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Botswana Medicines Regulatory Authority



Approved By: 

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Director – Licensing and Enforcement

21-04-2026

Date of Approval
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REVISION STATUS SHEET

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1. GUIDANCE ON RISK-BASED CLASSIFICATION OF DEFICIENCIES

Introduction

- 1.1 This document serves as an administrative tool intended to facilitate compliance by regulated facilities and to promote consistency among inspectors in the classification of Good Manufacturing Practice (GMP) observations based on risk.
- 1.2 It further provides guidance to industry on conditions and practices considered unacceptable by the Authority, which may result in the identification of deficiencies and impact the overall compliance status of a facility.

2. Definitions

2.1 Critical deficiency

A critical deficiency may be defined as an observation that has produced, or may result in a significant risk of producing, a product that is harmful to the user.

2.2 Major deficiency

A *major* deficiency may be defined as a non-critical observation that:

- a. has produced or may produce a product that does not comply with its marketing authorization and/or prequalification application (including variations);
- b. indicates a major deviation from the GMP guide;
- c. indicates a failure to carry out satisfactory procedures for release of batches;
- d. indicates a failure of the person responsible for quality assurance/quality control to fulfil his or her duties;
- e. consists of several other deficiencies, none of which on its own may be major, but which together may represent a major deficiency and should be explained and reported as such.

2.3 Minor/ Other deficiency

- a. A deficiency may be classified as minor/ *other* if it cannot be classified as either critical or major but indicates a departure from GMP. A deficiency may be *other* either because it is judged to be minor or because there is insufficient information to classify it as major or critical.
- b. Classification of a deficiency is based on the assessed risk level and may vary depending on the nature of the products manufactured, e.g. in some circumstances an example of another deficiency may be categorized as major.
- c. Inspectors will generally consider the following when assigning risk ratings:
- d. Risk will be assigned in relation to the nature of the product, nature of the deviation, and frequency of occurrences.

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- e. Risks maybe upgraded/ downgraded from one class to the next depending on the evidence supporting the non-conformance and the nature of the deficiency and how critical the observation is to the dosage form.
- f. When making a Critical observation—or when re-evaluating a Major observation as a Critical observation- Inspectors will bring this situation to the attention of the company's Senior Management.
- g. All observations shall be discussed with the Auditee and agreed upon during the inspection. In the event of disagreement, the Auditee should be able to defend their position with clear reputable references on the finding in a corrective action and preventative action (CAPA) response.
- h. Recurring observations from previous inspections maybe upgraded.

NB: The following are typical GMP non-conformances Inspectors may observe during an inspection. It is not intended to be an all-inclusive/ exhaustive list, and inspectors may identify other observations.

3. Abbreviations

- 3.1 CAPA – Corrective Action and Preventative Action
- 3.2 COA – Certificate of Analysis
- 3.3 HVAC – Heating, Ventilation and Air Conditioning
- 3.4 GMP – Good Manufacturing Practices
- 3.5 SOP – Standard operating procedure
- 3.6 QC – Quality Control

4. EXAMPLES OF CRITICAL, MAJOR, AND OTHER OBSERVATIONS

4.1 PREMISES

4.1.1 Critical Observations

- a. No air filtration system to eliminate airborne contaminants
- b. Generalised malfunctioning of the ventilation system(s)-Contamination evident.
- c. Inadequate segregation of manufacturing or testing areas from other manufacturing areas for high-risk products such as highly sensitizing drugs, biological, hormones, cytotoxic drugs or highly active drugs
- d. Design of premises does not allow unidirectional flow of material and personnel thus posing a risk of cross contamination

4.1.2 Major Observations

- a. Malfunctioning of the ventilation system that could result in possible localized or occasional cross-contamination.
- b. Maintenance/periodic verification such as air filter replacement, monitoring of pressure differentials not performed.

