Health Canada Santé Canada

Our Mandate:
To manage and deliver a national compliance and enforcement program for blood and donor semen; cells, tissues and organs; drugs (human and veterinary); medical devices and natural health products, collaborating with and across, all regions.

Health Products and Food Branch Inspectorate

Risk Classification of Good Manufacturing Practices (GMP) Observations

GUI-0023

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Canada

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1.0 Purpose

To classify the observations noted during establishment inspections according to their risk.

To ensure uniformity among the inspectors of the Health Products and Food Branch Inspectorate (Inspectorate) in the attribution of the rating following establishment inspections.

To inform the industry of the situations that the Inspectorate considers unacceptable and that will generate a Non-Compliant (NC) rating following an inspection.

2.0 Background

During an establishment inspection, deviations from the *Food and Drug Regulations* and the current edition of the Good Manufacturing Practices (GMP) Guidelines - 2009 Edition, Version 2 (GUI-0001) are noted by the inspector and these deviations appear as observations in the inspection Exit Notice. A judgement based on these observations is then made by the inspector and an overall recommendation is given. The possible ratings are defined below:

C (Compliant): At the time of the inspection, the regulated party has demonstrated that the activities it conducts are in compliance with the *Food and Drugs Act* and its associated Regulations. A "C" rating does not mean that there are no observations or corrective actions required.

NC (Non-Compliant): At the time of the inspection, the regulated party has not demonstrated that the activities it conducts are in compliance with the *Food and Drugs Act* and its associated Regulations.

Attribution of a NC rating may have serious consequences for a company, ranging from the implementation of important corrective measures to the temporary suspension or termination of the Establishment Licence (EL). Therefore, these situations of non-conformity have to be well defined, unambiguous and directly supported by the applicable regulations.

3.0 Scope

The definition of a drug in Canada covers a wide variety of products including pharmaceuticals and biologics products. This guidance document covers these products to which Division 2 of Part C of the *Food and Drug Regulations* applies and is based on the current edition of the Good Manufacturing Practices (GMP) Guidelines - 2009 Edition, Version 2 (GUI-0001). It is recognized that the evaluation of the conformity to the Good Manufacturing Practices (GMP) should be commensurate with the risk involved taking into account the nature and extent of the deviation in relation with the category of products evaluated. Nonetheless, most of the situations involving fraud, misrepresentation or falsification of products or data will generate a NC rating, irrespective of the category of products involved.

The appendix attached to the present document describes the observations related to each category of risk. Please note that the list of observations in the appendix is not exhaustive and that additional observations may be added where appropriate.

The numbering system assigned to each section in the appendix is a reference to the applicable regulations in the current edition of the "Good Manufacturing Practices (GMP) Guidelines - 2009 Edition, Version 2 (GUI-0001)".

4.0 Guide

4.1 Assignment of the Risk to an Observation

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

- The risk assigned will be in relation to the nature of the deviation as well as the number of occurrences.

- Generally, when only low risk products are involved, a risk 1 will not be assigned to observations described in Appendix 1, except for extreme situations such as fraud or widespread cross-contamination, infestation or unsanitary conditions.

- Where a risk 2 observation is re-evaluated as a risk 1 (risk 2 observation with an arrow), this situation is immediately brought to the attention of the company's officials, proper explanation will be provided to the establishment and this explanation should be captured in the *Inspector's Comments* field of the *Inspection Summary* in the Inspection Reporting System (IRS).

4.2 Assignment of the Inspection Rating

The overall inspection rating assigned is based on the risk involved taking into account the nature and extent of the deviations with the category of products evaluated.

Generally, a NC rating is assigned when a Risk 1 observation is noted during an inspection.

Such situation is immediately brought to the attention of the company's officials. The Inspectorate management is to be notified in a timely manner.

Where in the opinion of the inspector the resulting products present a significant health hazard, appropriate enforcement actions may be initiated.

