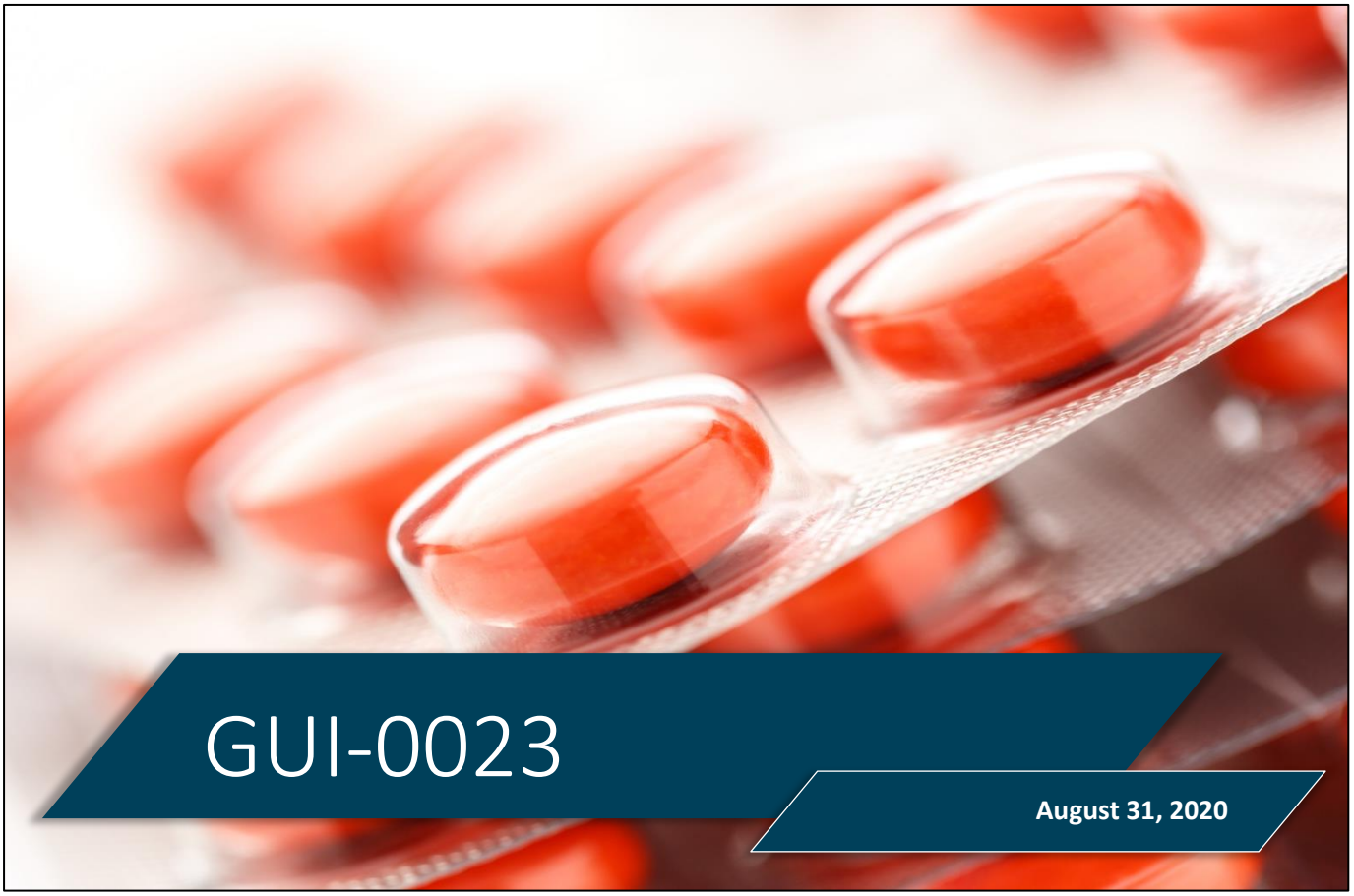
Risk classification guide for drug good manufacturing practices observations



GUI-0023

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Canada

Risk classification guide for drug good manufacturing practices observations (GUI-0023)

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About this document

1. Purpose

This document helps ensure consistency among Health Canada inspectors during drug establishment inspections when:

- classifying good manufacturing practices (GMP) observations according to risk.
- assigning an overall compliance rating to an inspection or to the paper review of GMP evidence.

