4.10 "**External Document**"

a) A legal, regulatory or technical document which is not written or created (not internally generated), issued or revised by Rwanda FDA.

b) "External document" can be used as reference in writing internal documents or as a manual for operating equipment.

4.11 "**Internal Document**": A document which is issued and revised by Rwanda FDA.

4.12 "**Master Document**" Original of a controlled internal document that contains original signatures of the authorities that checked/authorized and approved the document.

4.13 "**Objective**" A brief statement(s) describing the purpose of the document.

4.14 "**Policy**" A short statements derived from the applicable law(s), regulation(s), standard(s), resolutions(s), decision(s) or concept(s) that govern the document or provide a mandate or basis for the document.

4.15 "**Procedure**"

When used as a title, e.g. in a Standard Operating Procedure (SOP), or Work instruction, a procedure shall be written as follows:

1) Write clear, concise, step-by-step instructions on how to perform the procedure.
2) Write the instructions chronologically for the user to follow, without a lot of theoretical background.
3) Indicate the preliminary steps that must be done before beginning the actual procedure.
4) Number each step so that repeat steps can be referred to rather than making the SOP very long.
5) Number each sentence so as to make reference to it easy under document revision history when it is revised.
6) Include explanations and an example of how to do any required calculations.
7) Create and indicate the Form(s) where the results, observations or data should be recorded.

4.16 "**Responsibility**" indicates the designations or titles of the Rwanda FDA staff or member and briefly describe their specific responsibilities in performing the procedure in a document and in ensuring that the document is implemented and performed correctly and consistently.

4.17 "**Review Due Date**"

A date three years from the effective date, to ensure continued adequacy and suitability of a document. A document may remain valid beyond its review due date if no major change had happened in the process, until the revised document is authorized.

4.18 "**Review**"

Assessment of the correctness, suitability and adequacy of a document including technical, legal, regulatory, health, safety, and environment compliance issues.

4.19 "**Reviewer**"

The Reviewer shall be the person(s) who assesses a document for technical, legal, regulatory, health, safety, and environment compliance issues as per Section 9.3 of the Document Control SOP number QMS/SOP/001.

4.20 "**Revision Date**" The date when the document is approved and thereby becoming officially valid.

4.21 "**Revision Number**" A numerical figure that changes serially; the first document shall have revision number "0" and its first revision number "1", second revision number "2" and so on.

4.22 "**Safety Precautions**" When used in a procedure e.g. SOP, indicate all safety precautions that must be taken before the procedure is performed. Includes special precautions and protective garments (containment facility clothing, masks, hoods, goggles, gloves, cleanup of spills, etc.) for working with physical, chemical, radioactive, biological or microbiological hazards.

4.23 "**Scope**" A brief statement of where the document applies, when it need to be applied and any limitations of the document.

4.24 "**Title**" A title shall be a short, precise statement representing the contents of the procedures

4.25 "**Uncontrolled Copy**"

A document which is issued to persons or staff who are not part of the distribution list for that document for information purposes only and if any change or revision is made on the document, the Quality Management Systems Specialist is not in control of retrieval of the previous (superseded) document.

4.23 **"GMP"**

Good manufacturing practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards.

5.0 Responsibility

5.1 Head of Food and Drugs Inspection & Safety Monitoring Department Ensure decisions on all manufacturing facilities are implemented in a timely manner and in accordance with the legislation to protect human health

5.2 The Division manager, Food and Drugs Inspection & Compliance ensures that administrative or enforcement actions are undertaken as appropriate and update databases and prepare communication by letter or email

5.3 Quality assurance analyst ensures the use of update version of the SOP, recalls obsolete documents and keeps document master list.

5.4 GMP Inspectors are responsible for generating a GMP inspection report with conclusion on the status of the manufacturing facility and to review the CAPA and submit comments

5.5 The technical Committee is responsible for reviewing the inspection report and make a final conclusion on the submitted GMP inspection report.