A NC rating may also be assigned in the following situations:

- When numerous Risk 2 observations are noted during an inspection indicating that the company does not control its processes and operations sufficiently.

- Repetition of many Risk 2 and Risk 3 observations noted during previous inspections indicating that the company did not:

    - implement the corrective actions submitted following the previous inspection or
    - did not put in place adequate preventive actions in a timely manner to avoid recurrence of such deviations.

Generally, a C rating is assigned when Risk 2 observations are noted and in all situations where only Risk 3 observations are noted during an inspection.

4.3 Additional Guidance

When a NC rating is assigned, the inspector will issue a draft inspection Exit Notice during the exit meeting. The draft inspection Exit Notice will be reviewed for quality assurance purposes before the final report is issued to an establishment.

When observation(s) leading to a NC rating are made, the inspection Exit Notice could be issued with a C rating if, during the inspection:

- the establishment immediately implements all necessary actions to resolve the cause(s) of the observation(s) leading to the NC rating and,
- sufficient assurance can be provided to prevent a recurrence.

In such instances, the risk assigned to the observation will remain the same.

If the management of the company wishes to dispute the results of the inspection report, the “Dispute resolution and appeals” mechanism described in the *Drug Good Manufacturing Practices (GMP) and Establishment Licencing (EL) Enforcement Directive (POL-0004)* () should be followed.

Appendix A

Premises C.02.004

Note: Certain Risk 2 observations may be upgraded to a Risk 1. They are indicated with an arrow (↑)

Risk (Critical) Observations

- No air filtration system to eliminate airborne contaminants that are likely to be generated during fabrication or packaging.
- Generalized malfunctioning of the ventilation system(s) with evidence of widespread cross-contamination.
- Inadequate segregation of manufacturing or testing areas from other manufacturing areas for high risk products.

Risk 2 (Major) Observations

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

Risk 3 (Other) Observations

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

Equipment C.02.005

Note: Certain Risk 2 observations may be upgraded to a Risk 1. They are indicated with an arrow (↑)

Risk 1 (Critical) Observations

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

Risk 2 (Major) Observations

- Equipment does not operate within its specifications. (↑)
- Equipment used during the critical steps of fabrication, packaging/labelling, and testing, including computerized systems, is not qualified. (↑)
- Tanks for manufacturing of liquids and ointments not equipped with sanitary clamps.
- Stored equipment not protected from contamination. (↑)
- Inappropriate equipment for production: surfaces porous and non-cleanable/material sheds particles. (↑)
- Evidence of contamination of products by foreign materials such as grease, oil, rust and particles from the equipment. (↑)
- No covers for tanks, hoppers or similar manufacturing equipment.
- No inadequate precautions taken when equipment such as oven or autoclave contains more than one product (possibility of cross-contamination or mix-ups). (↑)
- Equipment location does not prevent cross-contamination or possible mix-ups for operations performed in common area. (↑)
- Purified water system not maintained or operated to provide water of adequate quality. (↑)
- Leaking gaskets with potential impact on product quality. (↑)
- No calibration program for automatic, mechanical, electronic or measuring equipment/no records maintained.
- No preventative maintenance program for major equipment/no records maintained.
- No equipment usage logs.

Risk 3 (Other) Observations

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

Personnel C.02.006

Risk 1 (Critical) Observations

- Individual in charge of Quality Control (QC) or production for a fabricator 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.

Risk 2 (Major) Observations

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

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

Risk 3 (Other) Observations

- Inadequate training records.
- Insufficient written training program

Sanitation C.02.007 – C.02.008

Note: Certain Risk 2 observations may be upgraded to a Risk 1. They are indicated with an arrow (↑)

Risk 1 (Critical) Observations

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

Risk 2 (Major) Observations

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

Risk 3 (Other) Observations

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

Raw Material Testing C.02.009 – C.02.010

Risk 1 (Critical) Observations

- Evidence of falsification or misrepresentation of analytical results.
- No evidence of testing Certificate of Analysis (COA) available from the supplier/synthesizer and no testing done by the Canadian fabricator

Risk 2 (Major) Observations

- Reduced testing program in place without adequate certification of the vendors/suppliers.
- Water used in the formulation is not of acceptable quality.
- Insufficient testing of raw material.
- Incomplete specifications.
- Specifications not approved by QC.
- Test methods not validated.

