Format: QMS/FMT/001 Revision No: 0 Effective Date: 13 Jan 2020	Department/Division	Food and Drugs Inspection and Safety Monitoring Department
Document Type: **Standard Operating Procedure**		Doc. Number : DIS/SOP/139 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: **CRITERIA FOR CATEGORIZATION OF INSPECTION FINDINGS BASED ON QUALITY RISK MANAGEMENT**	

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1.0 Purpose

This Standard Operating Procedure is to:

1.1 Provide instructions on criteria for categorization of findings based on Quality Risk Management during Good Manufacturing Practices Inspections conducted by Rwanda FDA inspectors.

1.2 Provide a tool to support the risk based classification of GMP deficiencies from inspections and to establish consistency amongst Inspectorates.

2.0 Scope

This Standard Operating Procedure:

2.1 Applies to all GMP inspections of all manufacturers of medicinal products within and outside Rwanda whose products are registered or subjected to registration in Rwanda; irrespective of their size, type of products, product range or location of the manufacturing facilities.

3.0 Policy

3.1 The Law Nº 003/2018 of 09/02/2018 Establishing Rwanda Food and Drugs Authority and Determining its Mission, Organization and Functioning states in:

Article 3 (13) … *"premises used in the manufacture of products regulated by this Law"* and

3.2 ISO 9001:2015 Clause 7.5.3.1 states that "*Documented information required by the quality management system and by this International Standard shall be controlled".*

3.3 Guidelines N^0 DIS/GDL/003 Guidelines on Good Manufacturing Practices on Pharmaceutical Products_Annexes issued by Rwanda FDA

3.4 ICH Q9 Guideline on Quality Risk Management and World Health Organization (WHO) guidelines on quality risk management, Annex 2 TRS-981.

3.5 PIC/S Guidance on Classification of GMP Deficiencies-Version PI 040-1 of 1 January 2019

4.0 Definition and Abbreviation

4.1 **GMP**: Good Manufacturing Practices

4.2 **Critical Deficiency**: When the deviation affects a quality attribute, a critical process parameter, an equipment or instrument critical for process or control, of which the impact to patients (or personnel or environment) is highly probable, including life threatening situation, the deviation is categorized as Critical requiring immediate action, investigated, and documented as such by the appropriate SOP.

a. A deficiency which has produced, or leads to a significant risk of producing either a 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.
b. A "Critical" deficiency also occurs when it is observed that the manufacturer has engaged in fraud, misrepresentation or falsification of products or data.
c. A "Critical" deficiency may consist of several related deficiencies, none of which on its own may be "Critical", but which may together represent a" Critical" deficiency, or systems' failure where a risk of harm was identified and should be explained and reported as such.

4.3 **Major Deficiency:** A deficiency that is not a "Critical" deficiency, but which:

a) has produced or may produce a product which does not comply with its Marketing Authorization, Clinical Trial Authorization, product specification; pharmacopoeia requirements or dossier;
b) does not ensure effective implementation of the required GMP control measures;
c) indicates a major deviation from the terms of the manufacturing authorization;
d) indicates a failure to carry out satisfactory procedures for release of batches or failure of the authorized person to fulfill his/her duties;
e) consists of several **"Minor/Other"** related deficiencies, none of which on its own may be "Major", but which may together represent a "Major" deficiency or systems failure and should be explained and reported as such.

4.4 **Minor/Other Deficiency:** A deficiency that is not classified as either "Critical" or "Major", but indicates a departure from Good Manufacturing Practice (GMP). A deficiency may be judged as **"Minor"** because there is insufficient information to classify it as "Critical" or "Major".

4.5 Rwanda FDA Guide to GMP (Chapter 1, Clauses 1.12 and 1.13) **describes Quality Risk Management (QRM)** as a systematic process to proactively or retrospectively manage risk to product quality using risk assessment, risk control, risk communication and risk review.

4.6 Rwanda FDA Guide to GMP (Annex 20, Clause 8) defines **risk** as **"The combination of the probability of occurrence of harm and the severity of that harm"**.

5.0 Responsibility

5.1 The Director General is responsible for ensuring that decisions on all manufacturing facilities are implemented in a timely manner and in accordance with the Rwanda FDA mission and vision to protect human health.

5.2 The Head of food and drugs inspection and safety monitoring department is responsible for ensuring that administrative or enforcement actions are undertaken as appropriate.

5.3 The lead and/or co-inspector is responsible of the following:

a) To generate a GMP inspection report with categorization of inspection findings based on quality risk management as described in this SOP and provide conclusion on the status of the inspected manufacturing facility.

b) To review the CAPA and submit comments

5.4 The Peer Review/Technical Committee is responsible to review the categorization of findings based on QRM following the GMP inspection report and make a final conclusion on the submitted GMP inspection report.

5.5 The Division Manager of food and drugs inspection and compliance is responsible for:

a) Ensuring the implementation of recommendations of the Peer Review Committee

b) Ensure that the database is updated and communication with inspected premise is done by letter or email.

5.6 Staffs: Analysts and Specialists are responsible for updating databases and preparing communication by letter or email under supervision of the line division manager.

