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# Good manufacturing practices guide for drug products

## GUI-0001

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Canada

# Good manufacturing practices guide for drug products (GUI-0001)


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## Disclaimer

This document does not constitute part of the *Food and Drugs Act* (the Act) or its regulations and in the event of any inconsistency or conflict between the Act or regulations and this document, the Act or the regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the regulations and the applicable administrative policies.

Ce document est aussi disponible en français.

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# About this document

## 1. Purpose

This guide is for people who work with **drugs** as:

- fabricators
- packagers
- labellers
- testers
- distributors
- importers
- wholesalers

It will help you understand and comply with Part C, Division 2 of the Food and Drug Regulations, which is about good manufacturing practices (GMP).

## 2. Scope

These guidelines apply to these types of drugs:

- pharmaceutical
- radiopharmaceutical
- biological
- veterinary

The scope of this document does not include:

**Establishment licensing** — To understand how to comply with GMP requirements to get an establishment licence, see *Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees (GUI-0002)*.

**Active pharmaceutical ingredients** — Guidelines for active pharmaceutical ingredients (APIs) are described in Health Canada's *Good Manufacturing Practices Guidelines for Active Pharmaceutical Ingredients (GUI-0104)*.

# 3. Introduction

These guidelines interpret the requirements for good manufacturing practices (GMP) in Part C, Division 2 of the Food and Drug Regulations (the Regulations). They were developed by Health Canada in consultation with stakeholders.

Guidance documents like this one are meant to help industry and health care professionals understand how to comply with regulations. They also provide guidance to Health Canada staff, so that the rules are enforced in a fair, consistent and effective way across Canada.

Health Canada inspects establishments to assess their compliance with the *Food and Drugs Act* (the Act) and associated regulations. When we conduct an inspection, we will use this document as a guide in assessing your compliance with GMP requirements.

To better understand how risk ratings are assigned during inspections, see *Risk Classification of Good Manufacturing Practices (GMP) Observations (GUI-0023)*.

These guidelines are not the only way GMP regulations can be interpreted, and are not intended to cover every possible case. Other ways of complying with GMP regulations will be considered with proper scientific justification. Also, as new technologies emerge, different approaches may be called for.

Guidance documents are administrative and do not have the force of law. Because of this, they allow for flexibility in approach. So use this guide to help you develop specific approaches that meet your unique needs.

The guidance in this document has been written with a view to harmonize with GMP standards from:

- the World Health Organization (WHO)
- the Pharmaceutical Inspection Cooperation/Scheme (PIC/S)
- the International Council on Harmonisation (ICH)
- other regulatory agencies in other countries

This document also takes into account current mutual recognition agreements (MRA) between Health Canada and other international regulatory authorities, as well as agreements with other parties.

The 2017 edition of this document reflects recent regulatory amendments, clarifies existing requirements, incorporates common questions from industry, and provides an updated list of annexes.

## Checklist – GMP regulations by activity

This chart shows which GMP regulations apply to which licensable activities (by type).

Chart 1.0: GMP regulations applicable to licensable activities

| Section | Regulation | F | P/L | I | D | W | T |
|---|---|---|---|---|---|---|---|
| Premises | C.02.004 | ✔ | ✔ | ✔ | ✔ | ✔ | |
| Equipment | C.02.005 | ✔ | ✔ | | | | ✔ |
| Personnel | C.02.006 | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Sanitation | C.02.007 | ✔ | ✔ | | | | |
| | C.02.008 | ✔ | ✔ | | | | |
| Raw material testing | C.02.009 | ✔ | | | | | * |
| | C.02.010 | ✔ | | | | | * |
| Manufacturing control | C.02.011 | ✔ | ✔ | ✔ | ✔ | | |
| | C.02.012 | ✔ | ✔ | ✔ | ✔ | ✔ | |
| Quality control | C.02.013 | ✔ | ✔ | ✔ | ✔ | ✔ | |
| | C.02.014 | ✔ | ✔ | ✔ | ✔ | ✔ | |

Chart 1.0: GMP regulations applicable to licensable activities

| Section | Regulation | F | P/L | I | D | W | T |
|---|---|---|---|---|---|---|---|
| | C.02.015 | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Packaging material testing | C.02.016 | ✔ | ✔ | | | | * |
| | C.02.017 | ✔ | ✔ | | | | * |
| Finished product testing | C.02.018 | ✔ | ✔ | ✔ | ✔ | | * |
| | C.02.019 | | ✔ | ✔ | ✔ | | * |
| Records | C.02.020 | ✔ | ✔ | ✔ | ✔ | | ✔ |
| | C.02.021 | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| | C.02.022 | | | ✔ | ✔ | ✔ | |
| | C.02.023 | ✔ | ✔ | ✔ | ✔ | ✔ | |
| | C.02.024 | ✔ | ✔ | ✔ | ✔ | ✔ | |
| Samples | C.02.025 | ✔ | | ✔ | ✔ | | |
| | C.02.026 | ✔ | | ✔ | ✔ | | |
| Stability | C.02.027 | | | ✔ | ✔ | | * |
| | C.02.028 | | | ✔ | ✔ | | * |
| Sterile products | C.02.029 | ✔ | ✔ | | | | * |

* Where applicable, depending on the nature of the activities.

F = Fabricator
P/L = Packager/Labeller
I = Importer (MRA and non-MRA)
D = Distributor
W = Wholesaler
T = Tester

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# About quality management

## 4. Pharmaceutical quality system

### Guiding principles

Do you hold an establishment licence, or run an operation governed by Part C, Division 2 of the Food and Drug Regulations? If you do, you must make sure that you comply with these requirements—and the marketing or clinical trial authorization—when you fabricate, package, label, import, distribute, test and wholesale drugs. You must not place consumers at risk because of poor safety, quality or efficacy.

Your senior management is responsible for meeting the requirements outlined in this guidance. You will also need the help and commitment of your suppliers and personnel at all levels of your establishment.

To meet the requirements, you must:

- have a well-designed and correctly implemented pharmaceutical quality system (also known as a quality management system) that incorporates good manufacturing practices (GMP) and quality risk management
- fully document the pharmaceutical quality system and monitor its effectiveness
- make sure your entire pharmaceutical quality system is properly resourced with qualified personnel and suitable/sufficient premises, equipment and facilities

The basic concepts of quality management, good manufacturing practices and quality risk management are inter-related. They are described here to emphasize their relationships and fundamental importance to the production and control of drugs.

### Developing a pharmaceutical quality system

Quality management is a wide-ranging concept. It covers all matters that individually or collectively influence the quality of a drug. It is the total of the arrangements made to ensure that drugs are of the quality required for their intended use. It incorporates GMP.

GMP applies to all drug product lifecycle stages: from the manufacture of investigational drugs, to technology transfer, to commercial manufacturing, through to product discontinuation. The

pharmaceutical quality system can even extend to the pharmaceutical development lifecycle stage (as described in *ICH Q10: Pharmaceutical Quality System*). This should encourage innovation and continual improvement while strengthening the link between pharmaceutical development and full-scale manufacturing activities.

You should consider the size and complexity of your company's activities when developing a new pharmaceutical quality system or modifying an existing one. The system design should incorporate risk management principles, including the use of appropriate tools. While some aspects of the system can be company-wide and others site-specific, the effectiveness of the system is normally proven at the site level.

To ensure your pharmaceutical quality system is properly set up for fabricating, packaging, labelling, testing, distributing, importing or wholesaling drugs, you should:

1. Design, plan, implement, maintain and continuously improve on your system to allow the consistent delivery of products with proper quality attributes.
2. Manage product and process knowledge throughout all lifecycle stages.
3. Design and develop drugs in a way that takes into account GMP requirements.
4. Clearly outline management responsibilities.
5. Make arrangements for:
    a. manufacturing, supplying and using the correct starting and packaging materials
    b. selecting and monitoring suppliers
    c. verifying that each delivery is from the approved supply chain
6. Ensure processes are in place to properly manage outsourced activities.
7. Establish and maintain a state of control by developing and using effective monitoring and control systems for process performance and product quality.

To demonstrate a state of control, you must implement a data governance plan. Data must be appropriately reviewed and protected from accidental or intentional modification or deletion.

You may find additional information in the PIC/S Good Practices for Data Management and Integrity in Regulated GMP/GDP environments.

8. Take into account the results of product and process monitoring in batch release and in the investigation of deviations. This will allow you to take preventive action to avoid potential deviations in the future.

9. Carry out all needed controls on intermediate products, and any other in-process controls and validations.

10. Ensure continual improvement by making quality improvements appropriate to the current level of process and product knowledge.

11. Make arrangements to evaluate and approve planned changes before implementing them. Consider regulatory notification and approval where required.

12. After implementing any change, conduct an evaluation to confirm that your quality objectives were achieved. Ensure there was no unintended negative impact on product quality at the time of release and through its shelf life.

13. Apply a proper level of root cause analysis when investigating deviations, suspected product defects and other problems. This can be determined using quality risk management principles. In cases where the true root cause(s) of the issue cannot be determined, identify the most likely root cause(s) and address those.

    a. Where human error is suspected or identified as the cause, this should be justified with objective evidence. Ensure that process, procedural or system-based errors or problems have not been overlooked, if present.

    b. Determine the full impact of the deviation, and document how you reached your conclusion.

    c. Identify and carry out appropriate corrective actions and/or preventive actions in response to investigations. Monitor and assess the effectiveness of such actions, in line with quality risk management principles.

14. Make sure Quality Control certifies each production batch of drugs before you sell or supply them. You must produce and control drugs according to marketing authorization requirements and any other regulations relevant to the production, control and release of drugs.

15. Ensure that drugs—and the materials that go into making and packaging them—are stored, distributed and handled properly, so that quality is maintained throughout their shelf life.

16. Implement a process for self-inspection and/or quality audit, to regularly assess the effectiveness and applicability of your pharmaceutical quality system.

17. Have senior management participate actively in the pharmaceutical quality system. Their leadership is essential as they are ultimately responsible for ensuring an effective pharmaceutical quality system is in place. This includes making sure the system is properly resourced and that roles, responsibilities and authorities are defined, communicated and implemented throughout your organization. Senior management should also ensure staff—at all levels and sites within your organization—support and are committed to the pharmaceutical quality system.

18. Have senior management periodically conduct a management review of pharmaceutical quality system operations, to continually identify risks and opportunities to improve products, processes and the system itself.

19. Define and document your pharmaceutical quality system. You should have a quality manual or equivalent documentation that contains a description of the system, including management responsibilities.

## Good manufacturing practices for drugs

Good manufacturing practices (GMP) are part of quality assurance. They ensure that drugs are consistently produced and controlled. Drugs must meet the quality standards for their intended use—as outlined in the marketing authorization, clinical trial authorization or product specification.

GMP is concerned with both production and quality control. To meet basic GMP requirements, you must:

1. Clearly define all manufacturing processes. Review them systematically in the light of experience. Show that they are capable of consistently manufacturing drugs of the required quality that comply with their specifications.

2. Validate critical steps of manufacturing processes and key changes to the process.

3. Provide all key elements for GMP, including:
    a. qualified and trained staff
    b. adequate premises and space
    c. suitable equipment and services
    d. correct materials, containers and labels
    e. approved procedures and instructions
    f. suitable storage and transport

4. Write step-by-step instructions and procedures in clear and direct language, specifically applicable to the facilities used.

5. Train operators to properly carry out procedures. Ensure they understand the importance of meeting GMP requirements as part of their role in assuring patient safety.

6. Create records (manually and/or by recording instruments) during manufacture. Show that all the steps required by the defined procedures and instructions were in fact followed, and met relevant parameters and/or quality attributes. Show that the quantity and quality of the drug was as expected.

7. Document any deviations. Investigate significant deviations to determine the root cause and impact. Ensure proper corrective and preventive action is taken.

8. Keep records of fabrication, packaging, labelling, testing, distribution, importation and wholesaling in an easy-to-understand and accessible form. This allows the complete history of a lot to be traced.

9. Distribute products in a way that minimizes any risk to their quality and takes account of good distribution practice.

10. Control storage, handling and transportation of drugs and their ingredients to minimize any risk to their quality.

11. Have a system in place for recalling drugs from sale.

12. Examine complaints about drugs. Investigate the causes of quality defects. Take appropriate measures to prevent problems from happening again.

## Quality control

Quality control is the part of GMP that is concerned with:

- sampling
- specifications
- testing
- documentation
- release procedures

You must only release raw materials, packaging materials and products for use or sale if their quality is satisfactory. Quality control ensures that you carry out the necessary and relevant tests to ensure quality. It is not only done in labs—you must incorporate quality control into all activities and decisions about the quality of your products.

To meet basic quality control requirements, you must:

1. Ensure you have adequate facilities, trained personnel and approved procedures for sampling and testing of raw materials, packaging materials, intermediate bulk and finished products, and—where appropriate—for monitoring environmental conditions.

2. Take samples of raw materials, packaging materials and intermediate, bulk and finished products according to procedures approved by authorized personnel and methods.

3. Validate test methods. Qualify equipment, instruments and computer systems for their intended use.

4. Keep records (manually and/or by recording instruments) to show you carried out all required sampling, inspecting and testing procedures. Record and investigate any deviations.

5. Ensure finished products contain active ingredients complying with the qualitative and quantitative composition stated in the marketing or clinical trial authorization. Ensure they are of the purity required, enclosed within their proper containers, and correctly labelled and stored.

6. Document the results of your inspection and testing of intermediate, bulk and finished products and materials against specification.

7. Include in your product release procedures a review and evaluation of relevant production documentation, as well as an assessment of deviations from specified procedures.