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- c. Accessory supplies (steam, air, nitrogen, dust collection, etc.) not qualified.
- d. Heat, Ventilation, Air Conditioning (HVAC) and purified water system not qualified.
- e. Temperature and humidity not controlled or monitored when necessary (for example, storage not in accordance with labelling requirements).
- f. Damages (holes, cracks or peeling paint) to walls/ceilings immediately adjacent or above manufacturing areas or equipment where the product is exposed.
- g. Un-cleanable surfaces created by pipes, fixtures or ducts directly above products or manufacturing equipment.
- h. Surfaces finish (floors, walls and ceilings) that do not permit effective cleaning.
- i. Unsealed porous finish in manufacturing areas with evidence of contamination (mildew, mould, powder from previous productions, etc.).
- j. Insufficient manufacturing space that could lead to mix-ups.
- k. Physical and electronic quarantine accessible to unauthorized personnel/Physical quarantine area not well marked and/or not respected when used.
- l. No separate area/Insufficient precautions to prevent contamination or cross-contamination during raw material sampling.

4.1.3 Other Observations

- a. Doors giving direct access to exterior from manufacturing and packaging areas used by personnel.
- b. Un-screened/Un-trapped floor drains.
- c. Outlets for liquids and gases not identified.
- d. Damages to surfaces not directly adjacent or above exposed products.
- e. Non-production activities performed in production areas.
- f. Inadequate rest, change, wash-up and toilet facilities

4.2 EQUIPMENT

4.2.1 Critical Observations

- a. Equipment used for complex manufacturing operations of critical products not qualified and with evidence of malfunctioning or lack of appropriate monitoring.

4.2.2 Major Observations

- a. Equipment does not operate within its specifications.
- b. Equipment used during the critical steps of fabrication, packaging/labelling, and testing, including computerized systems, is not qualified.
- c. Tanks for manufacturing of liquids and ointments not equipped with sanitary clamps.
- d. Stored equipment not protected from contamination.

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- e. Inappropriate equipment for production: surfaces porous and non-cleanable/material sheds particles.
- f. Evidence of contamination of products by foreign materials such as grease, oil, rust and particles from the equipment.
- g. No covers for tanks, hoppers or similar manufacturing equipment.
- h. No inadequate precautions taken when equipment such as oven or autoclave contains more than one product (possibility of cross-contamination or mix-ups).
- i. Equipment location does not prevent cross-contamination or possible mix-ups for operations performed in common area.
- j. Purified water system not maintained or operated to provide water of adequate quality. Leaking gaskets with potential impact on product quality.
- k. No calibration program for automatic, mechanical, electronic or measuring equipment/no records maintained.
- l. No preventative maintenance program for major equipment/no records maintained.
- m. No equipment usage logs.

4.2.3 Other Observations

- a. Insufficient distance between equipment and walls to permit cleaning.
- b. Base of immovable equipment not adequately sealed at points of contact.
- c. Use of temporary means or devices for repair.
- d. Defective or unused equipment not removed or appropriately labelled.
- e. Minor equipment used for non-critical products not qualified.

4.3 PERSONNEL

4.3.1 Critical Observations

Individual in charge of Quality Control (QC) or production for a manufacturer of critical/high risk products does not hold a university degree in a science related to the work being conducted and does not have sufficient practical experience in their responsibility area.

4.3.2 Major Observations

- a. Individual in charge of QC or Production for a manufacturer, packager/labeller, importer, distributor or tester does not hold a university degree in a science related to the work being conducted.
- b. Individual in charge of QC or Production for a manufacturer, packager/labeller, importer, distributor or tester does not have sufficient practical experience in their responsibility area.

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- c. Individual in charge of QC for a wholesaler or secondary labeller is not qualified by academic training and experience.
- d. Delegation of responsibilities for QC or Production to insufficiently qualified persons.
- e. Insufficient personnel for QC or Production operations resulting in a high probability of error.
- f. Insufficient training for personnel involved in production and QC resulting in related GMP deviations

4.3.3 Other Observations

- a. Inadequate training records.
- b. Insufficient written training program

4.4 SANITATION & HYGIENE

4.4.1 Critical Observations

- a. Evidence of widespread accumulation of residues/extraneous matter indicative of inadequate cleaning.
- b. Evidence of gross infestation.