6.0 Distribution

6.1 Director General

6.2 Head of Food and Drugs Inspection and Safety Monitoring

6.3 Division Manager of food and drugs inspection and compliance

6.4 GMP inspectors

6.5 The Peer Review/Technical Committee members

6.6 Staffs: Analysts and Specialists

6.7 A QMS shared folder on Rwanda FDA head office server on the following link: (\\rwandafdaserver\qms\sops\)

6.8 Hard copies to staff that have no access to the Rwanda FDA server.

7.0 Safety Precautions

Not applicable to this SOP

8.0 Materials and equipment

9.0 GMP Guidelines and SOPs related to GMP inspection and QRM related documents
9.1 Checklists for receiving applications for GMP Inspections

9.0 Procedure

9.1 Conducting the inspection

9.1.1 The Lead Inspector shall ensure that standardized procedures are followed by all inspectors when conducting GMP inspections and to ensure consistency approach in performance between different inspectors. Standardized procedures shall always be in compliance with written procedures approved by The Authority. They shall include (but not limited to): SOP for conducting inspection, SOP for follow-up on non-compliances observed after GMP inspections, SOP for preparation and planning GMP inspections of manufacturers of regulated products, SOP for preparation and review of the GMP inspections reports.

9.1.2 10.2 A QRM process shall always consider two primary principles:

a) The evaluation of the risk to quality is based on scientific knowledge and experience with the process and ultimately links to the protection of the patient

b) The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk.

9.2 Findings Categorization

9.2.1 The findings of inspection shall be categorized into **critical, major and minor/other deficiencies** as defined in clauses 4.2, 4.3 and 4.4 above.

9.2.2 Upon correction and submission of CAPA, the internal committee review members shall meet within 5 days from the investigation and conclude about the feedback and re-authorize the operational license

9.3 Management Tool to Support Consistent and Objective Categorization of GMP Deficiencies in accordance with Risk Management Principles

9.3.1 When classifying a deficiency as “Critical”, inspectors should determine if there is clear evidence by considering risk of harm as in the definition. An example is provided in the flow chart found in Appendix 1, Figure 1.

9.3.2 When a “Critical” deficiency is not clearly evident, the deficiency may be rated as “Critical”, “Major” or “Other”. A determination on the classification should be made for which the following guidance may be followed:

a) Perform a detailed evaluation of the deficiency to determine an initial classification as per Appendix 1, Figures 2-5; then

b) Perform an evaluation of factors that would either increase or reduce the risk regardless of the initial classification as described in Appendix 2; then

c) Make a decision as to whether the initial risk classification may be as described in Appendix 1, Figure 1:

- **Upgraded due to effects that increase the risk, i.e. risk-increasing effects,**
- **Maintained, or**
- **Downgraded due to effects that reduce the risk, i.e. risk-reducing effects.**

9.3.3 Deficiency classification examples (a non-exhaustive list) are provided in Appendix 3 which can be used to assist in the classification determination if required.

9.4 Actions to be taken by Inspectors in Response to the reporting of Critical and Major Deficiencies

9.4.1 Compliance and enforcement measures are dependent upon a number of factors, including significance of violations such as a "Critical" deficiency and a large number of "Major" deficiencies, history of the site, potential risks to products, and assessment of the manufacturer's proposed corrective actions. Where appropriate, this may include assessment of interim risk mitigating actions while long term remediation continues.

9.4.2 If the findings are linked to patient safety, immediate action needs to be taken.

9.4.3 Additional factors that should be considered include:

a) the risk to health and safety;

b) compliance history of the manufacturer;

c) whether the manufacturer acted with indifference or premeditation;

d) the degree of co-operation offered;

e) the likelihood that the same problem will reoccur;

f) the likelihood of the enforcement action being effective.

9.4.4 Typically, the first steps could include a letter of warning/cautionary letter or a re-inspection or reassessment inspection for which failure to address risk with repeat deficiencies may result in a non-compliance or similar rating.

9.5 Depending upon the severity of the deficiency the inspectorate will determine if appropriate inspectional or regulatory actions are needed.

9.6 The actions that can be taken may include:

a) compliance related communications which alert the manufacturer to the inspectorate's concern, and possibility for future regulatory action if remedial action is not effective;
b) regulatory action against the site authorization or GMP approval (refusal, suspension or amendment of an establishment license);
c) market actions such as recall (voluntary or mandated by the Authority);
d) prohibition of supply / importation;
e) suspension or cancellation of Marketing Authorization/Product License;
f) Health product label or packaging changes.

10.0 References

10.1 The Rwanda FDA Law Nº 003/2018 of 09/02/2018 Establishing Rwanda Food and Drugs Authority and Determining its Mission, Organization and Functioning.