8. Do not release drugs for sale or supply before they are approved by your quality control department.

9. Keep sufficient samples of raw material and finished product to allow future examination if needed.

## Quality risk management

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of a drug across the product lifecycle. It can be applied both proactively and retrospectively.

The principles of quality risk management are that:

- The evaluation of the risk to quality is based on scientific knowledge and experience with the process, and ultimately links to the protection of the patient.
- The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

Examples of quality risk management processes and applications can be found in *ICH Q9: Quality Risk Management*.

# Guidance

# 5. Regulations

For each section below, the exact text from Part C, Division 2 of the Food and Drug Regulations (the Regulations) is provided first. This is followed by the rationale (why the rule is important) and Health Canada's interpretation (what you should do to be compliant), where needed.

### C.02.002

In this Division,

-"medical gas" means any gas or mixture of gases manufactured, sold, or represented for use as a drug;

-"packaging material" includes a label;

-"specifications" means a detailed description of a drug, the raw material used in a drug, or the packaging material for a drug and includes:

*(a)* a statement of all properties and qualities of the drug, raw material or packaging material that are relevant to the manufacture, packaging, and use of the drug, including the identity, potency, and purity of the drug, raw material, or packaging material,

*(b)* a detailed description of the methods used for testing and examining the drug, raw material, or packaging material, and

*(c)* a statement of tolerances for the properties and qualities of the drug, raw material, or packaging material.

234 ## C.02.002.1

This Division does not apply to fabricating, packaging/labelling, testing, storing and importing of antimicrobial agents.

Guidelines for antimicrobial agents can be found in *Standard for the Fabrication, Control and Distribution of Antimicrobial Agents for Use on Environmental Surfaces and Certain Medical Devices (GUI-0049)*.

235 # Sale

236 ## C.02.003

No distributor referred to in paragraph C.01A.003*(b)* and no importer shall sell a drug unless it has been fabricated, packaged/labelled, tested, and stored in accordance with the requirements of this Division.

237

238 ## C.02.003.1

No person shall sell a drug that they have fabricated, packaged/labelled, tested or stored unless they have fabricated, packaged/labelled, tested or stored it in accordance with the requirements of this Division.

239 C.02.003.2

(1) No person shall import an active ingredient into Canada for the purpose of sale unless they have in Canada a person who is responsible for its sale.

(2) No person who imports an active ingredient into Canada shall sell any lot or batch of it unless the following appear on its label:

*(a)* the name and civic address of the person who imports it; and

*(b)* the name and address of the principal place of business in Canada of the person responsible for its sale.

240 ## Use in fabrication

241 C.02.003.3

No person shall use an active ingredient in the fabrication of a drug unless it is fabricated, packaged/labelled, tested and stored in accordance with the requirements of this Division.

242 ## Premises

243 C.02.004

The premises in which a lot or batch of a drug is fabricated, packaged/labelled or stored shall be designed, constructed and maintained in a manner that

*(a)* permits the operations therein to be performed under clean, sanitary and orderly conditions;

*(b)* permits the effective cleaning of all surfaces therein; and

*(c)* prevents the contamination of the drug and the addition of extraneous material to the drug.

## Rationale

Your establishment should be designed and constructed in a way that promotes cleanliness and orderliness and prevents contamination. Regular maintenance is required to prevent deterioration of the premises. The main objective of these efforts is product quality.

## Interpretation

1. Take appropriate steps to minimize risks associated with building design and location, including measures to prevent contamination of materials or drugs.

2. Make sure your premises are designed, constructed and maintained so that they prevent the entry of pests or extraneous material into the building (or from one area to another).

    a. Ensure there are no holes or cracks in doors, windows, walls, ceilings and floors (other than those intended by design).

    b. Use doors that give direct access to the exterior from manufacturing and packaging areas for emergency purposes only. Make sure these doors are properly sealed. Ensure receiving and shipping areas do not allow direct access to production areas.

    c. Segregate production areas from all non-production areas. Clearly define individual manufacturing, packaging and testing areas, and segregate them if needed. Areas where biological, microbiological or radioisotope testing is carried out require special design and containment considerations.

    d. Do not locate other functions (such as research and development laboratories, diagnostic laboratories, and lab animal quarters) in the same building as manufacturing facilities unless you put in place enough measures to prevent cross-contamination. (See interpretation 11 for cross-contamination measures required.)

    e. Segregate mechanical areas such as boiler rooms and generators from production areas.

3. Take measures to prevent contamination in all areas where raw materials, primary packaging materials, in-process drugs or drugs are exposed (to the extent required).

    a. Ensure floors, walls and ceilings allow cleaning. Seal brick, cement blocks and other porous materials. Avoid surface materials that shed particles.

    b. Make sure floors, walls, ceilings and other surfaces are hard, smooth and free of sharp corners where extraneous material can collect.

    c. Seal joints between walls, ceilings and floors.

d. Ensure pipes, light fittings, ventilation points and other services do not create surfaces that cannot be cleaned.

e. Screen and trap floor drains.

f. Maintain air quality by controlling dust, monitoring pressure differentials between production areas (including between production and non-production areas), and checking and replacing air filters periodically. Ensure your air handling system is well defined, taking into consideration airflow volume, direction, velocity and the need to prevent cross-contamination. Check air handling systems periodically to ensure they comply with their design specifications. Keep records.

4. Control temperature and humidity to the extent needed to safeguard materials and the reliability of production processes.

5. Separate eating areas, rest, change, wash-up and toilet facilities from production areas. Make sure they are adequately sized, well ventilated and allow good sanitary practices.

6. Design site layout to avoid mix-ups and optimize the flow of personnel and materials. Make sure:

   a. There is enough space for receiving, storage and all production activities.

   b. Working spaces allow the orderly and logical placement of materials and equipment (including parts and tools).

   c. Where physical quarantine areas are used, they are well marked and segregated, with access restricted to designated staff. Where electronic inventory control is used, electronic access to change inventory status is restricted to designated staff.

   d. A separate sampling area is provided for raw materials. If sampling is performed in the storage area, it is done in a way that prevents contamination or cross-contamination.

   e. Working areas are well lit.

   f. Movement of personnel, equipment and materials is designed to prevent contamination. Special considerations should be made for movement between self-contained and other facilities—this should be minimized and may require areas for decontamination.

7. Identify in your Validation Master Plan and qualify the utilities and support systems for buildings where drugs are fabricated or packaged/labelled. This includes heating, ventilating and air conditioning, dust collection, and supplies of purified water, water for injection, steam, compressed air, and nitrogen. Perform periodic verification and maintain records. For more guidance, see *Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)*.

8. Clearly identify the content of distribution systems for liquids and gases at their outlets.

9. Maintain premises in a good state of repair. Ensure repair and maintenance operations do not affect drug quality.

10. Provide and maintain separate rooms (where required) to protect equipment and control systems sensitive to vibration, electrical interference, and contact with excessive moisture or other external factors.

11. If you are a fabricator or packager, you must show that your premises are designed in a way that minimizes the risk of contamination between products (i.e. cross-contamination).

    a. Use a quality risk management approach to assess and control cross-contamination risks. Base this on an evaluation of the products manufactured (such as potency and toxicological evaluation). Take into account factors including:

        - facility/equipment design and use
        - personnel and material flow
        - microbiological controls
        - physical, chemical and toxicological properties of materials used
        - process characteristics
        - cleaning processes
        - analytical capabilities

        The outcome of your quality risk management process should help you determine the need for and extent to which premises and equipment should be dedicated to a particular product or product family. This may include dedicating either specific product contact parts or the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a segregated, self-contained production area within a multi-product facility if you can justify it.

    b. Self-contained facilities are required when a product presents a risk:

        - that cannot be properly controlled by operational and/or technical measures
        - where scientific data does not support a safe threshold value for toxicity
        - where threshold values derived from the toxicological evaluation are below the levels of detection

- for certain classes of highly sensitizing drugs (such as penicillins and cephalosporins)

c. Ensure external contamination with drug product residues does not exceed established limits on the final container and primary packaging (for the situations listed in interpretation 11.b). You may store products in common areas once they are enclosed in their immediate final containers and controls are in place to minimize risks of cross-contamination.

d. Ensure no production activities of highly toxic non-pharmaceutical materials (such as pesticides and herbicides) are conducted in premises used for the production of drugs.

# Equipment

## C.02.005

The equipment with which a lot or batch of a drug is fabricated, packaged/labelled or tested shall be designed, constructed, maintained, operated, and arranged in a manner that

*(a)* permits the effective cleaning of its surfaces;

*(b)* prevents the contamination of the drug and the addition of extraneous material to the drug; and

*(c)* permits it to function in accordance with its intended use.

### Rationale

To fabricate drugs of consistent quality, you must make sure your equipment is appropriate for the intended use and performs as intended.

These requirements are meant to prevent the contamination of drugs by:

- other drugs
- dust and other airborne contaminants
- foreign materials, such as:
  - rust
  - lubricant

- particles coming from the equipment

Contamination can also be caused by poor maintenance, misuse of equipment, exceeding the capacity of the equipment, and use of worn-out equipment.

Arranging your equipment in an orderly way makes cleaning nearby areas easier and avoids interference with other processing operations. It also minimizes the circulation of personnel and optimizes the flow of materials.

## Interpretation

1. Make sure the design, construction and location of your equipment allows cleaning, sanitizing and inspection of the equipment.
    a. Ensure equipment parts that come in contact with raw materials, in-process intermediates or drugs are cleanable.
    b. Ensure tanks used in processing liquids and ointments are equipped with fittings that can be dismantled and cleaned. Ensure validated clean-in-place (CIP) equipment can be dismantled for periodic verification.
    c. Ensure filter assemblies are designed for easy dismantling.
    d. Locate equipment far enough away from other equipment and walls to allow cleaning of the equipment and adjacent area.
    e. Seal the base of immovable equipment properly along points of contact with the floor.
    f. Keep equipment clean, dry and protected from contamination when stored.
2. Ensure equipment does not add extraneous material to the drug. Make sure that:
    a. surfaces that come in contact with raw materials, in-process intermediates or drugs are smooth and made of material that is non-toxic, corrosion-resistant, non-reactive to the drug being fabricated or packaged, and capable of withstanding repeated cleaning or sanitizing
    b. equipment design minimizes the possibility of a lubricant or other maintenance material contaminating the drug
    c. equipment made of material that is prone to shed particles or to harbour microorganisms does not come in contact with or contaminate raw materials, in-process drugs or drugs(use metal detectors where there is a risk of metal contamination from the manufacturing process, such as with tableting)
    d. chain drives and transmission gears are enclosed or properly covered
    e. tanks, hoppers and other similar fabricating equipment are equipped with covers

3. Operate equipment in a way that prevents contamination.

    a. Ensure ovens, autoclaves and similar equipment contain only one raw material, in-process drug or drug at a time (unless precautions are taken to prevent contamination and mix-ups).

    b. Locate equipment in a way that prevents contamination from extraneous materials.

    c. Place equipment in a way that optimizes the flow of material and minimizes the movement of personnel.

    d. Locate equipment so that production operations in the same area are compatible and to prevent cross-contamination between operations.

    e. Label fixed pipework clearly to indicate the contents and (where applicable) the direction of flow.

    f. Provide dedicated production equipment where appropriate.

    g. Operate water purification, storage and distribution equipment in a way that ensures a reliable source of water of the proper chemical and microbial purity.

4. Maintain equipment in a good state of repair.

    a. Ensure that equipment surfaces are free from cracks, peeling paint and other defects.

    b. Ensure gaskets are functional.

    c. Avoid the use of temporary devices (such as tape).

    d. Maintain equipment parts that come in contact with drugs to ensure drugs are fabricated or packaged in a way that keeps them free from contamination.

    e. Maintain equipment used for significant processing or testing operations according to a written preventative maintenance program. Keep maintenance records.

5. Design, locate and maintain equipment so that it serves its intended purpose.

    a. Ensure measuring devices are of a proper range, precision and accuracy. Calibrate this equipment on a scheduled basis and keep records.

    b. Remove equipment that is unsuitable for its intended use from fabrication, packaging/labelling and testing areas. When removal is not possible, clearly label equipment as unsuitable.

    c. Ensure equipment used during the critical steps of fabrication, packaging/labelling and testing (including computerized systems) is subject to installation qualification, operational qualification and performance qualification (as identified in your Validation Master Plan). Document all equipment

qualification. For more information, see *Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)* and *PIC/S Annex 11: Computerised Systems*.

Requirements for computerized systems are detailed in section C.02.015 interpretation 8.f and section C.02.020–C02.024.1 interpretations 5 to 7.

d. Calibrate, inspect or check equipment used for significant processing and testing operations according to a written program. Keep records. Ensure a system is in place to support identification of calibration status (you may use status labelling (tag) or some other method).

e. Identify equipment used for major processing or testing operations with a unique number or code and maintain usage logs. These logs should include identification of products, dates of operation, cleaning and downtime due to frequent or serious malfunctions or breakdowns. Information collected will help identify negative performance trends.

# Personnel

## C.02.006

Every lot or batch of a drug shall be fabricated, packaged/labelled, tested and stored under the supervision of personnel who, having regard to the duties and responsibilities involved, have had such technical, academic, and other training as the Director considers satisfactory in the interests of the health of the consumer or purchaser.

### Rationale

Your senior management is responsible for providing adequate resources (materials, personnel, facilities and equipment). They must continually monitor and improve the effectiveness of your pharmaceutical quality system.

Who you hire is one of the most important elements in any pharmaceutical operation. Without proper staff with the right attitude and training, it is almost impossible to fabricate, package/label, test or store good quality drugs.

