



MCAZ ADDENDUM GUIDELINE FOR CLASSIFICATION OF cGMP DEFICIENCIES.

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Medicines Control Authority of Zimbabwe

106 Baines Avenue

P O Box 10559

Harare

Email: mcaz@mcaz.co.zw

Website: www.mcaz.co.zw

Written by: SRO

Signature

08/12/2025

Date

Checked by HoD/HoU:

Signature

08/12/2025

Date

Authorised for use by QM:

Signature

09/12/2025

Date

Approved by:
Director-General

Signature

.....15/12/2025.....

Date

1.0 APPLICATION

This Good Manufacturing Practice (GMP) guideline applies to;

- 1.1. Prospective pharmaceutical manufacturers in Zimbabwe.
- 1.2. Licensed pharmaceutical manufacturers in Zimbabwe.
- 1.3. Inspection of international pharmaceutical manufacturers who have products registered with the Authority or intend to register their products with the Medicines Control Authority of Zimbabwe.

This guideline must be read together with the MCAZ Good Manufacturing Practice Guideline MCAZ/LED/GL 09 and is intended as a guide. It is not exhaustive

2.0 PURPOSE

This guideline is to be used by both the regulator and industry in the classification of deficiencies:

- 2.1 During internal audits by manufacturers.
- 2.2 During regulatory inspections by MCAZ.

MCAZ adopts World Health Organisation GMP guidelines. This addendum:

- 2.3 Provides further detail on observation categorisation.
- 2.4 Incorporates risk-based criteria.
- 2.5 Considers quality indicators such as compliant products, compliant facilities, defective products, complaints and recalls.

The guideline is intended to:

- 2.6 Provide a tool that supports risk-based classification of GMP deficiencies.
- 2.7 Serve as an objective point of reference where there are differing opinions on classification between inspectors and manufacturers.

3.0 BACKGROUND / INTRODUCTION

Prior to the drafting of this guideline MCAZ did not have access to a guideline that provides detailed examples and a structured process for categorizing GMP observations. This can result in differences of opinion and varied classification approaches.

This guideline has therefore been developed to:

- 3.1 Standardize observation categorisation in line with Good Regulatory Practices.
- 3.2 Align MCAZ practice with PIC/S “Guidance on Classification of GMP Deficiencies” and Health Canada’s “Risk Classification Guide for Drug GMP Observations”, while retaining examples relevant to Zimbabwe and the region.

4.0 DEFINITIONS

Other definitions not detailed below are captured in MCAZ/LED/GL 09

4.1 Critical deficiency

A Critical deficiency is one which has produced or leads to a significant risk of producing:

4.1(a) A product that is harmful to the human patient.

4.1(b) A product that is harmful to the veterinary patient.

4.1(c) A product which could result in a harmful residue in a food producing animal.

This represents a significant deviation or departure from GMP regulations that can impact the safety, quality or efficacy of a pharmaceutical product.

A Critical deficiency also occurs when data integrity principles have been violated, for example:

4.1(d) Fraud.

4.1(e) Misrepresentation.

4.1(f) Falsification of products or analytical data.

A Critical system deficiency may consist of several related deficiencies. For example:

4.1(g) No control of worksheets and unaccounted samples in Quality Control.

4.1(h) Risk that failed analyses are unaccounted for.

4.1(i) A stability programme that is not in a state of control.

Taken together these can represent a Critical system deficiency in Quality Control.

A previously noted Major deficiency may be considered a Critical deficiency where:

4.1(j) The manufacturer repeatedly fails to address the deficiency.

4.1(k) There is no adherence to an agreed CAPA plan or commitments.

4.1(l) The residual risk to product quality or patient safety is high.

4.2 Major deficiency

A Major deficiency is one that is not Critical but which:

4.2(a) Has produced, or may produce, a product that does not comply with the market authorisation, product specification, pharmacopoeial requirements or dossier.

4.2(b) Indicates a major departure from the terms of the manufacturing authorisation or GMP requirements.

4.2(c) Does not ensure effective implementation of the required GMP control measures.

Several related Other or Minor deficiencies may together represent a Major system failure or deficiency and should be reported as such.