It also informs industry of the situations Health Canada considers unacceptable that may result in a non-compliant (NC) rating and/or compliance and enforcement actions.

2. Scope

These guidelines apply to any drugs regulated by Part C, Division 2 of the Food and Drug Regulations, including:

- pharmaceutical
- radiopharmaceutical
- biological
- active pharmaceutical ingredients for human drugs
- veterinary

This guidance document is based on the current edition of the *Good manufacturing practices guide for drug products (GUI-0001)* and the *Good Manufacturing Practices Guidelines for Active Pharmaceutical Ingredients (GUI-0104)*.

The Pharmaceutical Inspection Cooperation Scheme (PIC/S) document 'PIC/S Good Practices for Data Management and Integrity in Regulated GMP/GDP environments' outlines considerations specific to data integrity and can be consulted for further guidance.

3. Introduction

During a drug establishment inspection, an inspector notes deviations from the Food and Drug Regulations and the *Good Manufacturing Practices Guide for drug products (GUI-0001)* or *Good Manufacturing Practices for Active Pharmaceutical Ingredients (GUI-0104)*. These deviations appear as observations in the inspection Exit Notice provided to the establishment.

Health Canada inspectors also use this guide to assess observations or other information noted by foreign regulatory partners when they conduct paper review assessments of GMP evidence for foreign buildings. For more information on GMP evidence for foreign buildings see *Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites (GUI-0080)*

The inspector assigns a risk classification to each observation, ranging from 1 for "critical," to 2 for "major," to 3 for "other."

- **Critical observation (Risk 1)** – Describes a situation that is likely to result in a product that may result in an immediate or latent health risk, or that involves fraud, misrepresentation or falsification of processes, products or data.
- **Major observation (Risk 2)** – Describes a situation that may result in the production of a drug not consistently meeting its marketing authorization. Some Risk 2 observations may be upgraded to Risk 1, for example in cases where the issue identified is not isolated to one area or system —these are indicated with an arrow (↑) in Appendix A.
- **Other observation (Risk 3)** – Describes a situation that is neither critical nor major, but is a departure from the GMPs. Any Risk 3 observation could be upgraded to Risk 2.

See Appendix A for a list of sample observations Health Canada considers critical (Risk 1), major (Risk 2), and other (Risk 3). Please note that this list is not exhaustive, and other observations may be added where appropriate.

All observations recorded in the Inspection Report require corrective action, regardless of the overall inspection rating attributed to the inspection. Observations requiring immediate or expedited corrective actions will be identified for the regulated party.

The inspector makes a judgment based on these observations, taking into account the nature and extent of deviations, and gives an overall inspection rating recommendation for the establishment.

The possible inspection ratings are:

- 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.

An NC rating may result in compliance and enforcement actions which may include:

- the expedited implementation of corrective measures,
- adding terms and conditions to the establishment licence,
- a proposal to suspend the establishment licence, and/or
- the suspension of an establishment licence.

The immediate suspension of an establishment licence may be initiated in cases where it is deemed necessary to do so in order to prevent injury to the health of consumers.

Regardless of inspection rating (i.e. compliant or non-compliant), terms and conditions may be applied to the establishment licence to help protect the health and safety of Canadians.

Inspectors consider the level of risk when evaluating an establishment's conformity to the GMP. This includes the nature and extent of the deviation(s) in relation to the type of products being handled and the activities being conducted. However, most situations involving fraud, misrepresentation or falsification of processes, products or data will generally generate an NC rating, regardless of the activities being conducted or category of products involved.

The following table shows the two types of icons used in this document, and the way they are intended to be used.

Important: Key or cautionary information for people to know.

Information: Supplementary information like quotes and legal references.

Guidance

4. Guidance

1. Assigning risk to an observation

While it is impossible to foresee every situation that may generate a risk, inspectors will generally consider the following when assigning risk ratings:

- The nature of the deviation and number of occurrences.
- The nature of the product(s) being produced or handled.
- Whether similar issues have been cited in past inspections indicating that the company did not implement appropriate corrective measures to prevent recurrence of the issue(s).

An observation may be considered as a repeat observation if:

- It is similar to any past observation
- It cites the same regulation as the past observation, and
- There is a reasonable expectation that the corrective measure(s) to past observation would have prevented recurrence of the GMP deficiency.