It is essential that only qualified staff supervise the fabrication of drugs, as the operations involved are highly technical in nature. They require constant vigilance, attention to detail, and a

high degree of employee competence. The reason products often fail to meet required standards is because of poorly trained staff or a lack of understanding of the importance of production control.

## Interpretation

1. The person in charge of your quality control department (if you are a fabricator, packager/labeller, tester, importer or distributor) and the person in charge of your manufacturing department (if you are a fabricator or packager/labeller):
    a. must hold a Canadian university degree or a degree recognized as equivalent by a Canadian university or accreditation body in a science related to the work being carried out
    b. must have practical experience in their area of responsibility
    c. directly controls and personally supervises on site each working shift during which activities under their control are being conducted (for importers and distributors, the person in charge can be off-site in Canada if they are fully accessible to the quality control department and have enough knowledge of on-site operations to fulfill the responsibilities of the position)
    d. may delegate duties and responsibility (for example, to cover all shifts) to a qualified person, while remaining accountable for those duties and responsibility (the person must have a diploma, certificate or other evidence of formal qualifications awarded after completion of a course of study at a university, college or technical institute in a science related to the work being carried out, combined with at least two years of relevant practical experience)
2. The person in charge of the quality control department of a wholesaler:
    a. must be qualified by relevant academic training and experience
    b. may delegate duties and responsibility to someone who meets the requirements under 2.a
3. The person responsible for packaging operations (including control over printed packaging materials and withdrawal of bulk drugs):
    a. must be qualified by training and experience
    b. is directly responsible to the person in charge of the manufacturing department (or a person having the same qualifications)
4. Secondary labellers and personnel in charge of labelling operations and the quality control department:
    a. must be qualified by relevant academic training and experience

b. can delegate their duties and responsibilities to a person who meets the requirements under 4.a

5. Senior management has ultimate responsibility for ensuring an effective pharmaceutical quality system is in place to achieve quality objectives. This includes making sure roles, responsibilities and authorities are defined, communicated and implemented throughout the organization. Your senior management should:

    a. establish a quality policy that describes the overall intentions and direction of your company related to quality

    b. ensure GMP compliance and the continuing suitability and effectiveness of your pharmaceutical quality system by participating in management review

    c. determine and provide adequate resources (human, financial, materials, facilities and equipment) to implement and maintain the pharmaceutical quality system and continually improve its effectiveness

6. Ensure enough personnel are available on site with the required qualifications and practical experience relevant to their responsibilities.

    a. Do not place so many responsibilities on any one individual that quality is put at risk.

    b. Record specific duties for all responsible staff in a written work description.

    c. Ensure personnel have the authority to carry out their responsibilities.

    d. When key personnel are absent, appoint qualified replacements to carry out their duties and functions.

    e. Ensure all personnel conducting GMP activities are able to understand the written procedures for those activities.

7. Your personnel must be aware of the principles of GMP that affect them. They must receive initial and continuing training relevant to their job responsibilities.

    a. Follow a written program and use qualified trainers to train personnel (including technical, maintenance and cleaning staff).

    b. Assess the effectiveness of continuing training periodically.

    c. Provide training before implementing new or revised standard operating procedures (SOPs).

    d. Maintain records of training.

    e. Give specific training to personnel working in areas where highly active, toxic, infectious or sensitizing materials are handled. Ensure access to relevant information (e.g. material safety data sheets, pathogen safety data sheets, etc.)

    f. Review the performance of all personnel periodically.

8. Consultants and contractors must have the necessary qualifications, training and experience to advise on the subjects they are hired for.

# Sanitation

## C.02.007

(1) Every person who fabricates or packages/labels a drug shall have a written sanitation program that shall be implemented under the supervision of qualified personnel.

(2) The sanitation program referred to in subsection (1) shall include:

*(a)* cleaning procedures for the premises where the drug is fabricated or packaged/labelled and for the equipment used in the fabrication or packaging/labelling of the drug; and

*(b)* instructions on the sanitary fabrication and packaging/labelling of drugs and the handling of materials used in the fabrication and packaging/labelling of drugs.

### Rationale

Sanitation in a pharmaceutical plant influences the quality of drug products, as well as employee attitude. Drug products must be fabricated and packaged in areas that are free from environmental contamination and contamination by another drug.

A written sanitation program provides some assurance that levels of cleanliness in your plant are maintained and that the provisions of sections 8 “Drugs” and 11 “Unsanitary manufacture, etc., of drug” in the *Food and Drugs Act* are satisfied.

### Interpretation

1. Ensure you have a written sanitation program available on site if you fabricate or package/label drugs.

2. Design your sanitation program using quality risk management principles. Identify and reduce contamination risks in your facility design and operation (see interpretation 11, section C.02.004 “Premises”). Your sanitation program must contain procedures that describe the following:

    a. cleaning requirements that apply to all production areas of your plant, with emphasis on manufacturing areas that require special attention

b. requirements that apply to processing equipment

c. cleaning intervals

d. products for cleaning and disinfection, along with their dilution and the equipment to be used

e. the responsibilities of any outside contractor

f. disposal procedures for waste material and debris

g. pest control measures

h. precautions needed to prevent contamination of a drug when rodenticides, insecticides and fumigation agents are used

i. microbial and environmental monitoring procedures (established based on quality risk management principles) that:

- define alert and action limits in areas where susceptible products are fabricated or packaged
- describe monitoring activities to ensure environmental conditions are met during production

j. the personnel responsible for carrying out cleaning procedures

3. Ensure your sanitation program is implemented and effective in preventing unsanitary conditions.

   a. Validate cleaning procedures for manufacturing equipment based on Health Canada's *Cleaning Validation Guidelines (GUI-0028)*. This guide also provides guidance for establishing acceptable product residue limits.

   b. Ensure removal of cleaning residues (such as detergents and solvents) from equipment.

   c. Ensure evidence is available to demonstrate that routine cleaning and storage does not allow microbial proliferation.

   d. Filter sanitizers and disinfectants (like isopropyl alcohol) to remove spores where needed.

   e. Validate analytical methods used to detect residues or contaminants. You can find guidance on analytical method validation in *ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology* or any standard listed in Schedule B to the Act.

   f. Campaign production can be accepted where—on a product by product basis—proper justification is provided, validation is conducted, and rigorous validated controls and monitoring are in place that show that any risk of cross-contamination is minimized.

4. Make sure the personnel who supervise your sanitation program are:
    a. qualified by training or experience
    b. directly responsible to a person who has the qualifications described under section C.02.006 “Personnel,” interpretation 1

5. Contain dusty operations. Avoid using unit or portable dust collectors in fabrication areas, especially in dispensing. If you do use them, ensure the effectiveness of their exhaust filtration is demonstrated and the units are regularly maintained according to written approved procedures.

## C.02.008

(1) Every person who fabricates or packages/labels a drug shall have, in writing, minimum requirements for the health and the hygienic behaviour and clothing of personnel to ensure the clean and sanitary fabrication and packaging/labelling of the drug.

(2) No person shall have access to any area where a drug is exposed during its fabrication or packaging/labelling if the person

*(a)* is affected with or is a carrier of a disease in a communicable form, or

*(b)* has an open lesion on any exposed surface of the body.

### Rationale

The health, behaviour and clothing of your employees can contribute to product contamination. Poor personal hygiene will offset even the best sanitation program and greatly increase the risk of product contamination.

### Interpretation

1. Make minimum health requirements available in writing.
    a. Ensure staff who have access to any area where a drug is exposed during fabrication or packaging/labelling have a thorough health exam before starting work. Staff should be periodically re-examined based on their job requirements.

You should not let anyone who is a known carrier of a communicable disease have access to any area where a drug is exposed.

The likelihood of a disease being transmitted through a drug product depends on the nature of the disease and the type of work the person carries out. Some diseases could be transmitted through a drug product if proper hygiene procedures are not followed by an infected person handling the product. You may need to consult with a doctor.

A person may also be a carrier of a communicable disease and not be aware of it. So in addition to having strict personal hygiene procedures, you should have systems in place to provide an effective barrier that prevents product contamination. All personnel must follow these procedures at all times. If an employee is found to be a carrier of a communicable disease, contact Health Canada and perform a risk assessment to determine if there is any product impact.

599 b. Tell employees to report any health conditions that could adversely affect drug
600 products to their supervisor.

601 c. Conduct supervisory checks to prevent any person who has an apparent illness or
602 open lesions that may adversely affect the quality of drugs from handling exposed
603 materials and drugs. The person must not handle exposed raw materials, primary
604 packaging materials, in-process drugs or drugs until the condition is no longer
605 judged to be a risk.

606 d. Assess each employee's health before allowing them to return to the workplace
607 after an absence due to an illness that may adversely affect the quality of products.

608 e. Ensure a procedure is in place that describes what actions to take if a person who
609 has been handling exposed raw materials, primary packaging materials, in-
610 process drugs or drugs is found to have a communicable disease.

611 f. Ensure all personnel who conduct visual inspections get periodic eye exams
612 and/or periodic requalification.

613 2. Clearly define clothing requirements and hygiene procedures for staff and visitors in
614 your written hygiene program.

615 a. Ensure employees wear clean clothing and protective covering where a potential
616 for contaminating a raw material, in-process material or drug exists. Have written
617 procedures in place covering basic clothing requirements (such as protective
618 garments and hair and beard covering) for any person entering manufacturing
619 areas.

You may need more stringent requirements (such as a mask, dedicated shoes and clothes providing a higher level of protection) for operators working with exposed product.

b. Operators must avoid direct skin contact with raw materials, primary packaging materials, equipment, in-process drugs or drugs.

c. Do not allow unsanitary practices (such as smoking, eating, drinking and chewing) or allow staff to keep plants, food, drink, smoking material or personal medicines in production areas (or any other areas where they might adversely affect product quality).

d. Outline requirements for personal hygiene (with an emphasis on hand hygiene). Ensure they are followed by employees.

e. Outline requirements concerning cosmetics and jewellery worn by employees. Ensure they are followed by employees.

f. Store soiled protective garments (if reusable) in separate containers until properly laundered and (if necessary) disinfected or sterilized. Ensure a formalized procedure for washing protective garments under the control of your company is in place. Washing garments in a domestic setting is unacceptable.

## Raw material testing

### C.02.009

(1) Each lot or batch of raw material shall be tested against the specifications for the raw material prior to its use in the fabrication of a drug.

(2) No lot or batch of raw material shall be used in the fabrication of a drug unless that lot or batch of raw material complies with the specifications for that raw material.

(3) Notwithstanding subsection (1), water may, prior to the completion of its tests under that subsection, be used in the fabrication of a drug.

(4) Where any property of a raw material is subject to change on storage, no lot or batch of that raw material shall be used in the fabrication of a drug after its storage unless the raw material is retested after an appropriate interval and complies with its specifications for that property.

(5) Where the specifications referred to in subsections (1), (2) and (4) are not prescribed, they shall

*(a)* be in writing;

*(b)* be acceptable to the Director who shall take into account the specifications contained in any publication mentioned in Schedule B to the *Act*; and

*(c)* be approved by the person in charge of the quality control department.

## Rationale

Testing raw materials before you use them has two objectives:

1. Confirm the identity of the raw materials.
2. Confirm that the raw materials have the properties that will provide the desired quality, quantity or yield in a given manufacturing process.

For guidance on the control and testing of raw materials used for the manufacture of active pharmaceutical ingredients (APIs), see Health Canada's *Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients (GUI-0104*) and *ICH Q7: Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients*.

Health Canada encourages you to identify and qualify alternate suppliers for critical raw materials, with appropriate regulatory approval where applicable.

## Interpretation

1. Ensure each raw material used to produce a drug is covered by specifications (see section C.02.002). These specifications must be approved and dated by the person in charge of your quality control department or by a designated alternate who meets the requirements described under section C.02.006, interpretation 1.d.
2. Ensure your specifications for any raw material include or provide reference to (if applicable):
    a. a description of materials, including the:
        i. designated name and internal reference code

ii. reference (if any) to the applicable standard for the raw material (e.g. prescribed standard, pharmacopoeia, in-house standard)

iii. approved fabricator

b. a list of tests, references to analytical procedures, and appropriate acceptance criteria

c. storage conditions and precautions

d. the maximum period of storage before re-test or expiry

3. Make sure your specifications of raw materials comply with current versions of:

a. the marketing authorization

b. a recognized pharmacopoeia

i. Where appropriate, include other properties or qualities not addressed by the pharmacopoeia (for example, particle size, polymorphs, density, etc.) in the specifications.

ii. Where a recognized pharmacopoeia (Schedule B of the *Food and Drugs Act*) contains a specification for microbial content, include that requirement.

4. Use purified water (that meets any standard listed in Schedule B of the Act) when formulating a non-sterile drug product, unless otherwise required in one of these standards or the marketing authorization.

a. Include requirements in your specifications for total microbial count, which should not exceed 100 colony forming units (cfu)/ml.

b. Monitor purified water on a routine basis to confirm absence of objectionable microorganisms. The purpose of the water and its use in different dosage forms will dictate which organisms are considered objectionable (for example, *Escherichia coli* and *Salmonella* for water used for oral preparations, *Staphylococcus aureus* and *Pseudomonas aeruginosa* for water used for topical preparations).

5. Use water for injection (WFI) to formulate parenteral, irrigation and intra-ocular products. Purified water may be used to formulate ophthalmic products.

a. Establish alert and action limits for bacterial endotoxins and microbial load. These limits should meet any standard listed in Schedule B to the Act.

b. While in use during processing, ensure WFI is sampled daily from at least two points on a rotating basis (so as to cover all outlets).

c. Test water used in the preparation of parenterals for endotoxins. Ensure it complies with its approved specifications.

d. Test water used for the final rinsing of container components that are used for parenteral drugs for endotoxins, unless such components are depyrogenated afterwards.

