National Drug Authority
Plot No. 46 - 48 Lumumba Avenue,
P.O. Box 23096, Kampala, Uganda.
email: ndaug@nda.or.ug; website: www.nda.or.ug
Tel: +256-414-255665, +256-414-347391/2

Doc. No.: INS/CLT/009
Revision No.: 1
Effective Date: 6 Nov 2014

Guide To Risk Classification Of GMP Non-Compliances (Deficiencies)

Definition[1]

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[2]

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;

[1] *Adopted from PIC/S SOP for inspection format, PI 013-3 1 Annex, 25 Sep 2007.*
[2] *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.*

Guide To Risk Classification Of GMP Non-Compliances (Deficiencies)

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:

- 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 microibial/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.

Guide To Risk Classification Of GMP Non-Compliances (Deficiencies)

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.

2.13 Stability 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 micro organisms 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.

Guide To Risk Classification Of GMP Non-Compliances (Deficiencies)

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 parenterals 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.

Guide To Risk Classification Of GMP Non-Compliances (Deficiencies)

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.

End of document