10.2 Rwanda FDA Guidelines on Good Manufacturing Practice for Finished Pharmaceutical Products-Part1: Document Ref: DIS/GDL/002, Effective Date: 01/10/2020, Revision: 0

10.3 Rwanda FDA Guidelines on Good Manufacturing Practices on Pharmaceutical Products-annexes. Document Ref: DIS/GDL/003, Effective Date: 05/10/2020, Revision: 0

10.4 WHO Technical Report 981 Annex 2: WHO guidelines on quality risk management

10.5 PIC/S Guide to Good Manufacturing Practice for Medicinal Products PE 009-10: Part I and II

10.6 PIC/S Guidance on Classification of GMP Deficiencies-Version PI 040-1 dated 01 January 2019

10.7 PIC/S Guide to Good Manufacturing Practice for Medicinal Products PE 009-10: Annex 20 Quality Risk Management

10.8 ICH Q9: Quality Risk Management

10.9 Rwanda FDA Suitability and Licensing of Premises Regulations and Guidelines.

11.0 Appendices

11.1 **APPENDIX 1: MANAGEMENT TOOL TO SUPPORT CONSISTENT AND OBJECTIVE CATEGORISATION OF GMP DEFICIENCIES IN ACCORDANCE WITH RISK MANAGEMENT PRINCIPLES**

11.2 **Appendix 1 Figure 1 – Classification Process – Overview**

11.3 **Appendix 1 Figure 2 – Classification Process – Detailed Assessment Step 1**

11.4 **Appendix 1 - Figure 3 – Classification Process – Detailed Assessment Step 2**

11.5 **Appendix 1 - Figure 4 – Classification Process – Detailed Assessment Step 3**

11.6 **Appendix 1 - Figure 5 – Classification Process – Detailed Assessment Step 4**

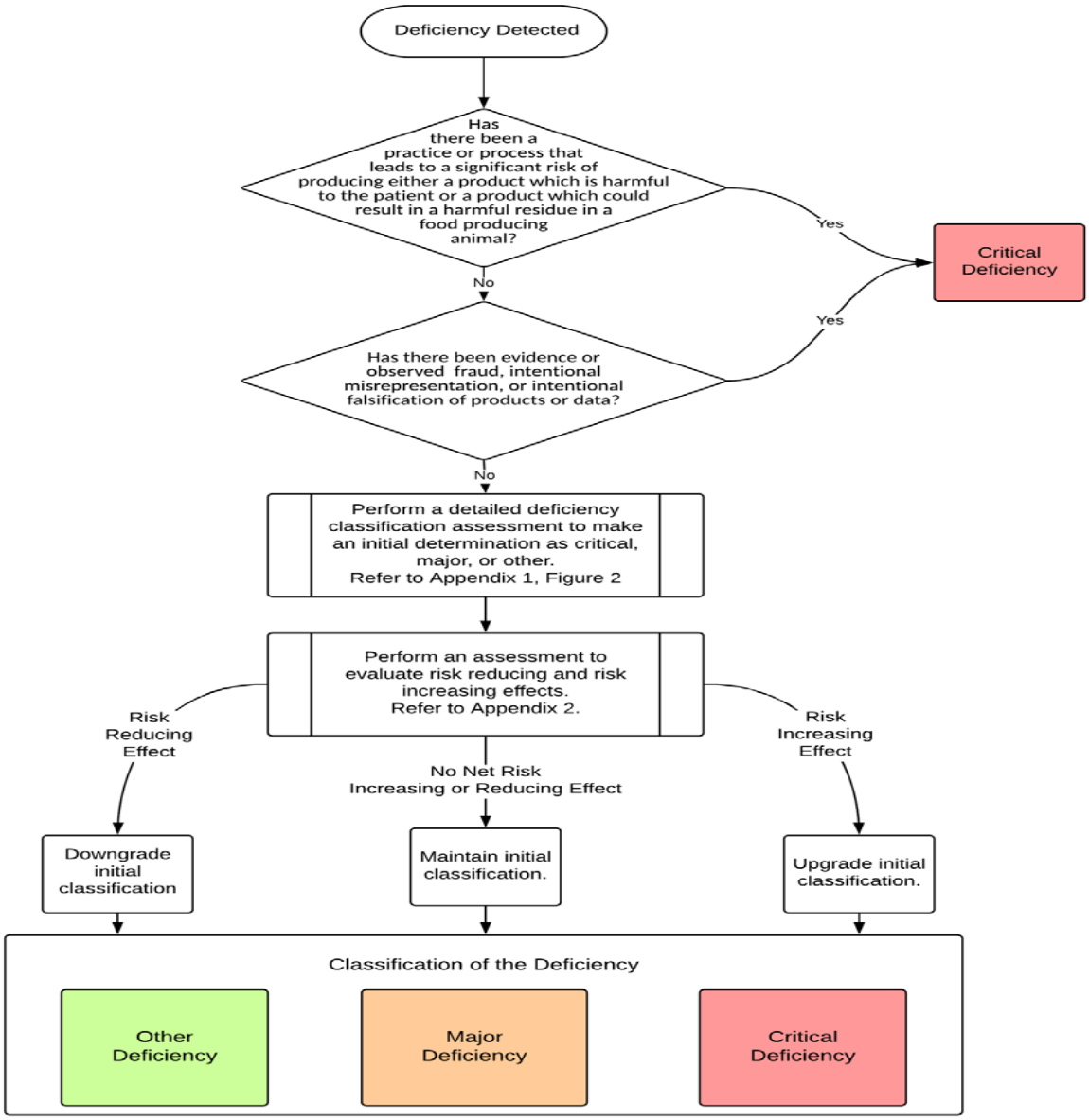
11.7 **APPENDIX 2: INTERPRETATIVE GUIDANCE ON RISK INCREASING OR REDUCING FACTORS**