When making a Risk 1 observation—or when re-evaluating a Risk 2 observation as a Risk 1 (Risk 2 observation with an arrow)—inspectors will bring this situation to the attention of the company's officials and ask them to take immediate corrective action.

The failure of a company to apply good pharmaceutical quality system principles, including quality risk management principles, will be considered in the assignment of risk to an observation.

2. Assigning an inspection rating

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

Generally, a C rating will be assigned in the following situations:

- Where few Risk 2 observations, focused on isolated issues are noted.
- Where only Risk 3 observations are noted.

Generally, an NC rating will be assigned in the following situations:

- When a Risk 1 observation is noted during an inspection.
- When numerous Risk 2 observations are noted during an inspection, indicating that the company does not control its processes and operations sufficiently.
- When Risk 2 observations identifying overarching systemic issues are noted.

When, in the inspector's opinion, and based on the nature of the deficiencies observed, the products being produced or handled present a significant health hazard, further enforcement action may be initiated to mitigate potential risk, and correct the observed non-compliance.

When an NC rating is under consideration, or the rating needs further review, the unrated inspection exit notice will be reviewed by Health Canada for quality assurance purposes, including consistency, before the final report is issued.

If a company wants to dispute the results of the inspection report or the final rating, methods of dispute will be outlined in the letter accompanying the unrated and final exit notices (or the letter to confirm an NC rating during foreign site paper review assessments).

If further enforcement action is considered (such as licence suspension), your company may be given the opportunity to be heard, the process to be followed will be outlined in the letter communicating the decision.

Appendices

Appendix A – Sample observations

The following are sample observations inspectors may note during an inspection. It is not intended to be an all-inclusive list, and inspectors may use other observations where appropriate.

Premises

C.02.004

Risk 1 (critical) observations

- There was no air filtration system to eliminate airborne contaminants likely to be generated during fabrication or packaging.
- There was generalized malfunctioning of the ventilation system(s), with evidence of widespread cross-contamination.
- Segregation of manufacturing or testing areas from other manufacturing areas was inadequate for higher risk products.

Risk 2 (major) observations

- Maintenance and scheduled verification (e.g. air filter replacement and monitoring of pressure differentials) were not done. (↑)

- The establishment's heat, ventilation and air conditioning (HVAC) and/or purified water systems were not qualified. (↑)
- Unsealed porous finish in manufacturing areas showed evidence of contamination (e.g. mildew, mould or powder from previous productions). (↑)
- There was insufficient manufacturing space, which could lead to mix-ups. (↑)
- Physical or electrical quarantine areas were not adequately controlled, identified, well-marked and/or not respected when used. (↑)
- There was malfunctioning of the ventilation system that could result in localized or occasional cross-contamination.
- Accessory supplies (e.g. steam, air, nitrogen and dust collection) were not qualified.
- Temperature and humidity were not controlled or monitored when necessary (i.e. products were not stored according to labelling requirements).
- Holes, cracks, peeling paint or other damages to walls and/or ceilings were observed immediately adjacent to or above:
    - manufacturing areas in which products were exposed.
    - equipment that handled products.
- The placement of pipes, fixtures or ducts directly above products or manufacturing equipment created surfaces that could not be cleaned.
- The finish of surfaces such as floors, walls and ceilings did not permit effective cleaning.
- Unauthorized staff had access to physical and electronic quarantine areas.
- A separate area was not assigned for raw material sampling.
- Proper precautions were not taken to prevent contamination or cross-contamination during raw material sampling.

Risk 3 (other) observations

- Personnel used doors with direct access to the exterior from manufacturing and packaging areas.
- Floor drains were not screened and/or trapped.
- Outlets for liquids and gases were not identified.
- Permanent pipeline installations in production areas were not identified appropriately.
- Damage was noted on surfaces not directly adjacent to or above exposed products.

- Non-production activities were performed in production areas.
- Rest, change, wash-up and/or toilet facilities were inadequate.

Equipment

C.02.005

Risk 1 (critical) observations

- Equipment used for the complex manufacturing of critical products was not qualified and there was evidence of malfunctioning or lack of appropriate monitoring.