6. Ensure gases used as utilities are of an appropriate grade. Monitor compressed air that comes into direct contact with primary contact surfaces, materials and/or the product to control the level of particulates, humidity, microbial contamination, and the absence of hydrocarbons (where applicable). The limits you use should take into consideration the stage of manufacture, product, and so on. Other tests might be needed depending on the nature of the product.

7. Validate test methods and document the results of validation studies. Full validation is not needed for methods included in any standard listed in Schedule B to the Act. But if you use one of these methods, you must establish its suitability under actual conditions of use. This may include using the method for monitoring additional specified impurities that are not listed in the compendial monograph. Conduct method transfer studies when applicable.

You can find guidance on validating particular types of methods in *ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology*, or in any standard listed in Schedule B to the *Food and Drugs Act*.

8. You should establish an impurity profile for each API based on the marketing authorization. An impurity profile describes the identified and unidentified impurities present in a typical batch produced by a specific controlled production process. Your impurity profile should include:

    - the labelling of impurities either by identity or by some qualitative analytical designation (e.g. retention time)
    - the range of each impurity observed
    - the classification of each identified impurity (e.g. inorganic, organic, solvent, degradation product)

    The impurity profile is normally dependent on the production process and source of the API.

9. Test a representative sample of each lot of raw material fully against specifications, using a statistically valid plan. Your sampling plan should be properly justified and based on a quality risk management principle.

10. Carry out and record sampling according to approved, written procedures that describe:

a. the method of sampling
b. the equipment to be used
c. the amount of sample to be taken
d. instructions for any required sub-division of the sample
e. the type and condition of sample container to be used
f. the identification of the container sampled
g. any special precautions to be observed, especially when sampling sterile or toxic materials
h. the storage conditions
i. instructions for cleaning and storing sampling equipment

11. In addition to the testing required in interpretation 8, test each container of a lot of raw material for the identity of its contents using a specifically discriminating identity test.

a. Instead of testing each container for identity, you may test a composite sample (derived from sampling each container), as long as you meet the following conditions:

i. A suitable test exists.

ii. The number of individual containers for each composite sample does not exceed 10.

iii. A potency test is performed on each composite sample to establish the mass balance of the composite sample.

b. Instead of testing each container for identity, you may test only a proportion of the containers, as long as there is evidence to ensure that no single container of raw material has been incorrectly labelled.

i. Interpretation 11.b applies to raw material coming from a single product fabricator or plant. It also applies if it comes directly from a manufacturer (or in the manufacturer's sealed container) and there is a history of reliability. (In this case, regular audits of the manufacturer's quality assurance system must be conducted by or on behalf of the purchaser/drug fabricator.)

ii. The available evidence should include an on-site audit report of the vendor by a person who meets the requirements of interpretation 1 under section C.02.006 "Personnel." The audit report should address at least the following:

- the nature and status of the manufacturer and the supplier, and their understanding of the GMP requirements of the pharmaceutical industry
- the quality assurance system of the raw material manufacturer

- the manufacturing conditions under which the raw material is produced and controlled

iii. Provided that you meet the requirements outlined in interpretations 11.b.i, you may conduct identity testing on representative samples. You should statistically determine the number of samples taken to prepare the representative sample and specify this number in a sampling plan. You should also define the number of individual samples that may be blended to form a composite sample, taking into account the nature of the material, knowledge of the supplier, and homogeneity of the composite sample.

iv. Interpretation 11.b does not apply when the raw material is used to formulate parenterals or is supplied by intermediaries (such as brokers), where the source of manufacture is unknown or not audited.

c. Ensure each container in a batch is sampled and its contents positively identified when the raw material is handled in any substantial way (e.g. repackaged by a third party) after leaving the site of its fabrication.

12. Only use raw materials that have been released by your quality control department and are not past their established re-test date or expiry date in fabrication.

    a. Ensure the re-test date or expiry date is based on acceptable stability data developed under predefined storage conditions (or based on any other acceptable evidence).

    b. If you have any raw material in storage after the established re-test date, you must quarantine it.

    c. A batch of raw material can be re-tested and used immediately (within 30 days) after the re-test, as long as it continues to comply with the current specifications.

    d. Do not use a raw material held in storage after the established expiry date in fabrication.

13. Identifying and choosing raw material vendors is an important operation. You should involve staff who have a particular and thorough knowledge of the materials and suppliers. Their knowledge of materials should include an understanding of risk and certification where required (e.g. BSE/TSE risks).

    a. Only source raw materials from approved fabricators named in the relevant specifications.

    b. Ensure active ingredients are manufactured by a Canadian fabricator holding an establishment licence, or by a foreign site identified on a Canadian establishment licence.

    c. Consider the quality compliance history of the raw material vendor when sourcing raw materials.

## C.02.010

(1) The testing referred to in section C.02.009 shall be performed on a sample taken

*(a)* after receipt of each lot or batch of raw material on the premises of the fabricator; or

*(b)* subject to subsection (2), before receipt of each lot or batch of raw material on the premises of the fabricator, if

(i) the fabricator

(A) has evidence satisfactory to the Director to demonstrate that raw materials sold to him by the vendor of that lot or batch of raw material are consistently manufactured in accordance with and consistently comply with the specifications for those raw materials, and

(B) undertakes periodic complete confirmatory testing with a frequency satisfactory to the Director, and

(ii) the raw material has not been transported or stored under conditions that may affect its compliance with the specifications for that raw material.

(2) After a lot or batch of raw material is received on the premises of the fabricator, the lot or batch of raw material shall be tested for identity.

### Rationale

Section C.02.010 outlines options for carrying out the testing required in section C.02.009. Sourcing raw materials is an important operation that requires specific and in-depth knowledge of the raw materials and their fabricator in order to maintain consistency when fabricating drug product. Raw materials should come from reliable fabricators.

### Interpretation

1. **Testing other than identity testing:** Perform testing on a sample of the raw material taken after the person who formulates the raw material into dosage form receives it on their premises (unless the vendor is certified).

If you have a raw material vendor certification program, document it in a standard operating procedure. At a minimum, your program must include the following:

a. a written agreement outlining the specific responsibilities of each party involved, and specifying:
    i. the content and format of the certificate of analysis, which presents actual numerical results and refers to the batch number, raw material specifications and validated test methods used
    ii. that the raw material vendor must inform the drug fabricator of any changes in the processing or specifications of the raw material
    iii. that the raw material vendor must inform the drug fabricator if there is any critical deviation during the manufacturing of a particular batch of raw material
b. an audit report
    i. For medicinal ingredients/APIs, the audit report must be issued by a qualified authority, a regulatory authority, a qualified body (such as the European Directorate for the Quality of Medicines and HealthCare (EDQM) or the World Health Organization (WHO)). The report must show that the API vendor complies with *ICH Q7: Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients* (or with any standard or system of equivalent quality). For certain drugs (or if a recent report is not available), an on-site audit of the API vendor (against the same standard or its equivalent) by a person who meets the requirements of interpretation 1 under Section C.02.006 “Personnel” is acceptable. See *Guidance on Evidence to Demonstrate Drug Good Manufacturing Practices Compliance of Foreign Sites (GUI-0080)* for more information.
    ii. For other raw materials, an audit report based on a regular on-site audit performed by a person who meets the requirements of interpretation 1 under section C.02.006 “Personnel” is acceptable.
c. full confirmatory testing of the first three lots of each raw material received from a vendor, and after any significant change to the manufacturing process
    i. You must also have a copy of the residual solvent profile and, for medicinal ingredients, a copy of the impurity profile.
d. a description of how re-testing failures and re-qualification of the vendor are to be addressed
e. the list of raw materials not subject to the reduced testing program (e.g. reprocessed lots)
f. full confirmatory testing on a minimum of one lot per year of a raw material received from each vendor (choose the raw material on a rotational basis)

i. In addition, where multiple raw materials are received from the same vendor, you must carry out confirmatory testing for each raw material at least once every five years.

g. a document issued for each vendor, verifying that the vendor meets the criteria for certification

i. The document must be approved by your quality control department and updated periodically.

Generally, due to the nature of its operations, a broker or wholesaler of raw materials cannot be directly certified. However, when a broker or wholesaler supplies materials received from the original vendor without changing the existing labels, packaging, certificate of analysis and general information, then certification of the original source is still acceptable.

If new certificates are issued by or on behalf of repackers/reprocessors, agents or brokers, these certificates should show the name, address and telephone number of the lab that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch certificate. Attach a copy of the original certificate to the new certificates.

2. Identity testing: Conduct specific identity testing on all lots of any raw material received on the premises of the person who formulates the raw material into dosage forms. Perform this identity testing according to section C.02.009 “Raw Material Testing,” interpretations 8 to 10.

3. If you perform the identity test in C.02.010 “Raw Material Testing,” interpretation 2 and if your quality control department approves, you may use the lot of raw material selected for confirmatory testing in fabrication before completing all tests.

4. Ensure transportation and storage conditions prevent changes to the potency, purity or physical characteristics of the raw material. To show these conditions have been met, you must have standard operating procedures and records for shipping and receiving that contain:

a. the type of immediate packaging for the raw material

b. the labelling requirements (including storage conditions and special precautions or warnings) for the packaged raw material

c. the mode(s) of transportation approved for shipping the packaged raw material

d. a description of how the packaged raw material is sealed

e. the verification needed to ensure that each package has not been tampered with and that there are no damaged containers

f. evidence that special shipping requirements (like refrigeration) have been met if required

5. If a delivery or shipment of raw material is made up of different batches, you must consider each batch as separate for the purposes of sampling, testing and release.

6. If the same batch of raw material is received later on, you must also consider this batch as separate for the purposes of sampling, testing and release.

However, full testing to specifications may not be needed if all these conditions are met:

a. a specifically discriminating identity test or combination of tests is conducted

b. the raw material has not been repackaged or re-labelled

c. the raw material is within the re-test date assigned by its vendor

d. evidence is available to show that all pre-established transportation and storage conditions have been maintained

# Manufacturing control

## C.02.011

(1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003*(b)* and importer of a drug shall have written procedures prepared by qualified personnel in respect of the drug to ensure that the drug meets the specifications for that drug.

(2) Every person required to have written procedures referred to in subsection (1) shall ensure that each lot or batch of the drug is fabricated, packaged/labelled and tested in compliance with those procedures.

### Rationale

You must take measures to maintain the integrity of a drug product. This includes from the moment the raw materials enter your plant to the time you release the finished dosage form for

sale and distribution. These measures ensure that all of your manufacturing processes are clearly defined, monitored, and systematically reviewed. They also demonstrate that your manufacturing processes can consistently produce drug products that comply with their established specifications for quality.

## Interpretation

### General

1. Restrict production area access to designated personnel. Review the list of designated personnel periodically.

2. Handle all raw materials, products and packaging materials according to pre-approved written procedures or instructions. This includes receiving, quarantining, sampling, storing, tracking, labelling, dispensing, processing, packaging and distributing. Keep records.

3. Ensure that when you receive raw materials, packaging materials, in-process (intermediate) drugs and bulk drugs, you account for, document, label and hold them in quarantine until they are released by your quality control department.

4. Clean containers (where necessary) when you receive them, and label them with the required information.

5. For each delivery, check all containers for:

    a. correct labelling (including the name used by the supplier as stated in the specification)

    b. compliance with information on the purchase order and shipping documentation

6. Record damage to containers, broken seals, evidence of tampering or contamination, and any other problems (such as temperature excursions) that might adversely affect the quality of a material. Report these problems to your quality control department and investigate them.

7. You must have procedures in place to ensure the identity of the contents of each container. Identify the containers that samples have been taken from.

8. Confirm identity before mixing incoming materials with existing stock (e.g. solvents or stocks in silos). Create procedures for preventing mix-up when discharging incoming materials into existing stock.

9. If bulk deliveries are made in non-dedicated tankers, you should have measures in place to prevent cross-contamination (such as obtaining a certificate of cleaning, testing for trace impurities, or auditing the supplier).

10. Ensure labels for bulk drugs, in-process drugs, raw materials and packaging materials have the following information (or provide traceability under a validated electronic system to):

    a. the designated name and (if applicable) the code or reference number of the material

    b. the specific batch number(s) given by the vendor, and receiving batch number issued upon receipt by the fabricator or packager/labeller

    c. the disposition status of the contents (e.g. in quarantine, on test, released, rejected, to be returned or recalled)

    d. an expiry date or retest date

    e. the stage of manufacturing of in-process material (if applicable)

11. Make sure raw materials, packaging materials, intermediates, bulk drugs and finished products are:

    a. stored in locations that are separate and removed from immediate manufacturing areas, with controls in place that ensure batch segregation and stock rotation

    b. transported under conditions determined by your quality control department to preserve their quality and safety

12. Only use materials released by your quality control department that are within their expiry date/retest date.

13. Before starting any processing operation, take and document all needed steps to ensure that your work area and equipment are clean (within the validated clean hold time). Ensure they are free from any raw materials, products, product residues, labels or documents not required for the current operation.

    a. Operations on different products should not be carried out at the same time or after each other in the same room, unless there is no risk of mix-up or cross-contamination.

    b. If you implement validated changeover procedures, you may fabricate or package/label non-medicinal products in areas or with equipment that is also used to produce drugs.

c. Carry out checks to ensure that transfer lines, hoses and other pieces of equipment used to transfer products from one area to another are correctly connected and do not pose a contamination risk.