11.8 **1-Risk Increasing Factors – Upgrading Initial Classification**

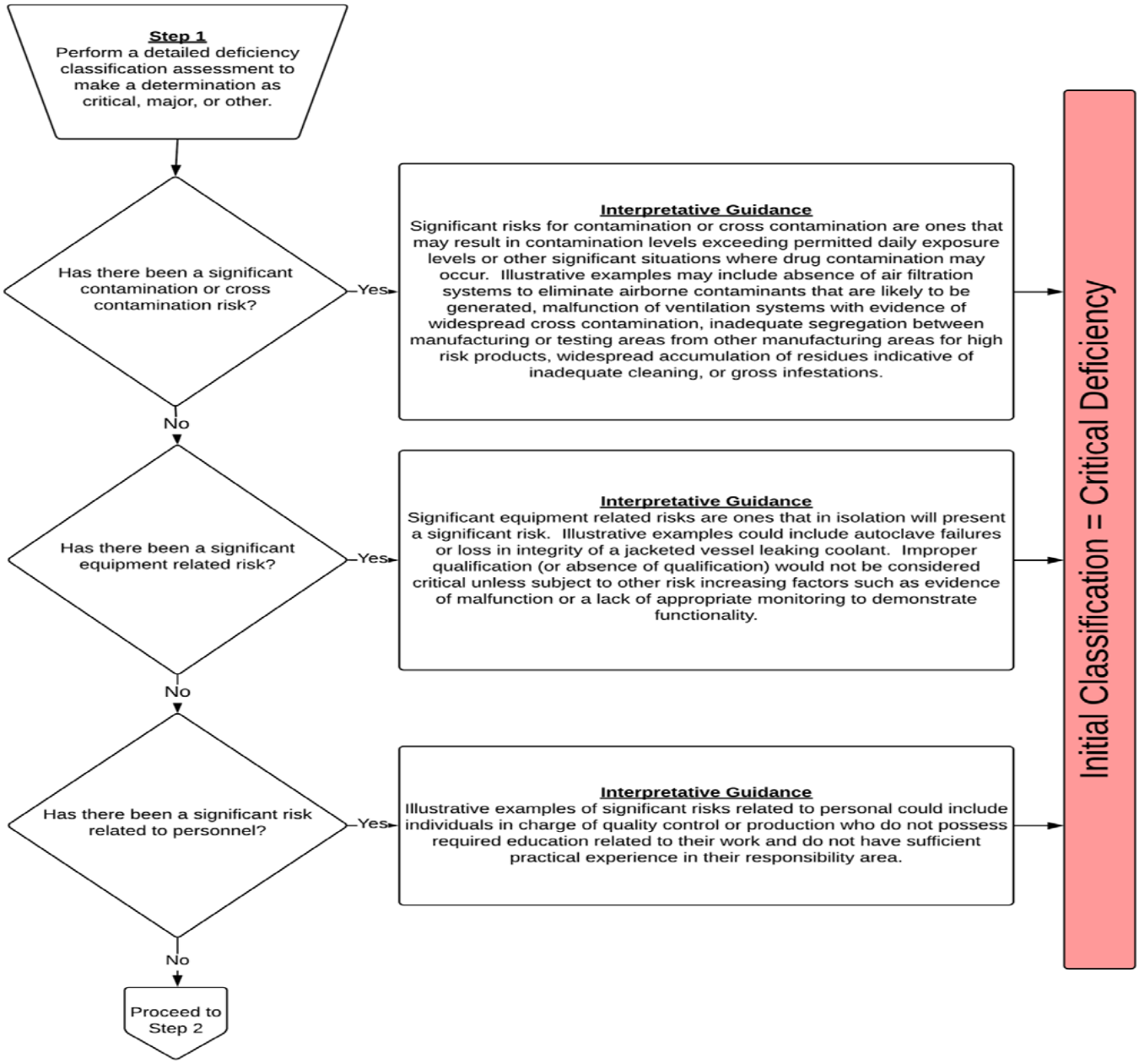
11.9 **2-Risk Reducing Factors – Downgrading Initial Classification**

APPENDIX 1: MANAGEMENT TOOL TO SUPPORT CONSISTENT AND OBJECTIVE CATEGORISATION OF GMP DEFICIENCIES IN ACCORDANCE WITH RISK MANAGEMENT PRINCIPLES