5.6 The GMP analyst is responsible for:

a) Updating and maintaining hard and electronic records arising from GMP inspections
b) Preparing covering letters and email communication to the inspected company. And
c) Preparing GMP certificates for facilities that are rated compliant to GMP

6.0 Distribution

6.1 Director General
6.2 The Head of Food and Drugs Inspection and Safety Monitoring Department
6.3 Division Manager of Food and Drugs Inspection and Compliance
6.4 Quality assurance analyst
6.5 GMP Inspectors.

7.0 Safety Precautions

Not applicable to this SOP

8.0 Materials and Equipment

8.1 GMP inspection Checklist
8.2 Laptop computers
8.3 Current Rwanda FDA GMP guidelines
8.4 Inspection reports
8.5 Site Master File
8.6 Inspection checklist used
8.7 Product dossier, if necessary

8.8 Compliance report following CAPA

9.0 Procedures

9.1 A site shall be considered non-compliant if it has:

a) One or more critical non compliances
b) Several major non compliances that imply a failure in the quality assurance system

9.2 The Rwanda FDA shall issue a GMP certificate and /or a manufacturing license where applicable for a site that is compliant i.e. has no critical or has minor observations

9.3 The Rwanda FDA shall demand for a corrective and preventive action report (CAPA) for review and where possible a follow up inspection for a site that has major non compliances may be done prior to issue of a GMP certificate and close out of the inspection.

9.4 The Rwanda FDA shall not issue a GMP certificate to a non-compliant manufacturing facility that has critical or several major non compliances

9.5 Local manufacturers shall require physical re-inspection for a site that has critical or several major non compliances until a satisfactory report is achieved

9.6 The re-inspection of a non-compliant facility shall be after submission of corrective action report (CAPA) and an application together with payment of the inspection fee.

9.1 Follow-up of GMP Inspection

9.7 The inspected company with major and/or other non-compliances shall send its response letter (including plan for corrective measures) to Rwanda FDA not later than one month from the date of the report.

9.8 The GMP analyst shall receive and record the response and corrective measures and preventative action plans and afterwards forward them to the Inspector team for review.

9.9 If the company fails to respond to the inspection report, the GMP analyst drafts a reminder letter, for signing by the Director General, to be sent to the company.

9.10 Within one month, the Lead inspector prepares a response letter in standard format. This letter should:

a) Acknowledge receipt of the company's plan for corrective measures;
b) State the dates of the inspection and the address of the site inspected
c) Provide an assessment of the corrective measures: this assessment may be carried out in collaboration with the other participating inspectors;
d) Include a statement of appreciation for co-operation with the inspection team;
e) Request for further correspondence, if needed.

9.11 Non-compliances may be considered as resolved if the company's response letter:

a) States that corrective and preventative measures have been implemented;
b) Includes supporting documentation
c) If necessary, includes a written commitment, providing a clear and reasonable schedule

for implementation of corrective and preventative measures

9.12 If the corrective and preventative measures taken by the company are not considered being acceptable, further correspondence with the company may be necessary.

9.13 In case of non-complaint rating of the inspected site the need for a follow-up inspection to ensure that corrective measures have been implemented should be discussed within the inspectors' team. Such follow-up inspection would represent a new inspection's process to be undertaken by another GMP Inspection team in the case of foreign manufacturing facilities

9.14 The follow-up inspection of a foreign non-compliant facility shall be after submission of corrective action report and an application together with payment of the prescribed inspection fee.

9.15 Manufacturing facilities with registered products that fail to comply with GMP shall have: Their products removed from the Rwanda drug register thus halting further manufacture or importation of the products.

a) Their products recalled from the market depending on the criticality of the findings
b) In case of local manufacturing facilities, Rwanda FDA may decide to withdraw the GMP certificate and/or revoke the manufacturing license due to a critical deficiency identified by the inspection team.
c) Upon careful consideration of the findings in the inspection report and where these affect the health of patients in a critical manner; Rwanda FDA may consider raising a rapid alert to the other six East African Community National Medicines Authorities (NMRAs), healthcare workers and patients.