Risk 2 (major) observations

- Equipment did not operate within its specifications. (↑)
- Equipment used during the critical steps of fabrication, packaging/labelling and testing—including computerized systems—was not qualified for its intended use. (↑)
- Stored equipment was not protected from contamination. (↑)
- Inappropriate equipment used for production had porous or uncleanable surfaces or was made of material that shed particles. (↑)
- There was evidence that foreign materials from equipment (e.g. grease, oil, rust or particles) contaminated products. (↑)
- When equipment such as ovens or autoclaves contained more than one product, inadequate precautions created the possibility of cross-contamination or mix-ups. (↑)
- Equipment location did not prevent cross-contamination or possible mix-ups for operations performed in a common area. (↑)
- The purified water system was not maintained or operated to provide water of adequate quality. (↑)
- Leaking gaskets were observed with the potential to impact product quality. (↑)
- Tanks, hoppers or similar manufacturing equipment did not have covers.
- Tanks used for manufacturing liquids and ointments were not equipped with sanitary clamps.
- There was no calibration program for automatic, mechanical, electronic or measuring equipment, or no calibration records were maintained.

- There was no preventative maintenance program for major equipment, and/or maintenance records were not maintained.
- The establishment did not keep equipment usage logs.
- Metal detecting equipment was not used where risk of metal contamination existed.

Risk 3 (other) observations

- There was not enough distance between equipment and walls to permit cleaning.
- The base of immovable equipment was not adequately sealed at points of contact.
- Temporary means or devices were used for equipment repair.
- Defective or unused equipment was not removed or appropriately labelled.
- Minor equipment used for non-critical products was not qualified.

Personnel

C.02.006

Risk 1 (critical) observations

- The person in charge of quality control or production for the fabrication of critical/high-risk products did not hold a university degree in a science related to the work being carried out and did not have sufficient practical experience in their area of responsibility.

Risk 2 (major) observations

- The person in charge of quality control or production for a fabricator, packager/labeller, importer, distributor or tester did not hold a university degree in a science related to the work being carried out.
- The person in charge of quality control or production for a fabricator, packager/labeller, importer, distributor or tester did not have sufficient practical experience in their area of responsibility.
- The person in charge of quality control for a wholesaler or secondary labeller did not have sufficient academic training and/or practical experience.
- Responsibilities for quality control or production were delegated to unqualified staff.

- Insufficient personnel for quality control or production operations increased the risk of error.
- Personnel involved in quality control and/or production did not have sufficient training, which resulted in deviations from good manufacturing practices.

Risk 3 (other) observations

- Training records were inadequate.
- The written training program was insufficient.

Sanitation

C.02.007 – C.02.008

Risk 1 (critical) observations

- Evidence of widespread residue and/or extraneous matter build-up showed cleaning was inadequate.
- There was evidence of gross infestation.

Risk 2 (major) observations

- Cleaning procedures for production equipment (including analytical methods) were not validated. (↑)
- The premises were in an acceptable state of cleanliness but there was no written sanitation program.
- There were no standard operating procedures for microbial and/or environmental monitoring.
- No action limits were set for areas where susceptible non-sterile products were manufactured.
- Sanitation records were not maintained.
- Cleaning procedures for production equipment were inadequate.
- The hygiene program and/or written health requirements were inadequate.
- The hygiene program and/or written health requirements were not properly implemented or followed.

Risk 3 (other) observations

- The written sanitation procedure was incomplete.
- The written sanitation program was not fully implemented.

Raw material testing

C.02.009 – C.02.010

Risk 1 (critical) observations

- There was evidence that analytical results were falsified or misrepresented.
- The supplier or manufacturer provided no evidence of the testing certificate of analysis and the Canadian fabricator did not perform testing.

Risk 2 (major) observations

- There was no sampling method or it was inadequate/not scientifically justified.
- A reduced testing program was in place without adequate certification of vendors and/or suppliers.
- Water used in the formulation was not of acceptable quality.
- Raw material was tested insufficiently.
- Recovered solvent testing was inadequate.
- Specifications were incomplete.
- The quality control department did not approve specifications.
- Test methods were not validated and/or the method suitability under actual condition of use was not verified.
- Raw material was used after the retest date without proper retesting.
- Raw material was used after its expiration date.
- Multiple lots of the same raw material, received at the same time, were not considered separately for sampling, testing and release.
- There were no written procedures for transportation and storage conditions.
- Transportation and storage records were not maintained.

- Vendors were certified without proper documentation.