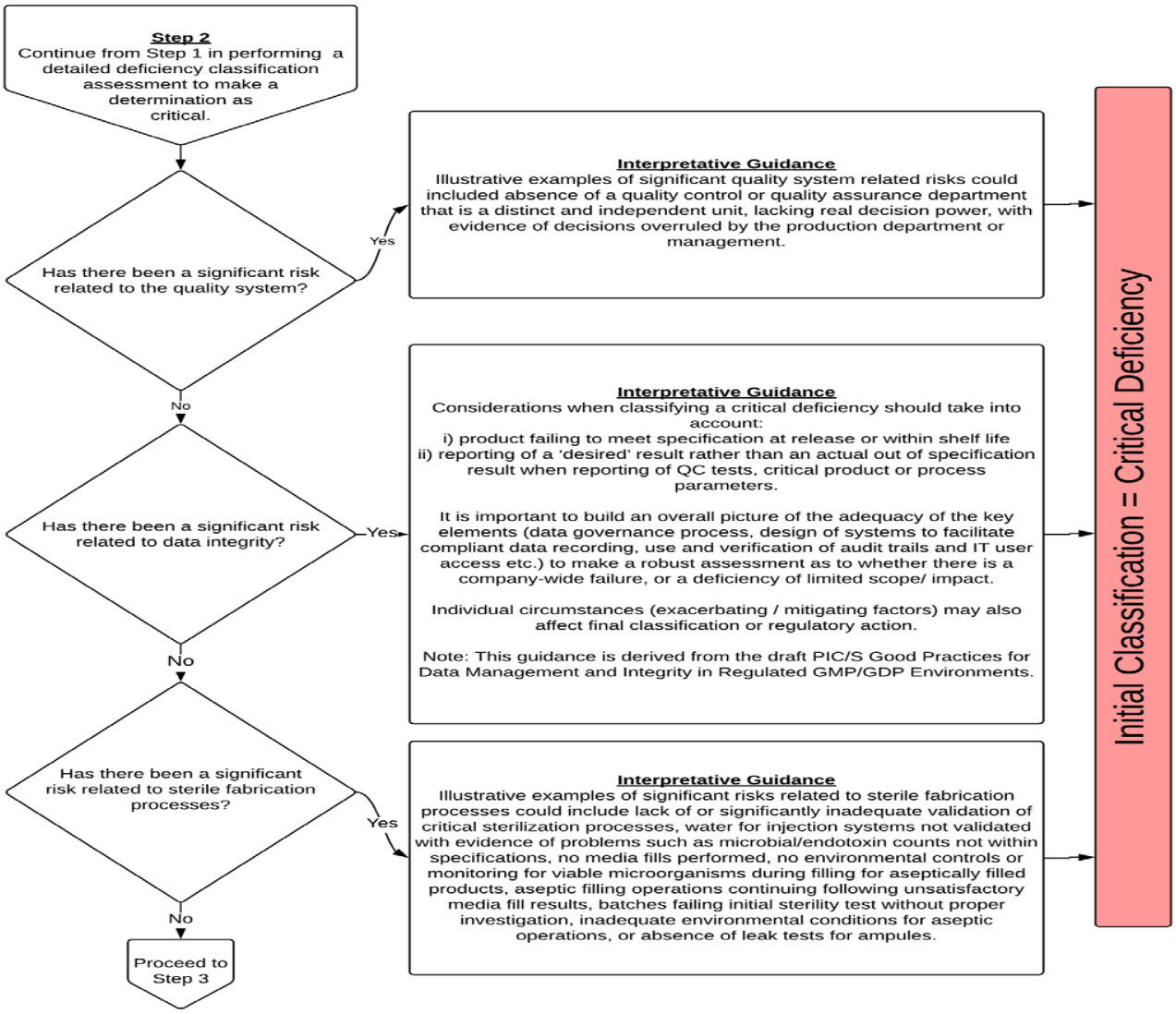
Appendix 1 Figure 1 – Classification Process – Overview



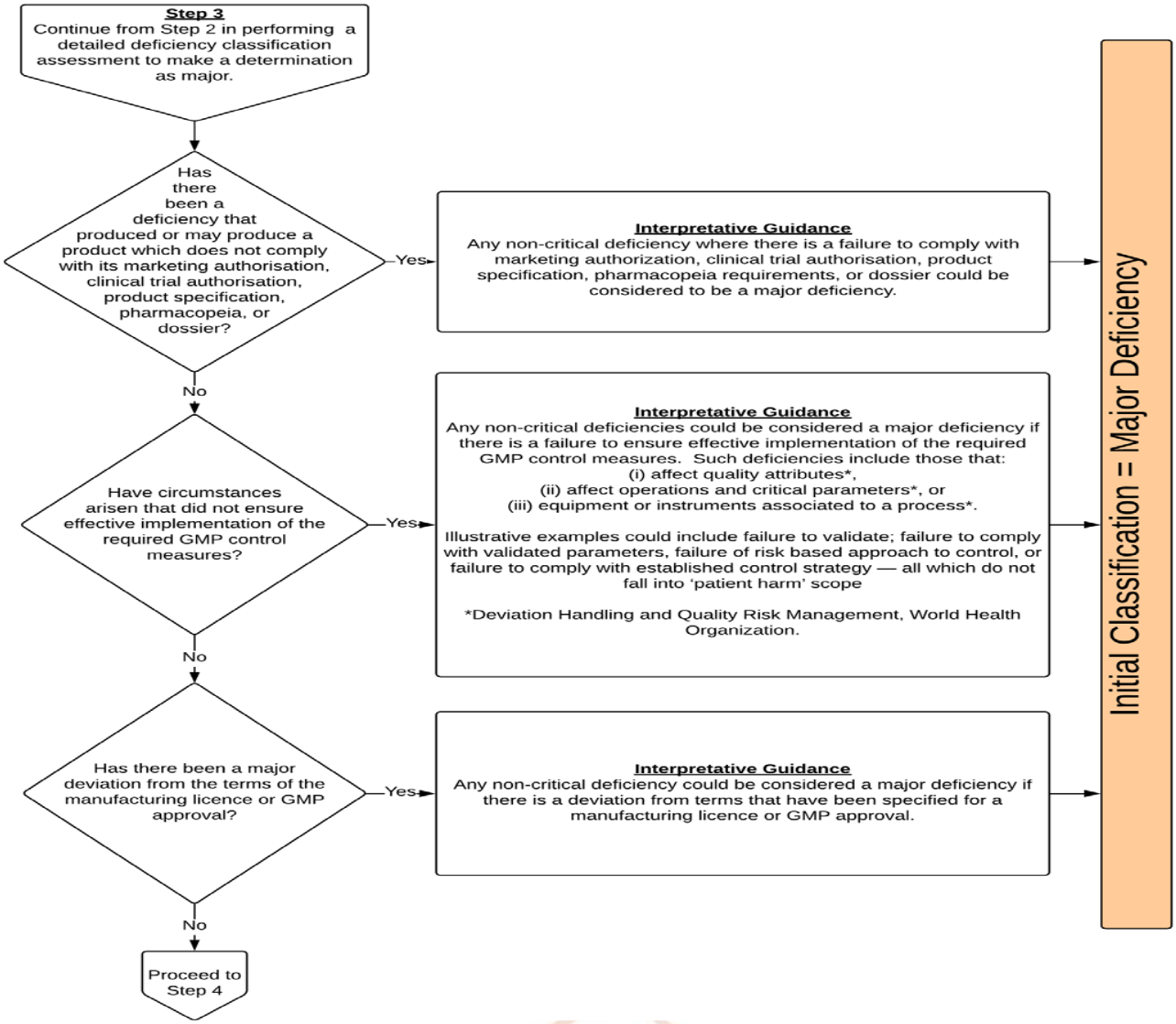
Appendix 1 Figure 2 – Classification Process – Detailed Assessment Step 1