10.0 Records

10.1 The quality manuals, master distribution list file, obsolete documents file and general list of documents shall be kept and maintained by QMS for a period specified in the respective document

10.2 Department list of documents shall be kept and maintained by the Head of Food and Drugs Inspection and Safety Monitoring Department

11.0 References

11.1 EAC SOP for follow-up of GMP inspection, 2014

11.2 EMA Compilation of Community Procedures on Inspection and exchange of information, 16 July 2012, EMA/INS/GMP/321252/2012 Rev 15, Compliance and Inspection

11.3 Rwanda FDA guidelines on Good Manufacturing Practices on Pharmaceutical Products

11.4 PIC/S Inspection Report Format, PI 013

11.5 PIC/S SOP on Team Inspections, PI 031-1, 29 July 2009

12.0 Appendices

12.1 Guide to Risk Classification of GMP non-compliances

12.2 Standard format for GMP certificate of compliance

13.0 Document Revision History

Date of revision	Revision number	Author(s)	Changes made and/or reasons for revision
16 Jul 2021	0	Rwanda FDA Staff	First Issue

End of Document

Annex 1: <u>GUIDE TO RISK CLASSIFICATION OF GMP NON-COMPLIANCES</u>

Definition

1.1 Critical" non-compliance

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

1.2 "Major" non-compliance

A non-critical deficiency which has produced or may produce a product, which does not comply with its marketing authorisation;

or

which indicates a major deviation from Good Manufacturing Practice;

or

(within PIC/S) which indicates a major deviation from the terms of the manufacturing authorisation;

or

which indicates a failure to carry out satisfactory procedures for release of batches

or (within PIC/S) a failure of the authorised person to fulfil his/her required duties;

or

a combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

1.3 "Other" non-compliance

A deficiency which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.

(A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as major or critical).

Risk Classification[1]

Whereas it is recognized that it is impossible to encompass every situation that may generate a risk, the following principles should be considered:

1. Classification of the observation is based on the assessed risk level and the number of occurrences. This may vary depending on the nature of the product, e.g. in some circumstances an example of major deficiency may be categorized as critical.
2. A deficiency that was reported at a previous audit and not corrected may be reported in **a higher classification.**
3. Generally, a GMP non-compliance (NC) rating is assigned when a critical observation is noted during an inspection.
4. Generally, a GMP compliance (C) rating is assigned when major observations are noted during an inspection. However, a NC rating may be assigned in the following situations;

a) When numerous major observations are noted during an inspection indicating that the company does not control its process and operations sufficiently.

b) Repetition of many major observations noted during previous inspections indicating that the company did not:

[1] *Adopted from Health Products and Food Branch Inspectorate of Health Canada, Risk Classification of Good Manufacturing Practices (GMP) Observations GUI-0023, 2012-09-11, Appendix A.*

- Implement the corrective actions submitted following the previous inspections.
- Did not put in place adequate preventive actions in a timely manner to avoid recurrence of such deviations.

Section 1.0: Critical GMP non-Compliances

1.1 Premises:

1. No air filtration system to eliminate airborne contaminants that are likely to be generated during manufacture or packaging.
2. Generalized malfunctioning of the ventilation system(s) with evidence of widespread cross-contamination.
3. Inadequate segregation of manufacturing of testing areas from other manufacturing areas for products that pose serious health hazards such as:
    a) Highly sensitizing drugs
    b) Biologicals
    c) Hormones
    d) Cytotoxic drugs
    e) Highly active drugs

1.2 Equipment

1. Equipment used for manufacturing operations of critical products not qualified with evidence of malfunctioning.
2. Evidence of contamination of products by foreign materials such as grease, oil, rust particles from the equipment.

1.3 Personnel

- Individual in charge of Quality Control or production does not hold a university degree in a science related to the work being conducted and does not have sufficient practical experience in their area of responsibility.

1.4 Sanitation

1. Evidence of widespread accumulation of residues/extraneous matter indicative of inadequate cleaning.
2. Evidence of gross infestation.

1.5 Raw material testing

1. Evidence of falsification or misrepresentation of analytical results.
2. No evidence of testing (COA) available from the supplier/synthesizer and no testing done by the manufacturer.

1.6 Manufacturing control

1. No written Master Formula.
2. Master Formula or manufacturing batch document showing gross deviations or significant calculation errors.