14. Ensure all materials, bulk containers, major items of equipment and rooms used are labelled (or otherwise identified). You should indicate the product or material being processed, its strength, the batch number, and (if appropriate) the stage of manufacturing. For equipment, vessels and rooms, this may include their clean status.

15. Protect products and materials properly from microbial and other contamination at every stage of processing.

16. Make sure qualified personnel dispense and verify raw materials following a written procedure. They must ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers. Ensure raw materials that are being staged are properly sealed and stored under conditions consistent with the accepted storage conditions for that material.

17. Check measuring devices regularly for accuracy and precision. Keep records of all checks.

18. Ensure that in-process control activities performed within production areas do not pose any risk to the quality of the product.

19. Carry out checks on yields and reconciliation of quantities at appropriate stages of the process to ensure that yields are within acceptable limits. Record and investigate deviations from expected yields.

20. Avoid any deviation from instructions or procedures. If deviations happen record them — have qualified personnel investigate and write a report that describes the deviation, the investigation, the impact of the deviation, the rationale for disposition, and any follow-up activities required. Your quality control department must approve the report and maintain records.

21. Clearly mark rejected materials and products. Store them separately in restricted areas, or control them using a system that ensures that they are either returned to their vendors or (where appropriate) reprocessed or destroyed. Record any actions taken.

## Validation

22. Validate all critical production processes. For more information, see *Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)*.

23. Conduct validation studies according to predefined protocols. Follow validation protocols approved in marketing authorization submissions at pre-market stage. Prepare, evaluate, approve and maintain a written report summarizing recorded results and conclusions.

24. Validate changes to production processes, systems, equipment, materials or suppliers that may affect product quality and/or process reproducibility before implementing them.

25. Evaluate critical processes and procedures periodically to ensure they remain capable of achieving the intended results.

## Manufacturing master formulae

26. Ensure processing operations are covered by master formulae. The master formulae should be in accordance with the marketing authorization. These master formulae must be prepared by—and subject to independent checks by—production and quality control personnel who have the qualifications described under section C.02.006 “Personnel,” interpretation 1.

27. Write master formulae to provide not less than 100% of label claim. Overages may be allowed to compensate for processing losses. They must be documented with justification and be in accordance with the marketing authorization. For more requirements on limits of variability, see section C.01.062 of the Regulations. In exceptional cases, overages to compensate for losses due to degradation during manufacturing or shelf life must be scientifically justified and in accordance with the marketing authorization.

    Master formulae must also include the following:

    a. an identifier of the product, with a reference code relating to its specifications
    b. the version number
    c. a description of the dosage form, strength of the product, and batch size
    d. a list of all raw materials to be used and the amount of each, using the designated name and a reference that is unique to that material, and including any processing aids that may not be present in the final product
    e. a statement of the expected final yield (along with the acceptable limits) and relevant intermediate yields (where applicable)
    f. identification of the principal equipment to be used and (if applicable) internal codes

g. the procedures (or reference to the procedures) to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilizing)

h. detailed stepwise processing instructions (e.g. checks on materials, pre-treatment, sequence for adding materials, mixing times, mixing speeds or temperatures)

i. the instructions for any in-process controls, along with their limits

j. where needed, the requirements for environmental controls, storage of products and in-process materials, labelling storage conditions, maximum validated hold time, and any special precautions to be observed

### Packaging master formulae

28. Ensure packaging operations are covered by master formulae. Where applicable, the master formulae should be in accordance with the marketing authorization. These master formulae must be prepared by—and subject to independent checks by—packaging/labelling and quality control personnel who have the qualifications described under section C.02.006 “Personnel,” interpretation 1.

29. In the case of a packaged product, ensure the master formula also includes the following for each product, package size and type:

    a. the name of the product, with a reference code relating to its specifications

    b. the version number

    c. a description of the dosage form and strength of the product

    d. the package size (expressed in terms of the number, weight or volume of the product in the final container)

    e. a complete list of all the packaging materials required for a standard batch size (including quantities, sizes and types), with the code or reference number relating to the specifications for each packaging material

    f. where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product are to be positioned

    g. special precautions to be observed, including a careful examination of the packaging area and equipment, including transfer lines and hoses (to ascertain the line clearance before operations begin)—record all verifications

    h. a description of the packaging operations, including any significant subsequent secondary operations and the equipment to be used

    i. details of in-process controls, with instructions for sampling and acceptance limits

    j. the expected final yield, with the acceptable limits

k. where needed, the requirements for environmental controls, storage conditions of bulk and finished products, maximum validated packaging time, and any special precautions to be observed

## Manufacturing operations

30. Check all materials in the production area when they are received for cleanliness, quantity, identity and conformity with the manufacturing records.

31. Ensure each batch processed is effectively governed by a uniquely numbered batch record. This record should be prepared and verified by qualified personnel from the master production documents in a way that prevents errors.

32. Include the following information on or with the manufacturing batch record, as it becomes available during the process

    a. dates and times of production and of the start and completion of significant intermediate stages (such as blending and heating)

    b. the receiving batch number and quantity of each raw material actually weighed and dispensed (for active raw material, the quantity is to be adjusted if the assay value is less than 98.0%, calculated on “as is” basis and on which the master formula was based)

    c. the identification of personnel performing each significant step of the process, and of the person who checked each of these steps (such as weighing and adding a material to the batch)

        i. When the weighing and adding of materials to the batch is performed by validated and automated equipment, the degree of verification needed depends on the level of automation and validation.

    d. the actual results of the in-process quality checks performed at appropriate stages of the process, and the identification of the person carrying them out

    e. the actual yield of the batch at appropriate stages of processing and the actual final yields, along with explanations for any deviations from the expected yield

    f. detailed notes on special problems, with written approval from your quality control department for any deviation from the master formula

    g. after completion, the signature of the person responsible for the processing operations

You may replace written batch records with validated electronic systems. Additional details on electronic systems can be found in the records section of this guide under C.02.020–C02.024.1.

Ensure all manufacturing records are created, maintained, processed and reviewed as outlined in your establishment's data governance plan.

33. Only combine batches with your quality control department's approval and according to pre-established written procedures.

    You must approve beforehand the introduction of part of a previous batch (conforming to the required quality) into the next batch of the same product at a defined stage of fabrication. Carry out this recovery according to a validated procedure and record it.

### Packaging operations

34. Perform packaging operations according to comprehensive and detailed written operating procedures or specifications. These procedures/specifications must include:
    a. the identification of equipment and packaging lines used to package the drug
    b. the proper separation and (if necessary) dedication of packaging lines that are packaging different drugs
    c. disposal procedures for unused printed packaging materials and rejected materials from the packaging operation

35. Ensure packaging orders are individually numbered and include the batch number, expiry date and quantity of bulk product to be packaged, as well as the planned quantity of finished product that will be obtained. This record should be prepared and verified by qualified personnel from the master production documents in a way that prevents errors.

36. Before beginning any packaging operation, check that the equipment and work station are clear of previous products, documents and materials that are not needed for the planned packaging operations. Ensure equipment is clean (within the validated clean hold time) and suitable for use. Record all checks.

37. Check all products and packaging materials on receipt at the packaging line for cleanliness, quantity, identity and conformity with the packaging instructions.

38. Take precautions to ensure that containers to be filled are free from contamination.

39. Ensure the name and batch number of the product being handled is displayed at each packaging station or line.

40. Ensure packaging orders include the following information (recorded at the time each action is taken):
    a. the date(s) and time(s) of the packaging operations
    b. the quantity, lot number, and/or analytical control number of each packaging material and bulk drug issued for use
    c. the packaging line used
    d. identification of the personnel who are supervising packaging operations and the withdrawal of bulks
    e. identification of the operators of the different significant steps
    f. the checks made for identity and conformity with the packaging instructions (including the results of in-process controls)
    g. a check for whether on-line printing is correct
    h. a check for the correct functioning of line monitors, electronic imaging, or vision systems
    i. handling precautions applied to a partly packaged product
    j. notes on any special problems, including details of any deviation from the packaging instructions (with written approval by qualified personnel)
    k. the quantity of finished product actually obtained
    l. a reconciliation of the quantity of printed packaging material and bulk drug used, destroyed or returned to stock
41. To prevent mix-ups, do not return samples taken away from the packaging line.
42. Whenever possible, attach samples of the printed packaging materials used (including specimens bearing the batch number, expiry date and any additional overprinting) to packaging orders.
43. Follow filling and sealing as quickly as possible by labelling. If labelling is delayed, follow a procedure to ensure that no mix-ups or mislabelling can occur.
44. Once the packaging operation is complete, destroy any unused batch-coded packaging materials and record their disposal. Follow a procedure if non-coded printed materials are returned to stock.
45. Destroy outdated or obsolete packaging materials and record their disposal.
46. Ensure that products involved in non-standard events during packaging are inspected and investigated by qualified personnel. Keep a detailed record of this operation.

47. When reconciling the amount of bulk product with the number of units packaged, investigate and account for any significant or unusual discrepancy observed before release.

48. When reconciling the amount of printed packaging materials with the number of units packaged, investigate and account for any discrepancy observed before release. If you validate electronic verification of all printed packaging materials on the packaging line, you may not need a full reconciliation.

49. Ensure printed packaging materials are:

    a. stored in an area with access restricted to designated personnel who are supervised by personnel qualified according to interpretation 3 or 4 of section C.02.006 “Personnel,” as applicable

    b. withdrawn against a packaging order

    c. issued and checked by personnel who have the qualifications outlined under interpretation 3 or 4 of section C.02.006 “Personnel,” as applicable

    d. identified in a way that makes them distinguishable during packaging operations

50. To prevent mix-ups, you should use roll-fed labels instead of cut labels. Avoid gang printing (printing more than one item of labelling on a sheet of material).

51. Store and transport cut labels, cartons and other loose printed materials in separate closed containers.

52. On-line verification of all labels by automated electronic means can be helpful in preventing mix-ups. Conduct checks to ensure that any electronic code readers, label counters or similar devices are operating correctly.

53. Take special care when cut labels are used, when overprinting is carried out off-line, and in hand-packaging operations. If cut labels are used, have one operator perform a 100% examination for correct labeling during or after labelling operations. Have a second operator independently verify this.

54. Check and record the performance of any printing (e.g. of code numbers or expiry dates) done separately or in the course of packaging to ensure it is correct.

55. Ensure every package of a drug is identified by a lot number and an expiry date.

### Finished products

56. Hold all in-process and finished products in quarantine. Identify them as such until released by your quality control department.

## Annual product quality review

57. Conduct annual quality reviews of all drug products. Verify the consistency of your existing process and the appropriateness of current specifications for raw materials, primary packaging materials and finished product. Highlight any trends and identify product and process improvements. Conduct and document these reviews for all products and batches produced using a common process, taking into account previous reviews. Include at least a review of:

    a. critical in-process controls, finished product testing results and specifications
    b. all batches that failed to meet established specification(s) and their investigation
    c. post-marketing commitments, where applicable
    d. all significant deviations or non-conformances, their related investigations, and the effectiveness of corrective and preventative actions taken
    e. all changes carried out to the processes, analytical methods, raw materials, packaging materials or critical suppliers
    f. the results of the continuing stability program and any adverse trends
    g. all quality-related returns, complaints and recalls, and the investigations performed at the time
    h. the adequacy of any previous corrective actions related to product process or equipment
    i. the qualification status of principal equipment and utilities
    j. agreements (to ensure they are up-to-date)

58. You may group quality reviews by product type (e.g. solid dosage forms, liquid dosage forms, sterile products) where scientifically justified.

59. Your quality control department (if you are an importer or distributor) should ensure that the annual product quality review is performed in a timely manner and is accurate.

60. Where required, you should have an agreement in place between the various parties involved in a review (e.g. importer, distributor, fabricator). This agreement should define each party's responsibilities in producing and assessing the quality review and taking any corrective and preventative actions. The scope of an importer's Annual Product Quality Report (APQR) should extend to all batches made using the same process, facilities and formulation as the imported product, not limited to the batches received in Canada.

61. Your quality control department should evaluate the results of this review, and assess whether corrective and preventative action or revalidation should be undertaken. Document reasons for any corrective actions. Carry out corrective and preventative

actions in a timely and effective way. You should have procedures for the ongoing management and review of these actions, and verify how effective these procedures are during self-inspection.

## C.02.012

(1) Every fabricator, packager/labeller, distributor referred to in section C.01A.003, importer and wholesaler of a drug shall maintain

*(a)* a system of control that permits complete and rapid recall of any lot or batch of the drug that is on the market; and

*(b)* a program of self-inspection.

(2) Every fabricator and packager/labeller and, subject to subsections (3) and (4), every distributor referred to in paragraph C.01A.003(*b)* and importer of a drug shall maintain a system to ensure that any lot or batch of the drug fabricated and packaged/labelled on premises other than their own is fabricated and packaged/labelled in accordance with the requirements of this Division.

(3) Subsection (2) does not apply to a distributor if the drug is fabricated, packaged/labelled and tested in Canada by a person who holds an establishment licence that authorizes those activities in respect of that drug.

(4) Subsection (2) does not apply to a distributor or importer if the drug is fabricated or packaged/labelled in an MRA country at a recognized building and both of the following requirements are met:

*(a)* the address of the building is set out in their establishment licence; and

*(b)* they retain a copy of the batch certificate for each lot or batch of the drug that they receive.