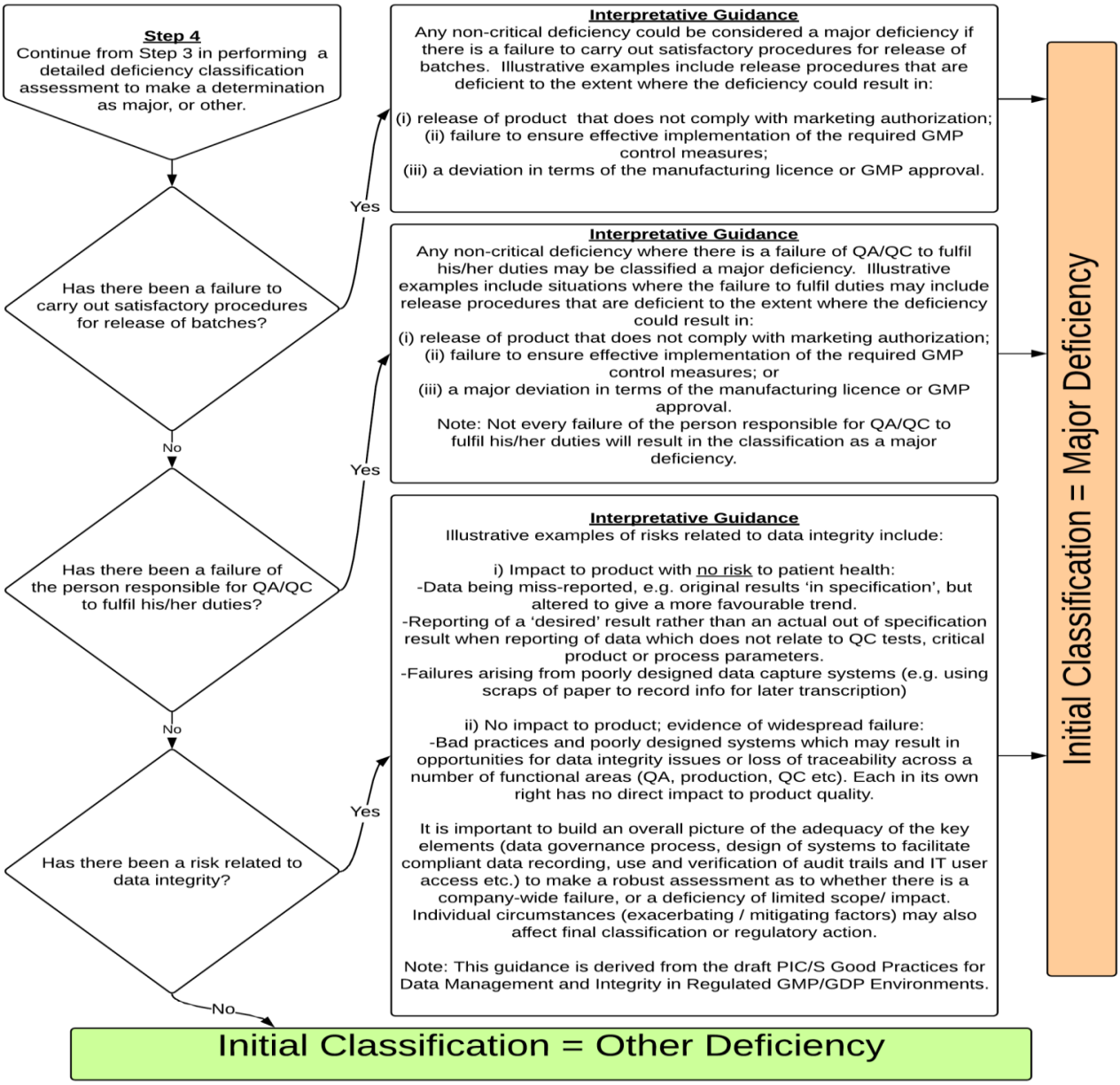
Appendix 1 - Figure 3 – Classification Process – Detailed Assessment Step 2