4.4.2 Major Observations

- a. Sanitation program not in writing but premises in acceptable state of cleanliness.
- b. No standard operating procedures (SOP) for microbial/environmental monitoring, no action limits for areas where susceptible non-sterile products are manufactured.
- c. Cleaning procedures for production equipment not validated (including analytical methods)
- d. Inadequate written health requirements and/or hygiene program
- e. Health requirements and/or hygiene program not properly implemented or followed.

4.4.3 Other Observations

- a. Incomplete written sanitation procedure.
- b. Incomplete implementation of the written sanitation program.

4.5 RAW MATERIAL TESTING

4.5.1 Critical Observations

- a. Evidence of falsification or misrepresentation of analytical results.

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- b. No evidence of testing Certificate of Analysis (COA) available from the supplier/synthesizer and no testing done.

4.5.2 Major Observations

- a. Reduced testing program in place without adequate certification of the vendors/suppliers.
- b. Water used in the formulation is not of acceptable quality.
- c. Insufficient testing of raw material.
- d. Incomplete specifications.
- e. Specifications not approved by QC.
- f. Test methods not validated.
- g. Use of raw material after retest date without proper retesting.
- h. Use of raw material after the expiration date.
- i. Multiple lots of the same raw material, comprising of one reception, are not considered as separate for sampling, testing and release.
- j. No SOP for conditions of transportation and storage.
- k. Certification of brokers or wholesalers allowed without proper documentation.

4.5.3 Other Observations

- a. Lots identified for confirmatory testing used in production without QC approval.
- b. Incomplete validation of test methods.

4.6 MANUFACTURING CONTROL

4.6.1 Critical Observations

- a. No written Master Formula.
- b. Master Formula or manufacturing batch document showing gross deviations or significant calculation errors.
- c. Evidence of falsification or misrepresentation of manufacturing and packaging orders.

4.6.2 Major Observations

- a. Master Formula prepared/verified by unqualified personnel.
- b. Lack of or incomplete validation studies/reports for critical manufacturing process (lack of evaluation/approval).
- c. Inadequate validation of changeover procedures.
- d. Unapproved/undocumented major changes compared to Master Production Documents.
- e. Deviations from instructions during production not documented and not approved by QC.

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- f. Discrepancies in yield or reconciliation following production not investigated.
- g. Line clearance between production of different products not covered by SOP and not documented.
- h. No regular checks for measuring devices/no records.
- i. Lack of proper identification of in-process materials and production rooms resulting in a high probability of mix-ups.
- j. Inadequate labelling/storage of rejected materials and products that could generate mix-ups.
- k. Upon receipt, bulk and in-process drugs, raw material and packaging material not held in quarantine until released by QC.
- l. Labels are not properly controlled.
- m. Production personnel using bulk and in-process drugs, raw material and packaging material without prior authorization by QC.
- n. Inadequate/inaccurate labelling of bulk/in-process drugs, raw material and packaging material
- o. Raw material dispensing not done by qualified persons, according to an SOP.
- p. Master Formula incomplete or showing inaccuracies in the processing operations.
- q. Changes in batch size not prepared/verified by qualified personnel.
- r. Inaccurate/incomplete information in manufacturing/packaging batch documents.
- s. Although documented, combination of batches done without QC approval/not covered by SOP.
- t. No written procedures for packaging operations.
- u. Non-standard occurrences during packaging not investigated by qualified personnel.
- v. Inadequate control of coded and non-coded printed packaging material (including storage, dispensing, printing, disposal).
- w. Inadequate handling of outdated/obsolete packaging material.
- x. No or inadequate self-inspection program/Program does not address all applicable sections of GMPs/Records incomplete or not maintained.
- y. Fabrication, packaging/labelling and testing operations carried out at a site not holding a valid manufacturing licence.
- z. No agreement between the contractor, the importer and the distributor covering the fabrication and packaging/labelling operations.
- aa. Recall:
 - a. Absence of recall procedure combined with distribution practices that would not permit an adequate recall (distribution records unavailable or not kept).
- bb. Improper quarantine and disposal practices that would allow recalled/rejected units to be returned for sale.
- cc. Batch not defined