4.3 Other or Minor deficiency

An Other or Minor deficiency is one that:

4.3(a) Is not classified as either Critical or Major but indicates a departure from GMP requirements.

4.3(b) Does not by itself pose a significant risk to product quality or patient safety.

4.3(c) Does not indicate a systemic failure of a GMP system.

A deficiency may be judged as Other or Minor because there is insufficient information to classify it as Critical or Major. Once-off minor discrepancies are often brought to the attention of the manufacturer as comments.

5.0 RISK MANAGEMENT TOOL FOR CLASSIFICATION

The classification of deficiencies is a risk management tool that supports consistent and objective categorization of GMP deficiencies.

When inspectors classify a deficiency as Critical, Major or Other they should apply recognised quality risk management principles and document the rationale, including:

5.1 Severity of actual or potential impact on patients, animals or product quality.

5.2 Likelihood of occurrence.

5.3 Detectability of the issue.

5.4 Nature of the products involved, for example.

5.4.1 Higher risk products such as sterile, biological, cytotoxic and narrow therapeutic index medicines.

5.4.2 Lower risk products where the same deficiency may be classified differently.

5.5 Whether similar issues have been cited in past inspections, indicating ineffective corrective actions.

Evidence supporting the classification must be presented clearly in the inspection report. Where doubt exists, the deficiency should normally be classified in the more serious category.

6.0 REFERENCE TO PIC/S GUIDANCE

The definitions and general approach to classification in this guideline are aligned with the PIC/S Guidance on Classification of GMP Deficiencies. The PIC/S management tool and interpretative guidance on risk increasing and risk reducing factors may be used by inspection teams when classification is complex.

7.0 MCAZ CRITICAL DEFICIENCY HANDLING PROCEDURE

On noting a Critical deficiency, the WHO Global Benchmarking Tool requires that inspectors make timely regulatory decisions on the impacted products to protect public health. For MCAZ this includes:

- 7.1 Identification and documentation of the Critical deficiency with clear reference to this guideline, MCAZ/LED/GL 09 and the relevant GMP code or WHO TRS.
- 7.2 Communication of the potential regulatory decision to MCAZ senior management prior to communication to the manufacturer.
- 7.3 Possible immediate regulatory decisions, including:
 - 7.3.1 Temporary halt of manufacture of defective, contaminated, adulterated or fraud prone products.
 - 7.3.2 Temporary halt of release of such products.
 - 7.3.3 Quarantine of impacted batches.
 - 7.3.4 Heightened oversight or rapid re-inspection.

Regulatory decisions are communicated:

- 7.4 During the closing meeting.
- 7.5 In an interim report which should normally be shared within 72 hours of the inspection after the QA meeting of inspectors.

The regulatory decision requires an immediate CAPA from the manufacturer, with a timeframe that:

- 7.6 Is proportionate to the risk.
- 7.7 Generally does not exceed 14 to 30 calendar days.

8.0 EXAMPLES OF CRITICAL, MAJOR AND OTHER OBSERVATIONS ACCORDING TO WHO SYSTEMS

The examples below illustrate how deficiencies may be categorized across different systems. They are not exhaustive but are intended to support consistent classification and to guide discussions between inspectors and manufacturers

8.1 Premises and facilities

8.1.1 Critical observations

- 8.1.1(a) Evidence of gross pest infestation.
- 8.1.1(b) Grossly unsuitable premises that can result in product mix ups.
- 8.1.1(c) Inadequate segregation of manufacturing or testing areas from other manufacturing areas, for example wash bays communicating directly with processing cubicles.