1.7 Quality Control Department

1. No full-time person in charge of QC.
2. QC department not a distinct and independent unit, lacking real decisional power, with evidence that QC decisions are overruled by production department or management.

1.8 Finished Product Testing

1. Finished product not tested for compliance with specifications by the manufacturer before release for sale.
2. Evidence of falsification or misrepresentation of testing results/forgery of COA.

2.8 Records

1. Evidence of falsification or misrepresentation of records.

1.10 Stability

1. No data available to establish the shelf-life of products.
2. Evidence of falsification or misrepresentation of stability data/forgery of certificate of analysis.
3. No stability chambers for on-going finished product stability studies for climatic zone IV.

1.11 Sterile Products

1. Critical sterilization cycle based on probability of survival not validated.
2. Water for infection (WFI) systems not validated with evidence of problems such as microbial/endotoxin counts not within specifications.
3. No media fills performed to demonstrate the validity of aseptic filling operations.
4. No environmental controls/no monitoring of viable microorganisms during filling for aseptically filled products.
5. Aseptic filling operations maintained following unsatisfactory results obtained for media fills.
6. Batches failing initial sterility test released for sale on the basis of a second test without proper investigation.
7. Inadequate room classification for processing /filling operations.
8. Aseptic manufacturing suites under negative pressure compared to clean (C-D) areas. Clean (C-D) areas under negative pressure to unclassified areas.

Section 2.0: Major GMP Non-Compliances

2.1 Premises

1. Malfunctioning of the ventilation system that could result in possible localized or occasional cross-contamination.
2. Maintenance/periodic verification such as air filter replacement, monitoring of pressure differentials not performed. *
3. Accessory supplies (steam, air, nitrogen, dust collection etc.) not qualified.
4. Heating Ventilation Air Conditioning (HVAC) and purified water (PW) system not qualified.
5. Temperature and humidity not controlled or monitored when necessary.
6. Damages to walls/ceilings immediately adjacent or above manufacturing areas or equipment where the product is exposed.
7. Un-cleanable surfaces created by pipes, fixtures or ducts directly above products or manufacturing equipment.
8. Surface finish (floors, walls, ceilings) that do not permit effective cleaning.
9. Unsealed porous finish in manufacturing areas with evidence of contamination (mould, powder from previous productions etc.) *
10. Insufficient manufacturing space that could lead to mix ups. *
11. Quarantine areas accessible to unauthorized personnel and not well marked. *
12. No separate area/Insufficient precautions to prevent contamination or cross-contamination during RM sampling.

2.2 Equipment

1. Equipment does not operate within its specifications.*
2. Equipment used for complex manufacturing operation not qualified.
3. Clean in place (CIP) equipment not validated.
4. Tanks for manufacturing of liquids and ointments not equipped with sanitary clamps.
5. Stored equipment not protected from contaminations. *
6. Inappropriate equipment for production: surfaces porous and non-cleanable/material to shed particles. *
7. No covers for tanks, hoppers or similar manufacturing equipment.
8. Equipment location does not prevent cross-contamination or possible mix ups for operations performed in common area.
9. PW not maintained or operated to provide water of adequate quality. *

10. Leaking gaskets.
11. No calibration program for measuring equipment /no records maintained. *
12. No equipment usage logs.

2.3 Personnel

1. Delegation of responsibilities for QC or production to insufficiently qualified persons.
2. Insufficient personnel in QC production resulting in a high possibility of error.
3. Insufficient training for personnel involved in production and QC resulting in related GMP violations.

2.4 Sanitation

1. Sanitation program not in writing but premises in acceptable state of cleanliness.
2. No Standard Operating Procedure (SOP) for microbial/environmental monitoring, no action limits for areas where susceptible non-sterile products are manufactured.
3. Cleaning procedure for production equipment not validated (including analytical methods).
4. Incomplete health requirements.

2.5 Raw Material Testing

1. Water used in the formulation is not of acceptable quality.
2. No testing done on materials by the manufacturer.
3. COA showing incomplete testing.
4. Incomplete specifications.
5. Specifications not approved by QC.
6. Testing methods not validated.
7. Use of materials after retest date without retesting.
8. Multiple lots comprising one consignment not considered as separate for sampling, testing and release.
9. No SOP for conditions of transportation and storage.