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4.6.3 Other Observations

- a. Incomplete SOPs for handling of materials and products.
- b. Access to production areas not restricted to authorized personnel.
- c. Inadequate checks for incoming materials.
- d. Written procedures incomplete for packaging operations.
- e. Incomplete recall procedure.
- f. No agreement between the wholesaler, the importer and the distributor relative to a recall of a drug when the importer or distributor assumes wholesaler's responsibilities with respect to recalls.
- g. Incomplete/inaccurate annual product quality review.

4.7 QUALITY CONTROL DEPARTMENT

4.7.1 Critical Observations

- a. No person in charge of QC available on premises.
- b. Quality Control department is not a distinct and independent unit, lacking real decisional power, with evidence that QC decisions are often overruled by production department or management.

4.7.2 Major Observations

- a. Background and limited access to non-essential personnel. Inadequate facilities, personnel and testing equipment.
- b. No authority to enter production areas.
- c. No SOPs approved and available for sampling, inspection and testing of materials.
- d. Products made available for sale without approval of QC department.
- e. Products released for sale by QC without proper verification of manufacturing and packaging documentation.
- f. Master production documents not in compliance with marketing authorization.
- g. Out of specification test results, deviations and borderline conformances not properly investigated and documented, according to an SOP.
- h. Raw material/packaging material used in production without prior approval of QC.
- i. Reprocessing/Reworking done without prior approval of QC department.
- j. Lack of or inadequate system for complaint handling.
- k. Returned goods are made available for sale without assessment and/or approval by QC.
- l. SOPs covering operations that can affect the quality of a product such as transportation, storage, etc. not approved by QC department/not implemented.
- m. Inadequate evidence to demonstrate that storage and transportation conditions are appropriate.

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- n. Lack of or insufficient change control system.
- o. For testing laboratories (in house or contract), 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.
- p. Products tested at a site not holding a valid GMP licence/ certificate.
- q. Sterility testing not performed in a Grade A environment within a Grade B background or in an isolator of a Grade A within an appropriate

4.7.3 Other Observations

- a. No agreement between the contract laboratory and the establishment covering the testing activities.
- b. Investigations of non-conformances not completed in timely manner.

4.8 PACKAGING MATERIAL TESTING

4.8.1 Major Observations

- a. Reduced testing program in place without adequate certification of vendors/suppliers.
- b. Lack of or insufficient testing of packaging material.
- c. Inadequate specifications.
- d. Specifications not approved by QC.
- e. No identity test done by the packager/labeller after receipt on its premises.
- f. Certification of brokers or wholesalers done without proper documentation.

4.8.2 Other Observations

- a. Inadequate procedures of transportation and storage.
- b. Inappropriate environment and/or precautions to prevent contamination of packaging material during sampling.

4.9 FINISHED PRODUCT TESTING

4.9.1 Critical Observations

- a. Finished product not tested for compliance with applicable specifications by the importer/distributor before release for sale and no evidence is available that the products have been tested by the manufacturer.
- b. Evidence of falsification or misrepresentation of testing results / forgery of COA.

4.9.2 Major Observations

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- a. Non-compliant products made available for sale.
- b. Incomplete/inadequate specifications.
- c. Finished product specifications not approved by QC.
- d. Incomplete testing.
- e. No identity testing upon receipt at site and/or no periodic complete confirmatory testing.
- f. Lack of or insufficient validation of test methods.
- g. No SOP for conditions of transportation and storage.
- h. Use of unique identifier principles not meeting the acceptable options.

4.9.3 Other Observations

- a. Inadequate method transfers for a validated analytical method.
- b. Method validation report does not specify the revision of the analytical method used at the time of validation.