8.1.2 Major observations

- 8.1.2(a) Design of the premises does not permit effective cleaning.
- 8.1.2(b) Insufficient manufacturing space that can lead to mix ups.
- 8.1.2(c) Absence of a suitably designed raw materials sampling area with suitable airlocks that ensure materials are opened in the recommended ISO grade.
- 8.1.2(d) Insufficient lighting in production or inspection areas resulting in mix ups or process failures.
- 8.1.2(e) Use of non GMP type doors made of wood or particle shedding materials and doors with crevices that are difficult to clean.
- 8.1.2(f) Finish of surfaces such as floors, walls and ceilings does not permit effective cleaning.
- 8.1.2(g) Use of drains that are not screened or trapped and with evidence of inadequate cleaning and sanitization.
- 8.1.2(h) Absence of fully qualified airlocks with fully functional interlock mechanisms as required in WHO TRS 1010 Annex 8

8.1.3 Other observations

- 8.1.3(a) Drains in production areas not identified.
- 8.1.3(b) Pipelines in production areas not identified.
- 8.1.3(c) non-production activities performed in production areas.
- 8.1.3(d) Use of non GMP tapes.

8.2 Good practices in production

8.2.1 Critical observations

- 8.2.1(a) Doors communicating directly to the outside without provision of airlocks in areas requiring environmental control.
- 8.2.1(b) Facilities designed without consideration of cross contamination.
- 8.2.1(c) Gross cross contamination noted from a poorly designed facility or from personnel movement, for example powders being swabbed from common clean corridors in shared facilities.
- 8.2.1(d) Intentional use of adulterated or failing starting materials with potential to impact the safety, efficacy or quality of the product.
- 8.2.1(e) Failure to identify key starting raw materials where this results in use of wrong or uncontrolled materials.

8.2.2 Major observations

- 8.2.2(a) Damage such as peeling paint to walls or ceilings that can result in contamination of the product.
- 8.2.2(b) Absence of sanitary clamps for liquids and creams.
- 8.2.2(c) Bulk intermediates used beyond their validated hold times without documented justification.
- 8.2.2(d) Use of unapproved master batch documents or unapproved changes to master batch documents that can result in product failure or non-compliance with the dossier.
- 8.2.2(e) No properly documented batch documentation system, resulting in production having unlimited access to batch manufacturing records.
- 8.2.2(f) Improper gowning practices that can result in street clothes being exposed in common clean corridors.
- 8.2.2(g) Improper gowning that can result in cross contamination as operators move from one process cubicle to the next.
- 8.2.2(h) Use of non-product dedicated fluidised bed bags and rapid mixer granulator vent filters that can result in product cross contamination.
- 8.2.2(i) Presence of non-justified overages on master batch formulae mainly to compensate for API degradation and not supported by stability or process data.
- 8.2.2(j) Absence of key components such as metal detectors and dust extractors where these are required based on risk.
- 8.2.2(k) Failure to document and monitor all critical process parameters as informed by the most recent process validation.
- 8.2.2(l) Use of process endpoints that result in product variability and potential out of specification results.
- 8.2.2(m) Absence of appropriate in process controls such as blend assay for general oral solid dosage forms.
- 8.2.2(n) Hold time studies not executed for dispensed materials, bulk granules and bulk tablets.

8.2.3 Other observations

8.2.3(a) Use of non-vendor specific material codes in batch manufacturing records which can result in use of non-dossier approved API sources.

8.2.3(b) SOPs for key stages of batch manufacturing not referenced in the batch record, resulting in unclear instructions

8.3. Good practices in quality control

8.3.1 Critical observations

8.3.1(a) Failure to conduct full specification testing where this is required for release of raw materials, intermediates or finished products.

8.3.1(b) Out of specification results not recorded and not investigated for raw materials and finished products.

8.3.1(c) Analysts reporting fraudulent analytical data for material and finished product release.

8.3.1(d) No ongoing stability programme and or no stability data for all commercial products.

8.3.2 Major observations

8.3.2(a) Head of QC not qualified by education, competency, training and experience.

8.3.2(b) Analytical methods not validated or not verified for their intended use.

8.3.2(c) Major laboratory incidents not documented or investigated and no CAPAs proposed.

8.3.2(d) No proper data archiving and retrieval processes that ensure traceability and integrity of data.

8.3.2(e) No SOP for growth promotion tests for media and absence of use of ATCC or pharmacopeial reference cultures as specified by the reference pharmacopoeia.

8.3.2(f) Absence of proper organism containment arrangements in the microbiology laboratory, for example absence of appropriate biosafety cabinets.