Risk 3 (other) observations

- Lots identified for confirmatory testing were used in production without quality control department approval.
- Validation of test methods was incomplete.

Manufacturing control

C.02.011 – C.02.012

Risk 1 (critical) observations

- There was no written master formula.
- The master formula or manufacturing batch document showed gross deviations from the formula, process described in the market authorisation, or significant errors in calculation.
- There was evidence that manufacturing and/or packaging orders were falsified or misrepresented.

Risk 2 (major) observations

- Validation studies or reports for a critical manufacturing process were missing or incomplete, or were not appropriately evaluated or approved. (↑)
- Validation of changeover procedures was inadequate. (↑)
- Unapproved and/or undocumented major changes were made, compared to master production documents. (↑)
- Labels were not properly controlled. (↑)
- Production staff used bulk and in-process drugs, raw material and/or packaging material without authorization from the quality control department. (↑)
- Fabrication, packaging/labelling and testing operations were carried out at a Canadian site that did not hold an establishment licence. (↑)
- Evidence of good manufacturing practices compliance for a foreign building was missing or inadequate. (↑)

- Foreign buildings required to be listed on an establishment licence were not appropriately listed on an establishment licence. (↑)
- The master formula was not prepared or verified by qualified personnel.
- Deviations from manufacturing instructions during production were not documented and approved by the quality control department.
- Discrepancies in yield or reconciliation after production were not investigated.
- The line clearance between the production of different products was not documented or covered by a standard operating procedure.
- Measuring devices were not subject to regular checks or there were no records kept of these checks.
- In-process materials and production rooms were not properly identified, resulting in a high probability of mix-ups.
- Labelling or storage of rejected materials and products was inadequate and could result in mix-ups.
- On receipt, bulk and in-process drugs, raw material and/or packaging material were not held in quarantine until released by the quality control department.
- Bulk/in-process drugs, raw material and/or packaging material were inadequately or inaccurately labelled.
- Raw materials were not dispensed by qualified staff or according to written procedure.
- The master formula was incomplete or showed inaccuracies in processing operations.
- Changes in batch size were not prepared or verified by qualified staff.
- Manufacturing and/or packaging batch documents were incomplete or inaccurate.
- Documented batch combinations were done without quality control department approval and/or were not covered by a standard operating procedure.
- There were no written procedures for packaging operations.
- Non-standard events during packaging were not investigated by qualified staff.
- Control of coded and non-coded printed packaging material (including storage, dispensing, printing or disposal) was inadequate.
- Handling of outdated or obsolete packaging materials was inadequate.
- There was no self-inspection program, or the self-inspection program was inadequate.
- The self-inspection program did not address all applicable sections of good manufacturing practices requirements.

- Self-inspection program records were incomplete or not maintained.
- There was no written agreement between the contractor, importer and distributor covering fabrication and packaging/labelling operations.
- The integrity of the supply chain was compromised (e.g. insufficient knowledge of the supply chain, failure to purchase from a licensed supplier where required, etc.).
- There was no recall procedure.
- Distribution practices would not have supported an adequate recall.
- Distribution records were not available or maintained.
- Improper quarantine and disposal practices could allow recalled or rejected units to be returned for sale.

Risk 3 (other) observations

- Standard operating procedures for handling materials and products were incomplete.
- Access to production areas was not restricted to authorized personnel.
- Checks for incoming materials were inadequate.
- Written procedures for packaging operations were incomplete.
- The establishment's recall procedure was incomplete.
- The wholesaler, importer and/or distributor had no defined agreement on how to recall a drug in situations where the importer or distributor assumed the wholesaler's recall responsibilities.
- The annual product quality review was incomplete or inaccurate.

Quality control department

C.02.013 – C.02.015

Risk 1 (critical) observations

- There was no person in charge of quality control available on the Canadian premises.
- The quality control department was not a distinct unit with true decision-making power.
- The production department or management overruled quality control decisions.
- Analytical samples, tests results or raw data were misrepresented or fabricated.

- Deleted or destroyed records, results or raw data were used to support release.