4.10 RECORDS

4.10.1 Critical Observations

- a. Evidence of falsification or misrepresentation of records.

4.10.2 Major Observations

- a. Lack of or incomplete Master Production Documents.
- b. Unavailability of documentation from suppliers in a timely manner.
- c. Lack of or incomplete records of sale.
- d. Lack of or incomplete records of complaints received respecting the quality of a drug.

4.10.3 Other Observations

- a. Incomplete plans and specifications for the manufacturing buildings
- b. Insufficient retention time for evidence and records to be maintained.
- c. No organization charts.
- d. Incomplete records for the sanitation program.

4.11 SAMPLES

4.11.1 Major Observations

- a. Retained samples not kept for finished products.
- b. Failure to submit retained samples when alternative sample retention granted.

4.11.2 Other Observations

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- a. Samples of raw material not available.
- b. Insufficient quantity for finished products or active pharmaceutical ingredients (API).
- c. Improper storage conditions.

4.12 STABILITY

4.12.1 Critical Observations

- a. No data available to establish the shelf-life of products.
- b. Evidence of falsification or misrepresentation of stability data/forgery of COA.

4.12.2 Major Observations

- a. Insufficient number of lots to establish shelf-life.
- b. Insufficient data to establish shelf-life.
- c. No action taken when data shows that the products do not meet their specifications prior to the expiry date.
- d. Lack of or inadequate continuing stability program.
- e. No stability studies pertaining to changes in manufacturing (formulation)/packaging material.
- f. Testing methods not validated.
- g. No consideration given to enrol worst case scenarios (for example, reworked/reprocessed lots).
- h. Inappropriate storage conditions for stability samples.

4.12.3 Other Observations

- a. Stability testing not performed at the time required by the written program.
- b. Review of stability data not performed in a timely manner.

5. STERILE PRODUCTS

5.1 Critical Observations

- a. Lack of or inadequate validation of critical sterilization cycles.
- b. Water for Injection (WFI) systems not validated with evidence of problems such as microbial/endotoxin counts not within specifications.
- c. No media fills performed to demonstrate the validity of aseptic filling operations.
- d. No environmental controls/No monitoring for viable microorganisms during filling for aseptically filled products.
- e. Aseptic filling operations continued following unsatisfactory media fill results obtained.

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- f. Batches failing initial sterility test released for sale on the basis of a second test without proper investigation.
- g. Inadequate environmental conditions for aseptic operations.
- h. Absence of leak test for ampules

5.2 Major Observations

- a. Aqueous-based products not subject to terminal steam sterilization without proper justification or approval through the marketing authorization.
- b. Inadequate room classification for processing/filling operations.
- c. Aseptic manufacturing suites under negative pressure compared to clean areas (C-D). Clean areas (C-D) under negative pressure to unclassified areas.
- d. Insufficient number of samples taken for environmental monitoring/inadequate sampling methods.
- e. Insufficient environmental controls/Insufficient monitoring for viable microorganisms during filling for aseptically filled products.
- f. Premises and equipment not designed or maintained to minimize contamination/generation of particles.
- g. Inadequate maintenance of purified water and WFI systems.
- h. Inadequate re-validation of purified water and WFI systems after maintenance, upgrading, out-of-specs trends.
- i. Inadequate training of personnel.
- j. Personnel involved in aseptic filling prior to completing successful media fill.
- k. Inadequate gowning practices for clean and aseptic areas.
- l. Inadequate sanitation/disinfection program.
- m. Inadequate practices/precautions to minimize contamination or prevent mix-ups.
- n. Non-validated time lapse between cleaning, sterilization, and use of components, containers and equipment.
- o. No consideration given to bio burden prior to sterilization.
- p. Non-validated time lapse between start of manufacturing and sterilization or filtration.
- q. Inadequate program for media fill.
- r. Capability of media to grow a wide spectrum of microorganisms not demonstrated.
- s. Misinterpretation of results for media fill.
- t. Samples for sterility testing insufficient in number or not representative of the entire production run.
- u. Each sterilizer load not considered as a separate lot for sterility testing.
- v. Purified water is not used as the feed water for the WFI system and the clean steam generator.
- w. Inadequate testing program for WFI.
- x. The WFI used for the final rinsing of containers and components used for parenteral drugs is not tested for endotoxins when those containers and components are not depyrogenated subsequently.