- Use of raw material after retest date without proper retesting.
- Use of raw material after the expiration date.
- Multiple lots of the same raw material, comprising of one reception, are not considered as separate for
- sampling, testing and release.
- No SOP for conditions of transportation and storage.
- Certification of brokers or wholesalers allowed without proper documentation.

Risk 3 (Other) Observations

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

Manufacturing Control C.02.011 – C.02.012

Note: Certain Risk 2 observations may be upgraded to a Risk 1. They are indicated with an arrow (↑)

Risk 1 (Critical) Observations

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

Risk 2 (Major) Observations

- Master Formula prepared/verified by unqualified personnel.
- Lack of or incomplete validation studies/reports for critical manufacturing process (lack of evaluation/approval). (↑)
- Inadequate validation of changeover procedures. (↑)
- Unapproved/undocumented major changes compared to Master Production Documents. (↑)
- Deviations from instructions during production not documented and not approved by QC.
- Discrepancies in yield or reconciliation following production not investigated.
- Line clearance between production of different products not covered by SOP and not documented.
- No regular checks for measuring devices/no records.
- Lack of proper identification of in-process materials and production rooms resulting in a high probability of mix-ups.
- Inadequate labelling/storage of rejected materials and products that could generate mix-ups.
- Upon receipt, bulk and in-process drugs, raw material and packaging material not held in quarantine until released by QC.
- Labels are not properly controlled. (↑)
- Production personnel using bulk and in-process drugs, raw material and packaging material without prior authorization by QC. (↑)
- Inadequate/inaccurate labelling of bulk/in-process drugs, raw material and packaging material
- Raw material dispensing not done by qualified persons, according to an SOP.
- Master Formula incomplete or showing inaccuracies in the processing operations.
- Changes in batch size not prepared/verified by qualified personnel.
- Inaccurate/incomplete information in manufacturing/packaging batch documents.
- Although documented, combination of batches done without QC approval/not covered by SOP.
- No written procedures for packaging operations.

- Non-standard occurrences during packaging not investigated by qualified personnel.
- Inadequate control of coded and non-coded printed packaging material (including storage, dispensing, printing, disposal).
- Inadequate handling of outdated/obsolete packaging material.
- No or inadequate self-inspection program/Program does not address all applicable sections of GMPs/Records incomplete or not maintained.
- Fabrication, packaging/labelling and testing operations carried out at a Canadian site not holding an EL. (↑)
- No agreement between the contractor, the importer and the distributor covering the fabrication and packaging/labelling operations.
- Products imported from foreign sites that are not listed on the Foreign Site Annex of the EL. (↑).

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

Risk 3 (Other) Observations

- Incomplete SOPs for handling of materials and products.
- Access to production areas not restricted to authorized personnel.
- Inadequate checks for incoming materials.
- Written procedures incomplete for packaging operations.
- Incomplete recall procedure.
- 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.
- Incomplete/inaccurate annual product quality review.

Quality Control Department C.02.013 – C.02.015

Note: Certain Risk 2 observations may be upgraded to a Risk 1. They are indicated with an arrow (↑)

Risk 1 (Critical) Observations

- No person in charge of QC available on premises in Canada.
- 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.