8.3.2(g) Unvalidated glassware cleaning procedures.

8.3.2(h) Improper handling of reference standards and working standards, including use of working standards that have not been fully qualified.

8.3.2(i) Key equipment such as HPLCs, UV Vis spectrophotometers, TOC analysers, conductivity meters, pH meters and dissolution apparatus without calibration and verification SOPs and with no records of calibration.

8.3.2(j) No proper analyst qualification system and records.

8.3.2(k) Improper sample handling procedures that may result in sample integrity challenges.

8.3.3 Other observations

- 8.3.3(a)** Absence of media hold time studies where these are expected.
- 8.3.3(b)** Use of non-type A glassware where type A glassware is required.
- 8.3.3(c)** Volumetric solutions not properly standardised and absence of hold time studies.
- 8.3.3(d)** Equipment for storage of working standards and reference standards without fail safe mechanisms such as temperature alarms

8.4 Materials management

8.4.1 Critical observations

- 8.4.1(a)** Absence of evidence of testing of a raw material from the supplier and the manufacturer not fully testing the material according to the approved specifications in situations where testing is mandatory.
- 8.4.1(b)** Absence of a vendor qualification programme for key starting materials, including lack of a risk-based approach and mandatory onsite audits for high-risk APIs.
- 8.4.1(c)** Intentional use of failing starting materials for formulation of commercial products with such products released onto the market.
- 8.4.1(d)** No data available to establish the shelf life of products.

8.4.2 Major observations

- 8.4.2(a)** Use of an unacceptable reduced testing programme for critical starting materials.
- 8.4.2(b)** Failure to test raw materials or to receive declarations from manufacturers for key risk items such as TSE or BSE, nitrosamines, elemental impurities, ethylene glycol and diethylene glycol, among others.
- 8.4.2(c)** Incomplete specifications with absence of key parameters such as related substances and impurities.
- 8.4.2(d)** No approved specifications for certain starting materials.
- 8.4.2(e)** Absence of ongoing vendor monitoring processes that can identify atypical trends in materials and vendors.
- 8.4.2(f)** Temperature mapping studies not fully executed in the raw material warehouse, including lack of consideration of seasonal variations.
- 8.4.2(g)** Absence of appropriate photo protection arrangements such as sodium lamps and other measures for photosensitive materials.

8.5 Utilities. HVAC and environment

8.5.1 Critical observations

8.5.1(a) Evidence of HVAC failure in critical areas such as production, common corridors and packing areas, as evidenced by failure to attain required non-viable particle counts, air changes per hour, room recovery times and microbiological limits as per WHO TRS 1010 Annex 8.

8.5.1(b) Evidence of backflow in ducts for multiproduct facilities that do not have scavenging filters, resulting in cross contamination.

8.5.1(c) Absence of containment mechanisms such as exhaust HEPA filters and scrubbers for sensitising products such as penicillin, contrary to WHO TRS 1010 Annex 8.

8.5.1(d) Absence of temperature and humidity control mechanisms in production areas for hygroscopic products and powder formulation plants where control is critical, contrary to WHO TRS 1010 Annex 8.

8.5.2 Major observations

8.5.2(a) Absence of temperature and humidity control mechanisms in production areas for non-hygroscopic products where such control is needed to ensure consistent quality.

8.5.2(b) HVAC system improperly designed with absence of proper filtration levels or recirculation design, resulting in potential cross contamination.

8.5.2(c) Absence of fail-safe mechanisms for HVAC components such as fan failure alarms and filter load indicators.

8.5.2(d) Plenum and duct leakages resulting in areas failing to meet the required air volume or air change rates.

8.5.2(e) Absence of qualified duct damper positions and or evidence of tampering during inspection.

8.5.2(f) Use of visibly damaged and dirty primary and fine filters.

8.5.2(g) Presence of unclassified areas that communicate directly with common clean corridors and production areas.

8.5.2(h) Evidence of HVAC shutdown without corresponding risk assessments and studies to support the practice.

8.5.2(i) Visibly malfunctioning magnehelic gauges that can result in failure to detect pressure differential failures.