Appendix 1 - Figure 4 – Classification Process – Detailed Assessment Step 3



Appendix 1 - Figure 5 – Classification Process – Detailed Assessment Step 4



Note: For data integrity issues an "Other" classification may be considered when there is no impact to product or limited evidence of failure such as:
i) Bad practice or poorly designed system which result in opportunities for data integrity issues or loss of traceability in a discrete area, or
ii) Limited failure in an otherwise acceptable system.

APPENDIX 2: INTERPRETATIVE GUIDANCE ON RISK INCREASING OR REDUCING FACTORS

1-Risk Increasing Factors – Upgrading Initial Classification

A "Major" and "Other" deficiency may be upgraded by one level to either a "Critical" or "Major" deficiency respectively when conditions may exist to satisfy the intent of the definition for the upgraded risk classification. This is considered to be achieved when defined risk increasing factors are present.

Risk increasing factors include:

- Repeat or recurring deficiencies (Appendix 2 Step 3)
- Grouping or combination of deficiencies (Appendix 2 Step 4)
- Product risk (Appendix 2 Step 5)
- Failure of a manufacturer's management to identify and take prudent measures to reduce the patient risk to an acceptable level for a product distributed and future production from a deficient practice or process.

2-Risk Reducing Factors – Downgrading Initial Classification

A "Critical" or "Major" deficiency may be downgraded by one level to either a "Major" or "Other" deficiency respectively when conditions may exist to satisfy the intent of the definition for the downgraded risk classification. This is considered to be achieved when defined risk reducing factors are present.

When considering risk reducing factors, it is important to ensure that these factors are both consistent and effective.

Risk reducing factors include:

- Minimizing product risk (Appendix 2 Step 5)
- Minimizing risk of patient harm
- Other risk reducing factors (Appendix 2 Step 6)
- Actions taken by the manufacturer e.g. CAPA plan to reduce the risk of the deficiency

The impact of product already distributed to market should be considered when downgrading a critical deficiency.

APPENDIX 2: INTERPRETATIVE GUIDANCE ON RISK INCREASING OR REDUCING FACTORS (Continued)

3-Repeat or Recurring Deficiencies – Upgrading Initial Classification

Repeat or recurring deficiencies are deficiencies that were also identified at a previous inspection where appropriate corrections or corrective actions have not been implemented.

In certain cases, recurring deficiencies may be considered to be subject to a risk enhancing effect to permit upgrading the initial risk classification, particularly if it is apparent that there is willful or unsatisfactory effort to resolve the deficiency. A risk increasing effect should only be considered when:

- There is a serious failure in the Quality System that fails to satisfactorily identify the potential root causes for the deficiency or fails to adequately address these causes without other risk reducing factors being present, or
- There are other factors for consideration such that the definition of the upgraded risk classification is achieved, for example, unreasonably protracted implementation of corrective actions.

  Note: It is expected that the upgrading of risk for a recurring deficiency will require understanding of potential factors that may have led to the reoccurrence.

4-Grouping or Combining of Deficiencies - Upgrading Initial Classification

Different issues identified during an inspection may be grouped or combined into one deficiency, if each issue supports or relates to the core deficiency that is stated.

A risk increasing effect can be applied to upgrade an initial risk classification by one level when the definition of the upgraded risk classification has been achieved.

Examples of several "Other" deficiencies, none of which on its own may be "Major" but which may together represent a "Major" deficiency should be explained and reported as such.

APPENDIX 2: INTERPRETATIVE GUIDANCE ON RISK INCREASING OR REDUCING FACTORS (Continued)

5-Product Risk – Upgrading or Downgrading Initial Classification

Some manufacturing sites have product and processes that involve much higher risks than others.

Product Risk Classification definitions:

- High risk- products that are highly susceptible to contamination through the manufacturing process including shelf life, e.g. microbial or chemical.
- Low Risk- products that have a lower chance of contamination through the manufacturing process including shelf life.

Both risk increasing and risk reducing factors may be applied after considering product risks as follows:

- High risk products may have certain "Major" deficiency or "Other" deficiency classifications respectively upgraded to a "Critical" deficiency or "Major" deficiency. This can be applied when circumstances of a deficiency under consideration meets the interpretation of the definition for a "Critical" deficiency.
- Low risk products may have certain "Critical" deficiency or "Major" deficiency classifications downgraded to a "Major" deficiency or "Other" deficiency respectively. For low risk products, a "Critical" deficiency may be downgraded to a "Major" deficiency unless the definition of "Critical" deficiency is achieved.

6. Other Risk Reducing Factors

When other risk reducing factors are evident to mitigate the risk associated with a deficiency then the risk rating may be downgraded.