### Rationale

A recall removes from the market a drug that either:

- does not conform to the Act or Regulations
- presents a risk to consumer health

Drugs that have left the premises of a fabricator, packager/labeller, distributor, wholesaler or importer may end up in a number of locations. Depending on the non-compliance and how

serious the health risk is, you may need to recall a product from the market. If you are a fabricator, packager/labeller, distributor, wholesaler or importer, you are expected to be able to recall to the consumer level if needed. More guidance on recalls can be found in *Recall Policy (POL-0016)*.

This regulation also requires fabricators, packagers/labellers, distributors, wholesalers and importers to maintain a program of self-inspection. The purpose of self-inspection is to evaluate whether all aspects of production and quality control comply with good manufacturing practices (GMP). A self-inspection program detects any shortcomings in the implementation of GMP and recommends corrective actions.

Drugs offered for sale—whether they are produced in Canada or imported—must meet the requirements of Part C, Division 2 of the Food and Drug Regulations. If production and analysis are contracted out, they must be correctly defined, agreed upon, and controlled to avoid misunderstandings that could result in a product, work or analysis of poor quality. There should be a written agreement between the parties involved, clearly establishing the duties of each party.

## Interpretation

### Recall

1. You must have a written recall system in place to comply with article 21.3 of the *Food and Drugs Act* and section C.01.051 “Recalls” of the Regulations. It must include the following steps:
    a. Notify Health Canada of the recall.
    b. Notify all Canadian and foreign establishments involved in the fabrication, distribution or importation of the recalled product.
    c. Take prompt action to recall a product suspected or known to be in violation, according to a pre-determined plan. The procedures to be followed must be in writing and known to all concerned.
    d. Identify the person(s) responsible for initiating and co-ordinating all recall activities.
    e. You must be able to carry out your recall procedure at any time, during and outside normal working hours. You may use a voice mail system or an electronic means as part of your provisions for off-hours product recall activation. It should indicate appropriate contact information. Include the use of any voice mail system or other electronic means functions and monitoring requirements in your written procedures.

f. Your recall procedure must outline the way to communicate and implement a recall and decide its extent.

g. Your distribution records must enable tracing of each drug product. This includes any products in transit, any samples that have been removed by the quality control department, and any professional samples that have been distributed.

h. If you are a wholesaler, you must get drug products from companies that hold an establishment licence as required in Part C, Division 1A of the Regulations. This facilitates a system of control that permits complete and rapid recall.

i. When the importer or distributor assumes some or all of the wholesaler's responsibilities with respect to recalls, a written agreement must clearly describe each party's responsibilities. The quality agreement must provide understanding of the wholesaler's drug distribution supply chain.

j. Identify recalled products and store them separately in a secure area until their disposition is determined.

k. Assess and record the progress and effectiveness of the recall at intervals. Issue a final report (including a final reconciliation).

l. Verify the adequacy of recall procedures periodically. This may be achieved by carrying out a mock recall. Your quality control department should review and approve reports of these mock recalls.

For more information on recall procedures, see:

- *Recall Policy (POL-0016)*
- *Product Recall Procedures*

## Self-inspection

2. You must have a self-inspection program appropriate to your establishment's operations. This program must ensure compliance with Part C, Division 2 of the Regulations.

   a. You must have a comprehensive written procedure that describes the functions of your self-inspection program.

   b. If you are a fabricator who processes a drug from raw material through to dosage form, your program must address itself to all aspects of the operation. If you are a packager/labeller, distributor, importer or wholesaler who only packages and/or distributes drugs fabricated by another fabricator, your written program must cover only those aspects of the operations that you exercise control over on your premises.

c. Your self-inspection team must include personnel or consultants who are suitably trained and qualified in GMP.

d. You must carry out periodic self-inspections.

e. Your senior management must review reports on the findings of the inspections and on corrective actions. Implement corrective actions in a timely way.

### Outsourced activities

3. If you outsource any fabrication, packaging/labelling or testing activities, you must have a written agreement between the contract giver and the contract acceptor. You must clearly establish the responsibilities of each party to avoid misunderstandings that could result in a product or operation of poor quality. Ensure all arrangements for contract fabrication, packaging/labelling or testing comply with the marketing authorization for the drug product and API concerned.

### The contract giver

4. If you are the contract giver, you are ultimately responsible to ensure processes are in place to control outsourced activities. Your quality system should include the control and review of any outsourced activities.

5. You are responsible for assessing the contract acceptor's continuing competence to carry out the work or tests required, according to the principles of GMP described in this guideline.

    a. If you are a distributor of drugs fabricated, packaged/labelled and tested at Canadian sites, evidence that the Canadian fabricator or packager/labeller or tester holds a valid Canadian establishment licence is considered adequate.

    b. If you are an importer of drugs fabricated, packaged/labelled or tested at a foreign site, you must meet the requirements described in *Guidance on Evidence to Demonstrate Drug Good Manufacturing Practices Compliance of Foreign Sites (GUI-0080)*.

6. You must provide the contract acceptor with all information needed to carry out contracted operations correctly, according to the marketing authorization and any other legal requirements. Ensure the contract acceptor is fully aware of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products.

7. Monitor and review the performance of the contract acceptor, and the identification and implementation of any needed improvement.

8. You are responsible for reviewing and assessing records and results related to outsourced activities. You should ensure that all products, services and materials provided by the contract acceptor comply with GMP, the marketing authorization and the quality agreement.

### The contract acceptor

9. If you are the contract acceptor, you must be able to properly carry out the work ordered by the contract giver (including having adequate premises, equipment, knowledge, experience and competent personnel).

10. Ensure that all products, materials and knowledge delivered to you are suitable for their intended purpose.

11. Do not subcontract to a third party any of the work entrusted to you under contract without the contract giver's prior evaluation and written approval. Arrangements made between you and any third party should ensure that information and knowledge—including from assessments of the suitability of the third party—are made available to the original contract giver.

12. Do not make unauthorized changes (outside the terms of the contract) that may adversely affect the quality of the outsourced activities for the contract giver.

### Agreement

13. Ensure there is a written agreement covering the fabrication, packaging/labelling or testing arranged among the parties involved. The agreement must specify the responsibilities of each party relating to the outsourced activities and control of the product.

    a. Technical aspects of the agreement must be drawn up by qualified personnel who are knowledgeable in pharmaceutical technology and GMP.

    b. The agreement should include the following:

        i. a description of who is responsible for:

            - writing and approving raw materials, packaging materials and finished product specifications
            - purchasing, sampling, testing and releasing raw materials and packaging materials
            - writing and approving manufacturing and packaging master formulae
            - undertaking production, quality and in-process controls

- conducting analytical method validation
- conducting process validation
- overseeing the stability program
- overseeing transport and storage logistics and conditions
- preparing specific sections of the annual product quality review

ii. a clause saying there should be no subcontracting of any work without written authorization of the contract giver

iii. the procedure used by the contract giver's quality control department to ensure that each lot or batch being released for sale has been fabricated, packaged/labelled and tested in compliance with GMP and marketing authorization requirements

iv. a requirement for the contract acceptor to investigate and notify the contract giver of any deviations and out-of-specification results that may have an impact on the quality of the products

v. a description of how to handle rejected raw materials, packaging materials, in-process drugs, bulk drugs and finished products

vi. a description of how complaints and information about potentially defective products received by the contract giver are (when applicable) handled and investigated by the contract acceptor (with results sent to the contract giver for review)

vii. a requirement for changes to be governed by a change control system and approved by the contract giver and contract acceptor

viii. a requirement for the contract acceptor to make all records related to the outsourced activities (e.g. fabrication, packaging/labelling and testing) available on request to the contract giver in a timely way

ix. permission for the contract giver to audit the facilities of the contract acceptor

x. a requirement to notify the contract giver of any significant changes in the regulatory status of the contract acceptor or their API vendors (this includes being notified of any recalls or other regulatory actions, such as statements of non-compliance, warning letters or import alerts/bans originating at any foreign buildings where drug product or API activities are conducted)

xi. for drug product importers, a clause requiring:

- foreign drug product fabricators to use APIs manufactured at GMP-compliant buildings (this should also enable foreign drug product fabricators to conduct GMP corporate audits on other buildings used or to request the relevant GMP compliance evidence)

- any API fabricator to provide ongoing stability data to importers on request via the foreign drug product fabricator
- the importer to be notified of any change to the API manufacturing process or supplier or specifications

xii. a requirement for drug fabricators to provide a copy of any API fabricator's Annual Product Quality Review (APQR) upon request

xiii. a requirement for drug fabricators to ensure that API supplier buildings are compliant with Canadian GMP or ICH Q7 guidelines

Drug fabricators, importers and distributors should ensure appropriate quality agreements exist with their API suppliers. Agreements should include (but not be limited to) a way for the drug fabricator, importer or distributor to be notified of any:

- change to the API manufacturing process or supplier or specifications
- recalls or other regulatory actions (such as statements of non-compliance, warning letters or import alerts/bans) regarding any buildings where API activities are conducted

Importers of drug products must have on their premises in Canada evidence of GMP compliance of the foreign buildings where the fabrication, packaging/labelling and testing of APIs occurs.

# Quality control department

## C.02.013

(1) Every fabricator, packager/labeller, wholesaler, distributor referred to in section C.01A.003 and importer of a drug shall have on their premises in Canada a quality control department that is supervised by personnel described in section C.02.006.

(2) Except in the case of a wholesaler or a distributor referred to in paragraph C.01A.003(*a*), the quality control department shall be a distinct organizational unit that functions and reports to management independently of any other functional unit, including the manufacturing, processing, packaging or sales unit.

## Rationale

The Regulations and this guideline use the term “quality control” to refer to any quality unit that satisfies this role. A quality unit independent of production fulfills both quality assurance and quality control responsibilities. It can be made up of separate units, a single individual or a group, depending upon the size and structure of the organization. Quality control is the part of GMP concerned with sampling, specifications and testing. It also includes organization, documentation and release procedures.

This regulation provides for a quality control department that helps facilitate assurances that the proper production steps and product tests are carried out. It also facilitates assurances that raw materials and packaging materials are not released for use—and products are not released for sale—until their quality has been judged to be satisfactory.

Quality control is not confined to lab operations. It must be incorporated into all activities and decisions concerning the quality of the product.

Manufacturing and quality control personnel share the same goal of ensuring that high-quality drugs are fabricated. But their interests may sometimes conflict in the short run as decisions are made that will affect a company's output. For this reason, you can best achieve an objective and accountable quality control process by creating an independent quality control department. The independence of the quality control department from manufacturing is considered fundamental.

The rationale for the requirement that the quality control department be supervised by qualified personnel is outlined under section C.02.006 “Personnel.”

## Interpretation

1. If you are a fabricator, packager/labeller, distributor, importer or wholesaler, you must have a person on site—or fully accessible to on-site quality control personnel—who is responsible for making quality control decisions. This person must have enough knowledge of on-site operations to fulfill the responsibilities of the position.

2. Your quality control department must have sufficient workspace, trained personnel, materials and equipment to fulfill its duties and responsibilities. Your senior management should determine and provide adequate and appropriate resources to implement and maintain the pharmaceutical quality system and continually improve its effectiveness.

3. Ensure approved written procedures are available for sampling, inspecting and testing raw materials, packaging materials, in-process drugs, bulk drugs and finished products.

4. Ensure quality control personnel have access to production areas to fulfill responsibilities.

## C.02.014

(1) Except in the case of a wholesaler or a distributor referred to in paragraph C.01A.003(*a*), no lot or batch of a drug may be made available for further use in fabrication or for sale unless the person in charge of the quality control department approves the further use or the sale.

(2) A drug that is returned to its fabricator, packager/labeller, wholesaler, distributor referred to in section C.01A.003 or importer shall not be made available for further use in fabrication or for further sale unless the person in charge of the quality control department approves the further use or further sale.

(3) No lot or batch of a raw material or packaging/labelling material shall be used in the fabrication or packaging/labelling of a drug unless the person in charge of the quality control department approves the use.

(4) No lot or batch of a drug shall be reprocessed unless the person in charge of the quality control department approves the reprocessing.

### Rationale

Your quality control department is responsible for approving all raw materials, packaging materials and finished products. It is very important for this department to exercise adequate controls to ensure the quality of the end product.

To maintain this level of quality, it is also important to examine all returned drugs, and to give special attention to reprocessed drugs.

### Interpretation

1. The person in charge of your quality control department (or a designated alternate meeting the requirements described under section C.02.006 “Personnel”) must sign and date all decisions made by the quality control department, according to section C.02.014 “Quality Control Department.”

2. Your quality control department’s assessment for the release of finished products must consider all relevant factors, including: production conditions, results of in-process

testing, fabrication and packaging documentation, compliance with the finished product specifications, an examination of the finished package, and (if applicable) a review of the storage and transportation conditions.

a. Evaluate deviations and borderline conformances according to a written procedure. Document the decision and rationale. Where appropriate, conduct trend analysis on batch deviations.

b. Assess any non-conformances, malfunctions, alarms or errors (including those related to premises, equipment, sanitation and testing) that may have an impact on the quality and safety of batches pending release or released. Document the rationale.

c. Your quality control department should ensure compliance to the current master production documents and marketing authorization (this does not apply to wholesalers).

When reviewing records for release of finished product, include a review of electronic records (where used) and relevant audit trails.

3. Your quality control department must ensure that raw materials and packaging materials are quarantined, sampled, tested and released before being used to fabricate or package/label a drug.

4. You must destroy finished products returned from the market, unless it has been determined that their quality is satisfactory. Returned goods may be considered for resale only after they have been assessed by your quality control department, according to a written procedure. The assessment must take into consideration:

- the reason for the return
- the nature of the product
- the storage and transportation conditions
- the product's condition and history
- the time elapsed since it was originally sold

Maintain records of any action taken. You must have documentation available to support the decision to place returned goods into inventory for further resale. Wholesalers should get guidance from importers/distributors to make an informed decision about restocking the product.