Risk 2 (Major) Observations

- Inadequate facilities, personnel and testing equipment.
- No authority to enter production areas. (↑)
- No SOPs approved and available for sampling, inspection and testing of materials.
- Products made available for sale without approval of QC department. (↑)
- Products released for sale by QC without proper verification of manufacturing and packaging documentation.
- Master production documents not in compliance with marketing authorization. (↑)

- Out of specification test results, deviations and borderline conformances not properly investigated and documented, according to a SOP. (↑)
- Raw material/packaging material used in production without prior approval of QC.
- Reprocessing/Reworking done without prior approval of QC department. (↑)
- Lack of or inadequate system for complaint handling.
- Returned goods are made available for sale without assessment and/or approval by QC.
- SOPs covering operations that can affect the quality of a product such as transportation, storage, etc... not approved by QC department/not implemented.
- Inadequate evidence to demonstrate that storage and transportation conditions are appropriate.
- Lack of or insufficient change control system.
- 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. (↑)
- Products tested at a Canadian site not holding an EL. (↑)
- Products tested at foreign sites that are not listed on the Foreign Site Annex of the EL. (↑)
- 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 background and limited access to non-essential personnel.

Risk 3 (Other) Observations

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

Packaging Material Testing C.02.016 – C.02.017

Note: Certain Risk 2 observations may be upgraded to a Risk 1. They are indicated with an arrow (↑)

Risk 2 (Major) Observations

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

Risk 3 (Other) Observations

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

Finished Product Testing C.02.018 – C.02.019

Note: Certain Risk 2 observations may be upgraded to a Risk 1. They are indicated with an arrow (↑)

Risk 1 (Critical) Observations

- 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 fabricator.
- Evidence of falsification or misrepresentation of testing results/forgery of COA.

Risk 2 (Major) Observations

- Non-compliant products made available for sale. (↑)
- Incomplete/inadequate specifications.
- Finished product specifications not approved by QC.
- Incomplete testing. (↑)
- No identity testing upon receipt in Canada from non-Mutual Recognition Agreement (MRA) country and/or no periodic complete confirmatory testing.
- Lack of or insufficient validation of test methods. (↑)
- No SOP for conditions of transportation and storage.
- Use of unique identifier principles not meeting the acceptable options.

Risk 3 (Other) Observations

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

Records C.02.020 – C.02.024

Risk 1 (Critical) Observations

- Evidence of falsification or misrepresentation of records.

Risk 2 (Major) Observations

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

Risk 3 (Other) Observations

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

Samples C.02.025 – C.02.026

Risk 2 (Major) Observations

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

Risk 3 (Other) Observations

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

Stability C.02.027 - C.02.028

Note: Certain Risk 2 observations may be upgraded to a Risk 1. They are indicated with an arrow (↑)

Risk 1 (Critical) Observations

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

Risk 2 (Major) Observations

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

Risk 3 (Other) Observations

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

Sterile Products C.02.029

Note: Certain Risk 2 observations may be upgraded to a Risk 1. They are indicated with an arrow (↑)

Risk 1 (Critical) Observations

- Lack of or inadequate validation of critical sterilization cycles.
- Water for Injection (WFI) systems not validated with evidence of problems such as microbial/endotoxin counts not within specifications.
- No media fills performed to demonstrate the validity of aseptic filling operations.
- No environmental controls/No monitoring for viable microorganisms during filling for aseptically filled products.
- Aseptic filling operations continued following unsatisfactory media fill results obtained.
- Batches failing initial sterility test released for sale on the basis of a second test without proper investigation.
- Inadequate environmental conditions for aseptic operations.
- Absence of leak test for ampules