Other risk reducing factors can typically be considered only when a secondary system has been established that can mitigate risks associated with a deficiency. For example, a validated packaging system vision system that provides 100% verification of every packaged product may

be considered as a risk reducing factor for a deficiency associated with printed primarily packaging materials stored in a disordered manner that could cause mix-up.
If there are a number of risk increasing and risk reducing factors, consider all risk factors at the same time and then determine an overall risk assessment to upgrade or downgrade initial risk.

APPENDIX 3: DEFICIENCY CLASSIFICATION EXAMPLES

The classification may be in the context of the physical inspection performed, information provided at the time and its associated risk. For complex deficiencies refer to Appendix 1 for more information on classification.

1. Critical Deficiency Examples

Examples of deficiencies rated as "Critical" (**in the absence of risk reducing factors**) include the following where it can be reasonably expected that the definition in this SOP is met. **A "Critical" deficiency is a serious situation that could result in regulatory action being considered.**

- **The following (but not limited to) are critical deficiencies:**

a. Sterilization record of product-contact material used in aseptic filling process not available or unacceptable (Relevant to all sterile products)
b. Lack of sterilization validation (Relevant to all sterile products)
c. Temperature out of control limit during detoxification stage
d. Expired or rejected API component used.
e. Lack of adequate control measures resulting in an actual or significant risk of, cross contamination above the level of the health based exposure limit in subsequent products.
f. Evidence of gross pest infestation (relevant to all manufacturers).
g. Falsification or misrepresentation of analytical results or records (relevant to all manufacturers).
h. Failure to ensure the quality and/or identity of starting materials (relevant to all manufacturers).
i. No master batch documents (relevant to all manufacturers).
j. Absence, falsification or misrepresentation of manufacturing and packaging records (relevant to all manufacturers).
k. Water system for sterile products not validated (for manufacturers of sterile products).
l. HVAC system for sterile products not validated (for manufacturers of sterile products).
m. Grossly unsuitable premises so that there is a high or likely risk of contamination (relevant to all manufacturers).
n. No evidence that mandated recall processes have been complied with (relevant to all manufacturers).

APPENDIX 3: DEFICIENCY CLASSIFICATION EXAMPLES (Continued)

2. Major Deficiency Examples:

Examples of deficiencies rated as "Major" (in the absence of risk reducing factors) include the following (**But not limited to**):

a) Lack of validation of critical processes (applicable to all medicines, but could be "Critical" for low dose/high potency products; particularly sterilization processes for sterile products)

b) No or grossly inadequate air filtration to minimize airborne contaminants (applicable to all medicines manufacturers - could be “Critical” if possible contaminants are a safety concern and “Critical” for sterile medicines)

c) Missing or ineffective control measures to provide adequate confidence that cross contamination will be controlled within the health based exposure limit in subsequent products. (would be “Critical” if resulting cross contamination has or is likely to exceed the health based exposure limit)

d) Damage (holes, cracks, peeling paint) to walls/ceilings in manufacturing areas where product is exposed in non-sterile areas

e) Design of manufacturing area that does not permit effective cleaning

f) Insufficient manufacturing space that could lead to mix-ups

g) No raw material sampling area for medicine manufacturers (could be classed as “Other” if adequate precautions are taken)

h) Sanitary fittings not used on liquid/cream manufacturing equipment

i) Stored equipment not protected from contamination

j) Individuals in charge of QC/production not qualified by education, competency training and experience

k) Inadequate initial and ongoing training and/or no training records

l) Cleaning procedures not documented and/or no cleaning records

m) Production equipment cleaning procedures not validated

n) Reduced QC testing of raw materials without data to certify suppliers

o) Incomplete testing of raw materials

p) Test methods not validated

q) Complex production processes for non-critical products not validated

r) Unapproved/undocumented changes to master batch or equivalent documents

s) Deviations from instructions not approved

t) No or inadequate internal inspection program

u) No proper release for supply procedure

v) Product reworked without proper approval

w) No system/procedures for handling complaints or returned goods

x) Inadequate testing of packaging materials

y) No ongoing stability program and/or stability data for all products not available

z) Insufficient lighting in production or inspection areas

aa) Containers from which samples have been taken not identified

bb) The temperature of critical temperature controlled storage areas not monitored and alarmed

cc) Inadequate change control system

dd) Inadequate deviation system

ee) No investigation into alarms and temperature excursions for deviations from storage or transport requirements

ff) Use of unapproved reference standard to test an API or drug product.

gg) Inadequately trained personnel to perform sterility tests (Relevant to all sterile products)

hh) Production started without line clearance.

ii) Filter integrity test has been carried out using equipment with no documented installation qualification completed.

jj) Gross misbehavior of staff in a critical aseptic process.

kk) Pressure differential out of established limits in aseptic fill areas.

ll) Operational parameter out of range for a parameter defined as non-critical.

mm) Untrained personnel responsible for segregating the approved and rejected raw material in the warehouse

APPENDIX 3: DEFICIENCY CLASSIFICATION EXAMPLES (Continued)

3. Minor/Other Deficiency Examples

Examples of deficiencies rated as **"Minor/other"** include the following (**But not limited to**):

a) Skip of FEFO principle (first expired-first out) in raw material handling.

b) Balance out of tolerance used to determine gross weight of raw materials upon reception

c) Pressure differential out of established limits in class D washing area.

d) Inadequately trained personnel to perform warehouse cleaning activities.

10.0 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