When you assess returned goods, you must consider the potential for counterfeit or tampering before considering for resale.

5. Identify rejected materials and products as such and quarantine them. Ensure they are either returned to the vendors, reprocessed or destroyed. Record actions taken.

6. Your quality control department must approve the reworking of any lot or batch of drug beforehand. This approval must be based on documented scientific data, which may include validation. You should only rework products due to quality concerns or failure to meet their specifications in exceptional cases. Reworking is permitted only when the following conditions are met:

    a. The quality of the finished product is not affected.

    b. The reworked lot meets specifications.

    c. It is done according to a defined procedure approved by your quality control department.

    d. All risks have been evaluated, including potential impact on drug stability and the need for stability testing (e.g. accelerated stability) before release for sale.

    e. The reworked lot is included in the continuing stability program.

    f. Complete records of the reworking are kept.

    g. A new batch number is assigned.

    h. An assessment is performed on the continuing suitability of the manufacturing process, along with the need for re-validation or modification to the manufacturing process.

7. Your quality control department must approve the reprocessing of any lot or batch of drug beforehand. You should only reprocess products due to quality concerns or failure to meet their specifications in exceptional cases. Reprocessing is permitted only when the following conditions are met:

    a. The quality of the finished product is not affected.

    b. The reprocessed lot meets specifications.

    c. It is done according to a defined procedure approved by your quality control department.

    d. All risks have been evaluated, including availability of applicable stability data from the continuing stability program.

    e. Complete records of the reprocessing are kept.

f. A new batch number is assigned.

g. Validation demonstrates that the quality of the finished product is not affected.

h. An assessment is performed on the continuing suitability of the manufacturing process, along with the need for re-validation or modification to the manufacturing process.

i. The reprocessing is in compliance with the marketing authorization, as applicable.

8. Your quality control department must evaluate and act on the need for additional testing of any finished product that has been reprocessed or reworked (or into which a recovered product has been incorporated). Maintain records.

Recovery is not considered to be either a reprocessing or a reworking operation. Guidance about recovery is found under section C.02.011, interpretation 33.

## C.02.015

(1) All fabrication, packaging/labelling, testing, storage and transportation methods and procedures that may affect the quality of a drug shall be examined and approved by the person in charge of the quality control department before their implementation.

(2) The person in charge of the quality control department shall cause to be investigated any complaint or information that is received respecting the quality of a drug or its deficiencies or hazards and cause any necessary corrective action to be taken, in the case where the complaint or information relates to an activity over which the department exercises quality control.

(2.1) In the case where the complaint or information that is received does not relate to an activity over which the quality control department exercises quality control, the person in charge of the department shall forward the complaint or information to the person in charge of the quality control department that exercises quality control over that activity.

(3) The person in charge of the quality control department shall cause all tests or examinations required pursuant to this Division to be performed by a competent laboratory.

## Rationale

Drug processes and products must be designed and developed taking GMP requirements into account. Production procedures and other control operations must be independently examined by your quality control department. Ensuring proper storage, transportation and distribution of materials and products minimizes any risk to their quality.

Complaints may indicate problems related to quality. By tracing their causes, you can determine which corrective measures to take to prevent them from happening again. Having tests carried out by a competent lab provides assurance that test results are genuine and accurate.

You must have written agreements for consultants and third party contractors (including contract labs) that describe the education, training and experience of personnel and the types of services provided. These agreements must be approved by the person in charge of your quality control department and available for examination and inspection. You must also maintain records of the activities contracted.

## Interpretation

Your quality control department is responsible for doing the following:

1. The person in charge of your quality control department (or a designated alternate who meets the requirements under section C.02.006 “Personnel,” as applicable to the activity) must sign and date all decisions made related to section C.02.015 “Quality Control Department.”

2. Establish and maintain written agreements clearly describing the respective responsibilities between the fabricator, packager/labeller, distributor, importer and wholesaler for any complaint or information that is received about the quality of a drug or its deficiencies or hazards. See interpretations 3 to 13 in section C.02.012 “Manufacturing Control” for written agreement requirements.

3. Ensure that guidelines and procedures are in place and implemented for storage and transportation conditions (such as temperature, humidity, lighting controls, stock rotation, sanitation, and any other precautions needed to maintain the quality and safe distribution of the drug). For more guidance on storage and transportation, see: *Guidelines for Temperature Control of Drug Products during Storage and Transportation (GUI-0069)*.

4. Ensure standard operating procedures and records for shipping and receiving are available and contain the following:

a. a description of the shipping configuration and type of packaging to be used for shipping the finished product

b. the labelling requirements (including storage conditions and special precautions or warnings) for shipments of the finished product

c. mode(s) of transportation approved for shipping the finished product

d. the verifications required to ensure that no finished product in the shipment has been tampered with and that there are no damaged containers

e. evidence that shipping requirements (e.g. temperature control) have been met (if required)

f. a written agreement clearly describing the respective responsibilities (between the fabricator, packager/labeller, distributor, importer, wholesaler and the transportation provider) with respect to storage, transportation, returns, complaints and recalls of the drug

5. Carry out the sampling of raw materials, packaging materials, in-process drugs, bulk drugs and finished products according to detailed written procedures. Ensure samples are representative of the batches of material they are taken from, and are handled in a way that prevents errors in sample identification and avoids adverse storage conditions. Ensure sampling plans are properly justified.

6. Review and assess all complaints—and other information about potentially defective products—according to written procedures that incorporate quality risk management principles. Record the complaint with all original details and thoroughly investigate. Take appropriate follow-up action after investigating and evaluating. Record all decisions and measures taken as a result, and reference them to the corresponding batch records. Review complaint records regularly for any indication of specific or recurring problems that need attention.

    a. Investigations into complaints that indicate a potential product quality defect should include the following:

        i. a description of the reported quality defect

        ii. a determination of the extent of the quality defect and potential for other batches or products to be impacted

        iii. an examination or testing of reference and/or retention samples (if required) and a review of the applicable records

        iv. evaluation of samples of the defective product from the complainant (where samples are not available, other appropriate strategies may be used)

        v. the distribution information for the batch(es) in question

        vi. the assessment of the risk(s) posed by the quality defect

vii. risk mitigation strategies using a defined decision-making process, including the need for product recalls

viii. an assessment of the impact that any recall action may have on the availability of the drug to patients/animals in any affected market, and the need to notify relevant authorities of any such impacts

ix. the internal and external communications that should be made about a quality defect and its investigation

x. the identification of the potential root cause(s) of the quality defect

xi. the identification of appropriate corrective and preventative actions (CAPAs) to be implemented, updated with an assessment of the effectiveness of those CAPAs

7. Establish a change control system to provide for ongoing process optimization and a continuing state of control. The quality control department must document, evaluate and approve all changes, identifying them with the appropriate effective date. Any significant change may require re-validation.

8. Tests must be performed by a lab that meets all relevant GMP requirements. Ensure that:

    a. Lab facilities are designed, equipped and maintained to conduct the required testing.

        i. In the microbiology lab, environmental monitoring is performed periodically. Microbiological cultures and sample testing are handled in an environment that minimizes contamination.

        ii. The facility used to perform sterility testing should comply with the microbial limits of an aseptic production facility (which should conform to a Grade A within a Grade B background or in an isolator of a Grade A within an appropriate background, with limited access to non-essential personnel).

    b. The individual in charge of the lab either:

        i. is an experienced university graduate who holds a degree in a science related to the work being carried out, with practical experience in his or her responsibility area, or

        ii. reports to a person who has these qualifications (C.02.006, interpretation 1)

    c. There are enough lab personnel qualified to carry out the work they undertake.

    d. Lab control equipment and instruments are suited to the testing procedures carried out. Equipment and records are maintained as per the interpretations under C.02.005.

e. All test methods are validated. A lab that is using a test method where the lab did not perform the original validation (e.g. the use of a compendial method) should verify the appropriateness of the test method. All testing as described in the marketing authorization should be carried out according to the approved methods.

   i. The transfer of test methodology from one lab to another should include an assessment to verify that the test method(s) complies with the market authorization. Also verify that the original validation(s) of the test method(s) complies with current International Council on Harmonisation (ICH) and/or Veterinary International Council on Harmonisation (VICH) requirements. A gap analysis should be performed and documented to identify any other validation requirements before starting the technical transfer process.

   ii. The transfer of test methodology should be described in a written protocol. This should include (but is not limited to) the following parameters:

      - the relevant test method(s) undergoing transfer
      - additional training requirements
      - standards and samples to be tested by both labs
      - any special processing, transport and storage conditions for test items
      - the testing to be performed
      - the acceptance criteria, which should be based on the current validation study of the methodology and ICH/VICH requirements

   iii. Deviations from the protocol should be investigated before closing the technical transfer process. The technical transfer report should document the comparative outcome of the process and should identify areas requiring further test method revalidation.

f. All lab data are created, maintained, processed and reviewed as outlined by the firm's data governance plan.

Data integrity is an important consideration. For other requirements relating to a data governance plan, see sections C.02.020 to C.02.024 "Records," interpretation 5.

The data governance plan (as it applies to lab data) must include enough detail to allow accurate and complete reporting and interpretation of all lab test data and ensure data integrity. This plan should include (but is not limited to) the following elements:

   i. Validate computerized systems for their intended use, with special attention to any that are used to create, process and store laboratory data. Qualify

spreadsheets used in the lab.

ii. Have systems and procedures in place to ensure that lab records are reliable, complete and accurate. These systems/procedures must also require that all test results that could affect the quality, safety or efficacy of a drug are reported, reviewed and assessed appropriately.

iii. Organize and store data in a way that is interpretable and traceable to the execution and purpose of test procedures (i.e. use of defined and meaningful naming conventions for samples, test sequences and data storage locations/folders).

iv. Put controls in place to ensure that test data are not deleted and that changes to testing records are documented and justified where required (e.g. audit trails must be enabled and reviewed).

v. Retain data in its original format. Original records (or a true copy), including electronic records, are subject to review by qualified personnel.

g. Water used for microbial and analytical tests meets the requirements of the test or assay it is used in.

h. All reagents and culture media are recorded upon receipt or preparation. Reagents made up in the lab are prepared according to written procedures and are properly labelled.

i. Prepared media are sterilized using validated procedures and stored under controlled temperatures.

ii. Prepared media are properly labelled with lot numbers, expiration date and media identification. The expiration date of media is supported by growth-promotion testing results that show that the performance of the media still meets acceptance criteria up to the expiration date.

iii. Sterility and growth-promotion testing are performed to verify the suitability of culture media.

iv. All purchased ready-to-use media received are accompanied by a certificate of analysis, with expiry date and recommended storage conditions, as well as the quality control organisms used in growth-promotion and selectivity testing of that media.

- Put procedures in place to ensure that media are transported under conditions that minimize the loss of moisture and control the temperature.
- Store media according to the vendor's instructions.
- Perform sterility and growth-promotion testing on lots received, unless the vendor is certified. Perform periodic confirmatory testing for ready-to-use media received from each certified vendor.

- Maintain records.

i. Reference standards are available in the form of the current reference standards listed in Schedule B to the Act. When such standards have not been established or are unavailable, primary standards can be used. Secondary standards are verified against a Schedule B reference standard or against the primary standard and are subject to complete confirmatory testing at predetermined intervals.

   All reference standards are stored and used in a way that will not adversely affect their quality. Records relating to their testing, storage and use are maintained.

j. Out of specification (OOS) test results are investigated to determine the cause of the OOS.

   i. Have procedures in place to describe the steps to be taken as part of the investigation.

   ii. In the case of a clearly identified lab error, you may invalidate the original results, then repeat the test and report the results. Keep records of the original results and record an explanation.

   iii. When the investigation reveals no clearly identified lab error or other potential root causes and retesting is performed, specify in advance in the procedure the number of retests to be performed on the original sample and/or a new sample, and the statistical treatment of the resulting data.

   iv. Report all valid test results (both passing and suspect) and fully consider them in batch release decisions.

   v. If the original OOS result is found to be valid, conduct a complete investigation (including the batch affected) and record the results. The investigation should be performed according to written procedures. It should include an assessment of root cause, description of corrective and preventive actions carried out, and conclusions.

k. To ensure the compliance of contractors conducting testing required under Part C, Division 2 of the Regulations:

   i. A Canadian contract lab must have a relevant valid establishment licence. A foreign testing site must be listed on a Canadian establishment licence, as described in *Guidance on Evidence to Demonstrate Drug Good Manufacturing Practices Compliance of Foreign Sites (GUI-0080)* and *Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees (GUI-0002)*.

   ii. All arrangements for external testing must comply with the marketing authorization for the drug product concerned (including the testing of in-process drugs, intermediates, raw materials, packaging materials, and all other testing required by Part C, Division 2 of the Regulations).

   iii. There must be a written agreement covering all testing activities between

the contract lab and the parties involved. The agreement must specify their respective responsibilities relating to all aspects of testing. The agreement should specify that contract test facilities are subject to evaluation and audit by the quality control department.

iv. Technical aspects of the agreement must be drawn up by qualified personnel suitably knowledgeable in the relevant lab testing and GMP. The agreement must:

    1. permit audit of the external lab's facilities and operations
    2. clearly describe (at a minimum) who is responsible for:
        a. overseeing collection, transportation and storage conditions of samples before testing
        b. keeping stability samples at predetermined temperatures and humidity, if applicable
        c. testing methods to be used, limits and test method validation
        d. retaining analytical results and supporting documentation (see additional guidance under C.02.021)

v. No subcontracting of any work should happen without written authorization.