8.5.3 Other observations

8.5.3(a) Absence of an approved non-viable particle count schematic diagram.

8.5.3(b) Failure to demonstrate the suitability of the aerosol used for HEPA leakage studies.

8.5.3(c) Adjustment screws of magnehelic gauges not tamper-proofed.

8.5.3(d) Action and alert limits not defined on magnehelic gauges.

8.3.1 Utilities. Purified water system (PWS)

8.6.1 Critical observations

8.6.1(a) Failed phase 1 and or phase 2 purified water qualification studies as per WHO TRS 1033 Annex 3.

8.6.1(b) Failure to control the chemical and microbiological quality of water, with out of specification results for key parameters such as TOC and conductivity not investigated, and water still used in production.

8.6.1(c) Absence of proof of water system qualification with respect to key components such as URS, FAT, design qualification, installation qualification, operational qualification and performance qualification, including flow studies, dead leg studies, borescope records, piping installation records and slope studies, contrary to WHO TRS 1033 Annex 3.

8.6.2 Major observations

8.6.2(a) Absence of online testing of TOC and conductivity where this is required, in line with WHO TRS 1033 Annex 3 section 7.2.1.

8.6.2(b) No documented sanitisation procedure for the water system and absence of sanitisation evidence, contrary to WHO TRS 1033 Annex 3 section 4.36.

8.6.2(c) No offline monitoring of key parameters with defined action and alert limits, contrary to WHO TRS 1033 Annex 3 sections 3.4, 4.3.8, 12.3 and 12.4.

8.6.2(d) Absence of a multidisciplinary internal audit report for the PWS, contrary to WHO TRS 1033 Annex 3 sections 14.2 and 15.1.

8.6.2(e) Absence of PWS critical quality attribute trend reports, contrary to WHO TRS 1033 Annex 3 sections 12.9 and 14.3.

8.6.2(f) PWS distribution loop and storage tanks made of material that is not suitable, for example non-SS 316L with potential to corrode, adsorb or leach, contrary to WHO TRS 1033 Annex 3 section 5.7.

8.6.2(g) Failure to document major changes and deviations to the PWS, contrary to WHO TRS 1033 Annex 3 section 5.5.

8.6.2(h) Water system not in a good state of repair with leakages noted on the distribution loop, contrary to WHO TRS 1033 Annex 3 section 5.7.

8.6.2(i) Absence of an efficient water sampling programme, contrary to WHO TRS 1033 Annex 3 section 5.7.

8.6.2(j) Use of non-sanitary type components in the water system such as threaded joints and non-sanitary valves, contrary to WHO TRS 1033 Annex 3 section 7.2.1.

8.6.2(k) Absence of an effective water system preventive maintenance plan with evidence of replacement of key components such as membranes and filters, contrary to WHO TRS 1033 Annex 3.

8.6.3 Minor observations

8.6.3(a) Components of the water system not labelled.

8.7 Quality Management Systems

8.7.1 Critical observations

8.7.1(a) Failure to properly execute a mandatory Class I or Class II recall.

8.7.1(b) A quality management system that is not in a state of control, resulting in defective products being released on the market.

8.7.1(c) Failure to identify assignable root causes for product defects and complaints.

8.7.1(d) Systemic product complaints that are not properly investigated and where the manufacturer does not put immediate corrective actions in place to mitigate risk to the public, for example microbial contamination, discoloration of the product, non-dissolving granules for suspension and broken tablets.

8.7.2 Major observations

8.7.2(a) Deviations not properly documented, investigated and approved.

8.7.2(b) Absence of an adequate change control system.

8.7.2(c) Absence of an adequate root cause analysis system.

8.7.2(d) No system or procedure for handling complaints or returned goods.

8.7.2(e) Absence of a fully controlled annual product quality review programme.

8.7.2(f) Absence of a fully documented and controlled self-inspection programme.

8.7.2(g) Absence of an authorised training programme with evidence that personnel are not trained on key systems such as data integrity and Quality Control.

8.8 Validation and qualifications

8.8.1 Critical observations

8.8.1(a) Absence of cleaning validation and undocumented cleaning procedures resulting in cross contamination or contamination of products.