Risk 2 (major) observations

- Quality control personnel did not have adequate access to the production areas for sampling and/or investigating. (↑)
- Products were made available for sale without quality control department approval. (↑)
- Products were released for sale by the quality control department without proper verification of manufacturing and packaging documentation, or without verifying that the product met all applicable requirements. (↑)
- Master production documents did not comply with the marketing authorization. (↑)
- Reprocessing and/or reworking was done without prior approval from the quality control department. (↑)
- For testing labs (in house or contract): proper systems and controls for the qualification, operation, calibration and maintenance of equipment, standards, solutions and/or record-keeping were not in place to assure accurate and reliable results and conclusions. (↑)
- Products were tested at a Canadian site that did not hold an establishment licence. (↑)
- Products were tested at foreign sites that were not listed on the applicable annex of the establishment licence. (↑)
- Test results that suggested a negative impact on product quality were not adequately documented, reported or investigated. (↑)
- The practice of performing of trial sample injections was identified. (↑)
- Activities were not documented at the time they were performed. (↑)
- Electronic records were not maintained as raw data where appropriate. (↑)
- Discrepancies were noted between electronically saved data and printed records. (↑)
- Complete data for out-of-specification results were not maintained. (↑)
- Out-of-specification test results, deviations and borderline non-conformances were not adequately reported, investigated and/or documented according to a written procedure. (↑)
- Atypical or unknown peaks in related substances, impurities or residual solvents, etc. were not investigated, where required. (↑)
- Use of media which failed to promote microorganism growth. (↑)

- Test methods were not validated or approved by the quality control department prior to use. (↑)
- Original records, entries or raw data used to support release were not retained. (↑)
- Modifications to raw data were not documented. (↑)
- Manual integration was used without being supported by a written procedure or without appropriate review. (↑)
- Procedures for handling lab samples were not scientifically justified. (↑)
- Facilities, personnel and/or testing equipment were inadequate.
- Written procedures were not approved or available for sampling, inspecting and testing materials.
- Raw material and/or packaging material was used in production without prior approval from the quality control department.
- There was no system for handling complaints, or the complaint handling system was inadequate.
- Returned goods were made available for sale without the quality control department's assessment and/or approval.
- Written procedures for operations that could affect product quality (e.g. transportation or storage) were not approved by the quality control department or were not implemented.
- There was inadequate evidence to show that storage and transportation conditions were appropriate.
- There was no change control system, or this system was inadequate.
- Sterility testing was not performed in a Grade A environment within a Grade B background or in an isolator of a Grade A within an appropriate background.
- The use of trial blank or standard injections was not governed by a written procedure.
- Activities were not attributable to the person who performed them.
- Records that were required to be maintained were not kept in a readable and readily accessible format for their required period.
- Method transfer was not performed, or was inadequate.
- There was no written procedure describing when analytical data could be reprocessed.
- Records were not named and organized in a manner that allowed adequate traceability.
- Management failed to prevent or deter poor data management practices.

- Lack of assurance that data are complete, consistent and accurate, throughout the data lifecycle.
- There was no requirement for an electronic data review or the review was inadequate.
- There was no agreement between the contract lab and the establishment to cover the testing activities.

Risk 3 (other) observations

- Investigations of non-conformances were not completed in a timely manner.
- There were no written procedures for archiving or retrieving electronic data.

Packaging material testing

C.02.016 – C.02.017

Risk 2 (major) observations

- Packaging material was not tested, or its testing was insufficient. (↑)
- The packaging (container and closure system) was different from the one approved. (↑)
- Vendors were certified without proper documentation.
- A reduced testing program was in place without adequate certification of vendors and/or suppliers.
- Specifications were inadequate.
- There was no sampling method or it was inadequate/not scientifically justified.
- The quality control department did not approve specifications.
- The packager/labeller did not perform an examination or test to confirm identification after receiving the packaging material product on its premises.

Risk 3 (other) observations

- Transportation or storage procedures were inadequate.
- Inappropriate environmental conditions and/or precautions were used to prevent contamination of packaging material during sampling.

Finished product testing

C.02.018 – C.02.019

Risk 1 (critical) observations

- The importer or distributor did not test the finished product for compliance with applicable specifications before releasing it for sale, and there was no evidence the fabricator tested the product.
- There was evidence that testing results were falsified or misrepresented and/or that the certificate of analysis was forged.