2.6 Manufacturing Control

1. Master Formulae prepared/verified by unqualified personnel.
2. Deviations from instructions during production not documented and not approved.
3. Discrepancies in yield or reconciliation following production not investigated.

4. Line clearance between productions of different products not covered by SOP and not documented.
5. No regular checks for measuring devices/no records.
6. Lack of proper identification of in-process materials and products resulting in a high probability of mix-ups.
7. Inadequate labelling /storage of rejected materials and products that could generate mix-ups.
8. Upon receipt, bulk and in-process drugs, RM and PM not held in quarantine until released by QC.
9. Production personnel using bulk and in-process drugs, RM and PM without prior authorization by QC. *
10. Inadequate/inaccurate labelling of bulk/in-process drugs, RM and PM.
11. RM dispensing not done by qualified persons, according to SOP.
12. Master Formulae incomplete or showing inaccuracies in the processing operations.
13. Changes in batch size not prepared/verified by qualified personnel
14. Inaccurate/incomplete information in manufacturing/packaging batch document.
15. Although documented, combination of batches done without QC approval/not covered by SOP.
16. No written procedures for packaging operations.
17. Non-standard occurrences during packaging not investigated by qualified personnel.
18. Inadequate control of coded and non-coded printed PM (including storage, dispensing, printing and disposal).
19. No or inadequate self-inspection program does not address all applicable sections of GMPs/Records incomplete or not maintained.

2.7 Recall

1. Absence of recall procedure combined with distribution practices that would not permit and adequate recall (distribution records unavailable or not kept).
2. Improper quarantine and disposal practices that would allow recalled/rejected units to be returned for sale.

2.8 Quality Control & Quality Assurance

1. Inadequate facilities, personnel and testing equipment.
2. No authority to enter production areas. *
3. No SOP approved and available for sampling, inspection and testing of materials.

4. Products made available for sale without approval of QC department. *
5. Products released for sale by QC without proper verification of manufacturing and packaging documentation.
6. Deviations and borderline conformances not properly investigated and documented, according to an SOP.
7. RM/PM used in production without prior approval of QC.
8. Reprocessing/Reworking done without prior approval of QC. *
9. No system for complaint handling and returned goods.
10. SOPs covering operations that can affect the quality of a product such as transportation, storage etc not approved by QC / not implemented
11. Absence of a change control system.
12. The systems and controls in place for the proper qualification, operation, calibration and maintenance of equipment, standards, solutions, and records keeping do not assure that the results and conclusions generated are accurate, precise and reliable.

2.9 Packaging Material Testing

1. Absence of testing of PM.
2. Specifications not approved by QC.

2.10 Finished Product Testing

1. Incomplete/inadequate specifications.
2. FP specifications not approved be QC.
3. Incomplete testing.
4. Test methods not validated.

2.11 Records

- Absence of Master Production Documents.

2.12 Samples

- Retention samples not kept for finished products.

2.13Stability studies

1. Insufficient number of batches/insufficient data to establish shelf life.
2. No action taken when data shows that the products do not meet their specifications prior to the expiry date.
3. No stability studies pertaining to changes in manufacturing (formulation) packaging materials.
4. Testing methods not validated.

2.14 Sterile Products

2 Aqueous based products not subjected to terminal steam sterilization without proper justification or approval through the marketing authorization.

3 Insufficient number of samples for room classification/inadequate sampling methods. *

4 Insufficient environmental controls/insufficient monitoring of viable microorganisms during filling for aseptically filled products. *