8.8.1(b) Production process for critical or essential products not validated.

8.8.2 Major observations

8.8.2(a) Transport validation not fully executed for finished products where transport conditions are critical.

8.8.2(b) Analytical methods not verified for their intended use.

8.8.2(c) Validations and qualifications not protocol driven or not performed according to approved protocols.

8.8.3 Minor observations

8.8.3(a) Validation protocols not approved by Quality Assurance and the relevant departments before execution

8.9 Equipment

8.9.1 Critical observations

8.9.1(a) Use of equipment that can result in contamination of the product, for example rusted or worn-out equipment.

8.9.1(b) Equipment for complex manufacturing of critical or essential products not qualified.

8.9.1(c) Evidence that foreign materials from equipment such as grease, oil, rust or particles have contaminated products.

8.9.2 Major observations

8.9.2(a) Equipment without P and ID diagrams and whose material of construction for product contact parts is unknown, for example potentially non-SS 316L product contact parts.

8.9.2(b) Use of unqualified equipment for non-essential products.

8.9.2(c) Stored equipment not protected from contamination.

8.9.2(d) No equipment utilisation and cleaning records for multi-use containers.

8.9.2(e) Accessory supplies such as steam, air, nitrogen and dust collection not qualified.

8.9.2(f) Gaskets not in a good state of repair and resulting in leakages that can impact product quality.

8.9.2(g) Absence of an adequate equipment preventive maintenance programme.

8.9.3 Other observations

8.9.3(a) Defective equipment not removed from use or clearly labelled as such.

8.10 Personnel

8.10.1 Critical observations

8.10.1(a) Individual in charge of Quality Assurance not qualified by education, competency, training and relevant experience.

8.10.2 Major observations

8.10.2(a) Absence of an adequate number of personnel for key processes such as production, QC and QA, as evidenced by failure to.

8.10.2(a)(i) Meet timelines for analysis of samples.

8.10.2(a)(ii) Review and approve batches timeously.

8.10.2(a)(iii) Investigate complaints adequately and timeously.

8.10.2(a)(iv) Generate product quality reviews.

9.0 PROCESS FLOW FOR COMMUNICATION OF CRITICAL OBSERVATIONS AND REGULATORY DECISIONS

When a Critical deficiency is identified the following sequence applies.

9.1 On noting a Critical deficiency as guided by this guideline and relevant appendices, the MCAZ inspectors escalate the issue to senior management.

9.2 A QA meeting of the inspectors is held, typically within 14 working days of the inspection, where observations and proposed regulatory decisions are discussed and where a Critical observation may be downgraded or a Major observation upgraded based on collective risk assessment.

9.3 Post validation of the Critical observations by the QA meeting, the inspectors prepare a memo to the Director General and or relevant Committee notifying them of the Critical observation and associated risk.

- 9.4** Upon signing of the Critical deficiency memo by the Director General, the inspectors finalise the inspection report and the regulatory decision letter.
- 9.5** The inspection report and regulatory decision letter are dispatched to the manufacturer.
- 9.6** Immediate regulatory decisions are communicated to the manufacturer and may include, among others, temporary halt of release or manufacture of the product to mitigate risk while a mitigation plan is proposed and implemented by the manufacturer.

10.0 REFERENCES

- 10.1.** World Health Organisation. 2017. Guidelines on heating, ventilation and air conditioning systems for non-sterile pharmaceutical products. WHO TRS 1010 Annex 8.
- 10.2.** World Health Organisation. 2014. WHO good manufacturing practices for pharmaceutical products. main principles. WHO Technical Report Series No. 986.
- 10.3.** Pharmaceutical Inspection Cooperation Scheme. 2019. PIC/S Guidance on Classification of GMP Deficiencies. PI 040.
- 10.4.** Health Canada. 2020. Risk Classification Guide for Drug Good Manufacturing Practices Observations. GUI 0023.

11.0 HISTORY

DOCUMENT HISTORY		
Revision Number	Date Approved	Reason for Change and Amendments
N/A	N/A	N/A