Risk 2 (major) observations

- Non-compliant products were made available for sale. (↑)
- Testing was incomplete or was not performed according to approved specifications. (↑)
- The validation and/or documentation of test methods were inadequate or missing. (↑)
- Use of process parametric release without market authorization. (↑)
- Written specifications were incomplete or inadequate.
- The person in charge of the quality control department (or his/her designated alternate) did not approve finished product specifications.
- No identity testing was done on a product received in Canada from a non-mutual recognition agreement or non-PIC/S country, and/or the first 5 lots were not tested and/or periodic complete confirmatory testing was not done.
- There were no written procedures for or records of transportation and storage conditions.
- The use of unique identifier principles did not meet acceptable options.

Risk 3 (other) observations

- The method transfer for a validated analytical method was inadequate.
- The method validation report did 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 showed that records had been falsified or misrepresented or inappropriately destroyed.

Risk 2 (major) observations

- Records, results, or raw data used to support release were deleted or destroyed. (↑)
- Test results suggesting that product quality had been negatively affected were not documented, reported or investigated. (↑)
- Activities were not documented at the time they were performed. (↑)
- Electronic records were not maintained as raw data, where appropriate. (↑)
- Discrepancies were noted between electronically saved data and printed records. (↑)
- There were no master production documents or these documents were incomplete.
- Suppliers did not provide documentation in a timely manner.
- Records of sale were incomplete or missing.
- Records of complaints received about the quality of a drug were incomplete or missing.
- Activities were not attributable to the person who performed them.
- Records that were required to be maintained were not kept in a readable and readily accessible format for an adequate period of time.
- Records were not named and organized in a manner that allowed for adequate traceability.
- Management failed to prevent or deter poor data management practices.
- There was no requirement for an electronic data review and/or this review was inadequate.
- Not all information from the original label and/or fabricator's certificate of analysis was made available to maintain the traceability of an active pharmaceutical ingredient.
- Records of validation and/or periodic requalification were missing or incomplete.

Risk 3 (other) observations

- Plans and specifications for manufacturing buildings were incomplete.
- Records did not include the company's organization charts.
- There were incomplete records for the sanitation program.
- There were no written procedures for how to archive and retrieve electronic data.

Samples

C.02.025 – C.02.026

Risk 2 (major) observations

- Samples were not retained for finished products.
- Retained samples were not submitted when alternative sample retention was granted.

Risk 3 (other) observations

- Samples of raw material were not available.
- Samples of finished products and/or active pharmaceutical ingredients were of insufficient quantity.
- The company did not store a sample from each lot or batch of a drug, raw material and/or an active ingredient under the proper conditions.

Stability

C.02.027 – C.02.028

Risk 1 (critical) observations

- No data were available to establish the shelf-life of products.
- There was evidence that stability data were falsified or misrepresented and/or that the certificate of analysis was forged.

Risk 2 (major) observations

- No action was taken when data showed that products were not projected to meet their specifications prior to the expiry date. (↑)
- There were an insufficient number of lots to establish shelf-life.
- There were insufficient data to establish shelf-life.
- The continuing stability program was missing or inadequate.
- There were no stability studies on changes in manufacturing (formulation) and/or packaging material.
- The company did not adequately validate the analytical test procedures used in the stability program.
- The stability program did not take into consideration worst-case scenarios (e.g. lots being reworked or reprocessed).
- The storage conditions for stability samples were inappropriate.

Risk 3 (other) observations

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

Sterile products

C.02.029

Risk 1 (critical) observations

- Critical sterilization cycles were not validated, or validation was inadequate.
- Water-for-injection systems were not validated and there was evidence of problems such as microbial or endotoxin counts outside specifications.
- No media fills were performed to demonstrate the validity of aseptic filling operations.
- There were no environmental controls during filling of aseptically filled products, and/or viable microorganisms were not monitored during filling.
- Aseptic filling operations continued after unsatisfactory media fill results were obtained.

- Batches failing an initial sterility test were released for sale on the basis of a second test without proper investigation.
- Environmental conditions for aseptic operation were inadequate.
- There was no leak test for ampules.