Risk 2 (Major) Observations

- Aqueous-based products not subject to terminal steam sterilization without proper justification or approval through the marketing authorization.
- Inadequate room classification for processing/filling operations. (↑)
- Aseptic manufacturing suites under negative pressure compared to clean areas (C-D). Clean areas (C-D) under negative pressure to unclassified areas. (↑)
- Insufficient number of samples taken for environmental monitoring/inadequate sampling methods. (↑)
- Insufficient environmental controls/Insufficient monitoring for viable microorganisms during filling for aseptically filled products. (↑)Premises and equipment not designed or maintained to minimize contamination/generation of particles. (↑)
- Inadequate maintenance of purified water and WFI systems.
- Inadequate re-validation of purified water and WFI systems after maintenance, upgrading, out-of-specs trends.
- Inadequate training of personnel.
- Personnel involved in aseptic filling prior to completing successful media fill.
- Inadequate gowning practices for clean and aseptic areas.
- Inadequate sanitation/disinfection program.
- Inadequate practices/precautions to minimize contamination or prevent mix-ups.
- Non-validated time lapse between cleaning, sterilization, and use of components, containers and equipment.
- No consideration given to bioburden prior to sterilization.
- Non-validated time lapse between start of manufacturing and sterilization or filtration.
- Inadequate program for media fill.
- Capability of media to grow a wide spectrum of microorganisms not demonstrated.
- Misinterpretation of results for media fill.
- Samples for sterility testing insufficient in number or not representative of the entire production run.
- Each sterilizer load not considered as a separate lot for sterility testing.
- Purified water is not used as the feed water for the WFI system and the clean steam generator.
- Inadequate testing program for WFI. (↑)
- 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.
- Inappropriate environment/controls for crimping following aseptic filling.
- Inadequate inspection for particles and defects. (↑)
- Gases used to purge solutions or blanket products not passed through a sterilizing filter. (↑)
- Inadequate integrity testing of sterilizing or vent filters. (↑)

Risk 3 (Other) Observations

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

Appendix B

Glossary of Terms

The following definitions supplement the definitions provided under the Glossary of Terms in the guideline Good Manufacturing Practices (GMP) Guidelines - 2009 Edition, Version 2 (GUI-0001).

Critical Product - A critical product is one for which any of the following criteria may apply:

- narrow therapeutic window
- high toxicity
- sterile product
- biological drug
- complex manufacturing process: process for which slight deviations in the control of parameters could result in a non-uniform product or product not meeting its specifications. As examples, powder mixing or granulation for low dosage solid forms, long acting/delayed action products, sterile products.

Note: Category IV products (as listed in Annex 1 to the Current Edition of the Good Manufacturing Practices Guidelines - Selected Category IV Monograph Drugs (GUI-0066)) should not be considered as critical products even when the manufacturing processes involved are complex.

High Risk Product - Any product that may trigger a health risk even at low levels, following cross-contamination. Those include but are not limited to penicillins, certain cytotoxic and biological products.

Low Risk Product - Products such as Category IV product (as listed in Annex 1 to the Current Edition of the Good Manufacturing Practices Guidelines - Selected Category IV Monograph Drugs (GUI-0066)), that are not a schedule drug or a sterile drug, and certain topical non prescription veterinary formulations registered as “old drugs”.

Observation - A deviation or deficiency to GMPs noted by an inspector during the inspection of a drug establishment that is confirmed in writing to the company in the inspection Exit Notice. The observations are classified as “Critical”, “Major” and “Other” and are assigned a risk classification, ranging from 1 for “critical” to 2 for “major” to 3 for “other”.

- **Critical observation (Risk 1):**
  Observation describing a situation that is likely to result in a NC product or a situation that may result in an immediate or latent health risk and any observation that involves fraud, misrepresentation or falsification of products or data.

  Refer to Appendix 1 for the list of observations that the Inspectorate considers critical which will be assigned a Risk 1.

- **Major observation (Risk 2):**
  Observation that may result in the production of a drug not consistently meeting its marketing authorization.

Refer to Appendix 1 for the list of observations that are considered major and which will be assigned a Risk 2. Certain Risk 2 observations may be upgraded to Risk 1. They are indicated with an arrow **(↑)**.

- **Other observation (Risk 3):**
  Observation that is neither critical nor major but is a departure from the GMPs.

  "Other" observations are not listed as such (Observations that are neither critical nor major are considered as "other" and will be assigned a Risk 3). All Risk 3 observations could be upgraded to Risk 2. Refer to Appendix 1 for the list.