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- y. Inappropriate environment/controls for crimping following aseptic filling.
- z. Inadequate inspection for particles and defects.
- aa. Gases used to purge solutions or blanket products not passed through a sterilizing filter.
- bb. Inadequate integrity testing of sterilizing or vent filters.

5.3 Other Observations

- a. Steam used for sterilization not monitored to assure suitable quality.
- b. Inadequate control on the maximum number of personnel present in clean and aseptic areas.

6. DECISION ON COMPLIANCE

The status of GMP compliance shall be determined based on the nature and number of deficiencies identified during inspection.

	SCENARIO	INSPECTION CONCLUSION
1	No deficiencies	Operating at an acceptable level of compliance with GMP guidelines
2	Only other/ minor deficiencies only	Operating at an acceptable level of compliance with GMP guidelines CAPA to be submitted within 60 calendar days. Implementation verified during the next routine inspection
3	Other/ minor observations + <6 major deficiencies	Decision on the level of compliance to be made after receipt and evaluation of CAPA
4	Any critical deficiency or ≥6 major deficiencies	Operating at an unacceptable level of compliance with GMP guidelines CAPA to be submitted within 60 calendar days Another inspection will be required to verify compliance Administrative and/or legal enforcement actions are applied as necessary.

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7. RECOMMENDED REGULATORY ACTIONS AGAINST OBSERVED NON-COMPLIANCES

	SCENARIO	REGULATORY ACTION
1	No deficiencies	No regulatory action
2	Only other/ minor deficiencies only	Operating at an acceptable level of compliance with GMP guidelines CAPA to be submitted within 30 calendar days. Implementation verified during the next routine inspection
3	Other/ minor observations + <6 major deficiencies	Decision on the level of compliance to be made after receipt and evaluation of CAPA a) CAPA to be submitted within 30 calendar days. b) Failure to submit CAPA, issue a warning letter for intention to suspend GMP certificate or close the inspection for the respective lines and/or marketing authorization of the products. Issue a final 30 calendar days for addressing the deficiencies.
4	Any critical deficiency or ≥6 major deficiencies	The facility is considered to be operating at an unacceptable level of compliance with GMP guidelines a) CAPA to be submitted within 30 calendar days. Submit evidence of implementation within 30 calendar days from the date of the report covering letter. Conduct re-inspection within 60 calendar days post final CAPA submission b) Failure to submit CAPA on time, issue a regulatory action letter notifying-, i. Suspension of the affected manufacturing lines, and/or; ii. Suspension or withdraw GMP certificate and/or; iii. Suspension or withdrawal of marketing authorization in case of products and/or; iv.

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	iv. Recommend not to grant marketing authorization for the new products. v. Seize API and products upon identified risk and extension of actions to recall products. In case of foreign facilities. a) Instruct the facility to prepare a CAPA plan within 30 calendar days. b) CAPA implementation report should be submitted as part of application for reinspection. c) Suspend marketing authorization of products. d) Recommend not to grant marketing authorization for the new products. e) Seize API and products upon identified risk and extension of actions to recall products
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8. REFERENCES

- a. Medicines and Related Substance Act, 2025
- b. Medicines and Related Substances Regulations, 2019
- c. WHO good manufacturing practices for pharmaceutical products: main principles. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva*, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2
- d. WHO Technical Report Series No. 996, 2016, Annex 4: Guidance on good manufacturing practices: Inspection report
- e. SADC Guideline for Good Manufacturing Practice (GMP) Inspections
- f. Health Canada-Risk classification guide for drug manufacturing practices observations (GUI-0023)

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