Risk 2 (major) observations

- Room classification for processing and/or filling operations was inadequate. (↑)
- Aseptic manufacturing suites were under negative pressure compared to clean areas (C-D). Clean areas (C-D) were under negative pressure compared to to unclassified areas. (↑)
- An insufficient number of samples were taken for environmental monitoring and/or inadequate sampling methods were used. (↑)
- During filling for aseptically filled products, insufficient environmental controls were used and/or viable microorganisms were insufficiently monitored. (↑)
- Premises and equipment were not designed or maintained to minimize contamination and/or generation of particles. (↑)
- Personnel used poor aseptic practices on an aseptic filling line. (↑)
- No consideration was given to bioburden prior to sterilization. (↑)
- The water-for-injection testing program was inadequate. (↑)
- Inspection for particles and defects was inadequate. (↑)
- Gases were used to purge solutions or blanket products that did not pass through a sterilizing filter. (↑)
- Disinfectants and sanitisers were not sterile filtered when used in Grades A or B areas. (↑)
- Integrity testing of sterilizing or vent filters was inadequate. (↑)
- Steam used for sterilization was not monitored to ensure it was of suitable quality. (↑)
- The maximum number of personnel present in clean and aseptic areas was inadequately controlled. (↑)
- Aqueous-based products were not subject to terminal steam sterilization without proper justification or approval through the marketing authorization.
- The maintenance of purified water and water-for-injection systems was inadequate.

- The re-validation of purified water and water-for-injection systems after maintenance, upgrading and/or out-of-specifications trends was inadequate.
- Personnel without appropriate training, qualifications, or successful participation in a process simulation study, performed aseptic processing.
- Gowning practices for clean and aseptic areas were inadequate.
- The sanitation and disinfection program was inadequate.
- Practices and precautions used to minimize contamination or prevent mix-ups were inadequate.
- The time lapse between cleaning, sterilizing, and use of components, containers and equipment was not validated.
- The time lapse between the start of manufacturing and sterilization or filtration was not validated.
- The program for media fill was inadequate.
- The ability of media to grow a wide spectrum of microorganisms was not demonstrated.
- Media fill results were misinterpreted.
- Samples for sterility testing were insufficient in number or were not representative of the entire production run.
- Each sterilizer load was not considered as a separate lot for sterility testing.
- The feed water for the water-for-injection system and the clean-steam generator was not purified water.
- The water for injection used for the final rinse of parenteral drug containers and components was not tested for endotoxins when the containers and components were not subsequently depyrogenated.
- The environment and/or controls for crimping after aseptic filling were inappropriate.

Appendix B – Glossary

Acronyms

API	Active pharmaceutical ingredient
C	Compliant
COA	Certificate of analysis
EL	Establishment licence
GMP	Good manufacturing practices
NC	Non-compliant
PIC/S	Pharmaceutical Inspection Co-operation Scheme
QC	Quality control
SOP	Standard operating procedure
WFI	Water for injection

Terms

These definitions supplement the definitions provided in the *Good Manufacturing Practices Guidelines (GUI-0001)*. If there is a conflict with a definition in the *Food and Drugs Act* or the Food and Drug Regulations, the definition in the Act/Regulations prevails.

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 (where slight deviations in the control of parameters could result in a non-uniform product or product not meeting specifications, such as

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)*) are generally not considered as critical products, even when the manufacturing processes involved are complex.

Higher risk product – Any product that may trigger a health risk, following cross-contamination, even at low levels (e.g. penicillins, certain cytotoxic and biological products).

Lower risk product – Products such as 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)*) that are not a scheduled 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, and confirmed in writing to the company in the inspection Exit Notice. Observations are assigned a risk classification ranging from 1 for "critical," to 2 for "major," to 3 for "other."

Appendix C – References

Annex 1 to the Current Edition of the Good Manufacturing Practices Guidelines - Selected Category IV Monograph Drugs (GUI-0066)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/annex-1-current-edition-selected-category-monograph-drugs-0066.html

Drug Good Manufacturing Practices (GMP) and Establishment Licencing (EL) Enforcement Directive (POL-0004)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/establishment-licences/directives-guidance-documents-policies/drug-good-manufacturing-practices-establishment-licensing-enforcement-directive-0004.html

Food and Drug Regulations
http://laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/index.html

Food and Drugs Act
http://laws-lois.justice.gc.ca/eng/acts/F-27/

Good Manufacturing Practices (GMP) Guidelines (GUI-0001)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-0001.html

Good Manufacturing Practices Guidelines for Active Pharmaceutical Ingredients (GUI-0104)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/guidelines-active-pharmaceutical-ingredients-0104.html

Good Manufacturing Practices (GMP) for Medical Gases (GUI-0031)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-0031.htm

Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites (GUI-0080)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/guidance-evidence-demonstrate-drug-compliance-foreign-sites-0080.html