5 Premises and equipment not designed or maintained to minimize contamination/generation of particles. *

6 Inadequate maintenance of PW WFI systems.

7 Inadequate re-validation of PW and WFI systems after maintenance, upgrading, out-of-specs trends.

8 Inadequate training of personnel.

9 Inadequate gowning practices for clean and aseptic areas.

10 Inadequate practices/precautions to minimize contamination or prevent mix-ups.

11 Non-validated time lapse between start of manufacturing and sterilization or filtration.

12 Inadequate procedures for media-fills.

13 Insufficient number of units filled during media-fills.

14 Media-fills do not simulate actual operations.

15 Capability of media to grow a wide range of micro-organisms not demonstrated.

16 Misinterpretation of results for media-fills.

17 Absence of leak test for ampoules.

18 Samples for sterility testing insufficient in number or not representative of the entire production run.

19 Each sterilizer load not considered as a separate batch for sterility testing.

20 PW is not used as the feed water for WFI system and the clean steam generator.

21 The WFI used in the preparation of parenteral is not tested for endotoxins.

22 The WFI used for final rinsing of containers and components used for parenteral drugs is not tested for endotoxins when those containers and components are not depyrogenated subsequently.

***May be elevated to critical observation**

Section 3.0: Minor (Other) GMP non-Compliances

3.1 Premises

1 Doors giving direct access to exterior from manufacturing and packaging areas used by personnel.
2 Un-screened/un-trapped floor drains.
3 Outlets for liquids and gases not identified.
4 Damages to surfaces not directly adjacent or above exposed products.
5 Non-production activities performed in production areas.
6 Inadequate rest, change, wash-up and toilet facilities.

3.2 Equipment

1 Insufficient space between equipment and walls to permit cleaning.
2 Base of immovable equipment not adequately sealed at points of contact.
3 Use of temporary means or devices for repair.
4 Defective or unused equipment used for non critical products not qualified.

3.3 Sanitation

1 Incomplete written sanitation program but premises in acceptable state of cleanliness.
2 Sanitation or Health and hygiene programs not properly implemented or followed by employees.

3.4 Raw Material Testing

- Incomplete validation of test methods.

3.5 Manufacturing Control

1 Incomplete SOPs for handling of materials and products.
2 Access to production areas not restricted to authorized personnel.
3 Inadequate checks for incoming materials.
4 Written procedures incomplete for packaging operations.
5 Incomplete recall procedure.

3.6 Packaging Material Testing

1 Inadequate procedures of transportation and storage.
2 Inadequate handling of outdated/obsolete PM.
3 Incomplete testing.
4 Inadequate specifications.

3.7 Finished Product Testing

- Incomplete testing of physical parameters.

3.8 Records

1. Incomplete records/documentation for a product.
2. Incomplete plans and specification for the manufacturing buildings.
3. Incomplete documentation pertaining to supervisory personnel.
4. Insufficient retention time for evidence and records to be maintained.
5. No organization charts.
6. Incomplete records for the sanitation program.

3.9 Samples

1. Samples of RM not available.
2. Incomplete testing parameters.
3. Improper storage conditions.

3.10 Stability studies

1. Insufficient number of batches in continuing stability program.
2. Incomplete testing parameters.
3. Improper storage conditions.

3.11 Sterile Products

1. Steam used for sterilization not monitored to assure suitable quality and absence of additives.
2. Inadequate control on the maximum number of personnel present in clean and aseptic areas.
3. Gases used to purge solutions or blanket products not passed through a sterilizing filter.
4. Inadequate inspection for particles and defects.

Annex 2: CERTIFICATE OF COMPLIANCE WITH GOOD MANUFACTURING PRACTICE

Rwanda Food and Drugs Authority

Rue. KG 9 Avenue, Nyarutarama Plaza

P.O. Box 1948, Kigali, Rwanda.

email: info@rwandafda.gov.rw;

website: www.rwandafda.gov.rw

QMS N°: DIS/FMT/018

Rev. N°: 0

Effective date:

Revision date: 16/04/2024

CERTIFICATE OF COMPLIANCE WITH GOOD MANUFACTURING PRACTICE

(Issued in accordance with Article 23 of the Regulations N° DIS/TRG/001 Rev. N° 0)

Certificate N°: Issue Date: Valid up to:

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

Name of facility:

Physical address:

License number:

Country:

E-mail:

Telephone:

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

On the basis of the carried out on it is certified that the pharmaceutical manufacturing facility indicated on this certificate complies with Good Manufacturing Practice for dosage forms listed in Table below:

N°	Dosage form	Category	Activities

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

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

Dr Charles KARANGWA

Ag. Director General