## Packaging material testing

### C.02.016

(1) Each lot or batch of packaging material shall, prior to its use in the packaging of a drug, be examined or tested against the specifications for that packaging material.

(2) No lot or batch of packaging material shall be used in the packaging of a drug unless the lot or batch of packaging material complies with the specifications for that packaging material.

(3) The specifications referred to in subsections (1) and (2) shall

*(a)* be in writing;

*(b)* be acceptable to the Director who shall take into account the specifications contained in any publication mentioned in *Schedule B* to the *Act*; and

*(c)* be approved by the person in charge of the quality control department.

## Rationale

Drug quality is directly dependent on packaging quality. If a drug product is presented in an inadequate package, the entire effort put into research, product development and manufacturing control is wasted. In many cases (such as metered-dose aerosols or injectables), packaging quality is critical to the overall performance and effectiveness of the drug product. Faults in the packaging and labelling of a drug product continue to be a cause of drug recalls.

Packaging materials must be tested or examined to ensure they are of good quality before being used to package drugs.

## Interpretation

1. Ensure each packaging material used in the packaging/labelling of a drug is covered by specifications (as defined under C.02.002). These specifications must be approved and dated by the person in charge of your quality control department (or by a designated alternate who meets the requirements described under section C.02.006 “Personnel,” interpretation 1.d).
    a. In addition to the definition of specification described in C.02.002, specifications for any primary and printed packaging material should include (or provide reference to, if applicable):
        i. a description of materials, including:
            - the designated name and the internal code reference
            - the reference (if any) to a pharmocopeial monograph
            - the approved suppliers
            - a specimen of printed materials
        ii. qualitative and quantitative requirements with acceptance limits
        iii. storage conditions and precautions
2. Ensure specifications comply with current versions of the marketing authorization and a recognized pharmacopoeia. The adequacy of test or examination methods that are not of pharmacopoeial or equivalent status must be established and documented.
3. Identifying and choosing primary and printed packaging material vendors is an important operation. You should entrust this activity only to staff who have a particular and thorough knowledge of the materials and suppliers. Staff knowledge of materials should include an understanding of risk and the need to avoid potential leachables (e.g. 2-

mercaptobenzotiazole (MBT) in rubber stoppers for injectables, or methyl benzophenone and derivatives in label adhesives).

4. Only buy primary and printed packaging materials from approved suppliers listed in the relevant specification.

5. Only use packaging materials in packaging/labelling that have been released by your quality control department.

6. Segregate outdated or obsolete packaging material until its disposition.

7. The number of samples taken should be determined statistically and specified in a sampling plan. Ensure the sampling plan for packaging materials takes into account:
    a. the quantity received
    b. the level of quality required
    c. the nature of the material (e.g. primary packaging materials and/or printed packaging materials)
    d. the production methods used by the packaging material manufacturer
    e. your knowledge of the quality assurance system used by the packaging material manufacturer

8. Ensure sampling takes place in an appropriate environment and with precautions to prevent contamination where needed.

## C.02.017

(1) The examination or testing referred to in section C.02.016 shall be performed on a sample taken

*(a)* after receipt of each lot or batch of packaging material on the premises of the person who packages a drug; or

*(b)* subject to subsection (2), before receipt of each lot or batch of packaging material on the premises of the person who packages a drug, if

(i) that person

(A) has evidence satisfactory to the Director to demonstrate that packaging materials sold to him by the vendor of that lot or batch of packaging material are consistently manufactured in accordance with and consistently comply with the specifications for those

packaging materials; and

(B) undertakes periodic complete confirmatory examination or testing with a frequency satisfactory to the Director,

(ii) the packaging material has not been transported or stored under conditions that may affect its compliance with the specifications for that packaging material.

(2) After a lot or batch of packaging material is received on the premises of the person who packages a drug,

*(a)* the lot or batch of the packaging material shall be examined or tested for identity; and

*(b)* the labels shall be examined or tested in order to ensure that they comply with the specifications for those labels.

## Rationale

Section C.02.017 outlines options for when you may carry out the testing or examination outlined in section C.02.016. As with raw materials, buying packaging materials is an important operation that must involve staff who have thorough knowledge of the packaging materials and vendor.

Packaging materials must come only from vendors named in the relevant specifications. All aspects of the production and control of packaging materials should be discussed between the manufacturer and vendor. Particular attention should be paid to printed packaging materials. Labels must be examined or tested after the person who packages a drug receives them on their premises.

## Interpretation

1. The person who packages a drug must perform testing or examination on a sample of the packaging material taken after receipt on site (unless the vendor is certified).

   If you use a packaging material vendor certification program, it must be documented in a standard operating procedure. At a minimum, such a program should include the following:

   a. a written agreement outlining the specific responsibilities of each party involved, specifying:

i. all the tests to be performed by the vendor, along with the content and format of the certificate of analysis (which shows actual numerical results, if applicable, and makes reference to product specifications)

ii. that the vendor must inform the drug packager/labeller of any changes in the processing or specifications of the packaging material

iii. that the vendor must inform the drug packager/labeller of any critical deviations during the manufacturing of a particular batch of a packaging material

b. in lieu of a written agreement, an on-site audit of the vendor's facilities and controls, conducted by qualified personnel

i. The audit must ensure that all criteria described under interpretation 1.a are verified. Audits must be performed at an appropriate frequency, and the results documented.

c. an outline of how re-testing failures and any further re-qualification are to be addressed

d. a document issued for each vendor, verifying that the certification criteria have been met

i. Each document must be approved by the quality control department and updated at an appropriate frequency.

e. complete confirmatory examination or testing of a minimum of one lot each year per vendor for primary packaging material (with packaging material selected on a rotational basis)

i. Also, where multiple packaging materials are received from the same vendor, confirmatory testing must be carried out for each packaging material at least once every five years.

Generally, because of the nature of its operations, a broker or wholesaler of packaging materials cannot be directly certified. However, when a broker or wholesaler supplies materials that are received from the original vendor without changing the existing labels, packaging, certificate of analysis or general information, certification of the original source is still acceptable.

2. As long as the material is properly identified, you may use the lot of packaging material selected for confirmatory testing in packaging before completing that testing. Your quality control department must approve use before completing testing.

3. Ensure conditions of transportation and storage prevent changes to the characteristics of the packaging material. To show these conditions have been met, ensure standard operating procedures and records are available and contain the following:

a. the type of packaging to be used
b. labelling requirements
c. mode of transportation
d. the type of seal used on the package
e. the verification needed to ensure that the package has not been tampered with and that there are no damaged containers

4. Examine labels and other printed packaging materials after receipt on site. Pay special attention to cut labels due to the higher inherent risk of inadvertent mix-up with incorrect labels. Inspect these labels when you receive them using an appropriate method.

5. Conduct positive identification of all primary packaging materials after received on site. Identity testing may be performed on primary packaging materials using visual inspection, provided that the vendor is certified and a certificate of analysis is available.

6. If a delivery or shipment of packaging material is made up of different batches, each batch must be considered as separate for the purposes of sampling, testing and release.

## Finished product testing

### C.02.018

(1) Each lot or batch of a drug shall, before it is made available for further use in fabrication or for sale, be tested against the specifications for that drug.

(2) No lot or batch of a drug shall be made available for further use in fabrication or for sale unless it complies with the specifications for that drug.

(3) The specifications referred to in subsections (1) and (2) shall

*(a)* be in writing;

*(b)* be approved by the person in charge of the quality control department; and

*(c)* comply with the *Act* and these *Regulations*.

## Rationale

Finished product tests complement the controls used during the manufacturing process. Each fabricator, packager/labeller, distributor and importer must have proper specifications and test methods to help ensure that each drug sold is safe and meets the relevant standard.

## Interpretation

1. The person in charge of your quality control department (or a designated alternate who meets the requirements under section C.02.006 "Personnel," as applicable to the activity) must approve written specifications.
    a. In addition to the definition of specification described in C.02.002, specifications for any finished product should include (or provide reference to, if applicable):
        i. the designated name of the product and code reference (where applicable)
        ii. the master formula
        iii. a description of the dosage form and package details
        iv. the qualitative and quantitative requirements, with acceptance limits
        v. the storage conditions and any special handling requirements, where applicable
        vi. the shelf life
        vii. a description of the unique identifier used for identity testing (if applicable)
    b. Specifications must be equal to or exceed a recognized standard (as listed in Schedule B to the *Food and Drugs Act*) and must comply with the marketing authorization.

For more guidance when creating your specification, see *ICH Q6A: Specifications: Tests Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*.

    c. If a recognized pharmacopoeia (see Schedule B to the Act) contains a specification for microbial content, include that requirement.
    d. Also include suitable microbial quality acceptance criteria for the dosage form. Products with significant water content (e.g. creams, ointments, gels and oral liquids) are likely to support microbial growth. Such products should include tests and limits for microbial content in both the batch release and stability specifications. Drugs must be free from objectionable organisms.
    e. Include specifications for preservative content (if present in product formulation).

2. Validate test methods and document the results of any validation studies. Conduct method transfer studies when applicable.

   Since compendial methods cannot include all possible formulations of a drug product, you must demonstrate that the particular compendial method you are using applies to your specific formulation of a drug. You must show there is nothing in the product that interferes with the compendial method or affects the method's performance. You must also prove that the impurities that would be expected from the active ingredient route of synthesis or finished product formulation are detected by the compendial method.

For guidance on validating particular types of methods, see *ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology*, or any standard listed in Schedule B to the *Food and Drugs Act*.

3. Perform all tests according to the approved specifications. These tests may be carried out by the distributor/importer or by their contracted testing lab when a written agreement specifically excludes the fabricator from this obligation.

4. Quarantine any lot or batch of a drug that does not comply with specifications until final disposition. Do not make it available for sale.

## C.02.019

(1) A packager/labeller of a drug, a distributor referred to in paragraph C.01A.003(*b*) and an importer of a drug other than an active ingredient shall perform the finished product testing on a sample of the drug that is taken either

*(a)* after receipt of each lot or batch of the drug on their premises in Canada; or

*(b)* before receipt of each lot or batch of the drug on their premises in Canada if the following conditions are met:

(i) the packager/labeller, distributor or importer

(A) has evidence satisfactory to the Director to demonstrate that drugs sold to them by the vendor of that lot or batch are consistently manufactured in accordance with and consistently comply with the specifications for those drugs, and

(B) undertakes periodic complete confirmatory

testing, with a frequency satisfactory to the Director, and

(ii) the drug has not been transported or stored under conditions that may affect its compliance with the specifications for that drug.

(2) If the packager/labeller, distributor or importer receives a lot or batch of a drug on their premises in Canada the useful life of which is more than 30 days, the lot or batch shall be tested for identity and the packager/labeller shall confirm the identity after the lot or batch is packaged/labelled.

(3) Subsections (1) and (2) do not apply to a distributor if the drug is fabricated, packaged/labelled and tested in Canada by a person who holds an establishment licence that authorizes that activity.

(4) Subsections (1) and (2) do not apply to a distributor or importer if the drug is fabricated, packaged/labelled and tested in an MRA country at a recognized building and both of the following requirements are met:

*(a)* the address of the building is set out in their establishment licence; and

*(b)* they retain a copy of the batch certificate for each lot or batch of the drug that they receive.

## Rationale

Section C.02.019 outlines options for carrying out the testing required in section C.02.018. The options vary depending on the activities performed and the location where fabrication, packaging/labelling and testing occurs. Paragraph C.02.019(1)*(b)* outlines requirements you must meet as a packager/labeller, distributor or importer of a drug if the finished product testing is done before receipt on your site. Paragraphs C.02.019(3) and C.02.019(4) describe exemptions to finished product testing.

## Interpretation

1. If you are a packager/labeler – You must confirm identity after the lot or batch is packaged.

### Sites holding a Canadian establishment licence

2. If you are a distributor of drugs fabricated, packaged/labelled and tested at Canadian sites only – You only need to have a copy of the authentic certificate of analysis from the

licensed Canadian fabricator to show you comply with finished product specifications. This certificate must show actual numerical results and refer to the product specifications and validated test methods used. Re-testing, including identity testing, is not required.

### Sites recognized by a regulatory authority in an MRA country

3. **If you are an importer of drugs fabricated, packaged/labelled and tested at recognized buildings authorized by a regulatory authority and identified on your establishment licence** – You only need to have a batch certificate (in the format agreed on by the MRA partners in *International Harmonized Requirements for Batch Certification*) for each lot or batch of the drug received to show you comply with finished product specifications. Re-testing, including identity testing, is not required when the drug is fabricated, packaged/labelled and tested in an MRA country.

### Sites in non-MRA countries

4. **If you are a packager/labeller or importer** – You must meet the following conditions for testing (other than identity testing) if you choose to rely on test results provided by an establishment in a non-MRA country:

    a. You must have an ongoing certification program outlining the conditions under which test results can be relied upon from drugs fabricated, packaged/labelled or tested in non-MRA countries that are not recognized as members of the Pharmaceutical Inspection Co-operation Scheme (PIC/S). This certification program must include periodic on-site audits—relevant to the products being imported—that review overall site compliance and confirm adequacy of processes to ensure integrity of data. The audits should be performed by a person who meets the requirements of interpretation 1 under section C.02.006 "Personnel." In the absence of a certification program, you must test each batch.

To be able to rely on testing performed in foreign jurisdictions, importers need to have knowledge and evidence that suppliers operate with appropriate GMP compliance. This provides assurance that products are consistently manufactured according to their master documents, and consistently comply with the specifications for those drugs.

    b. Ensure each lot comes with a certificate of analysis. If the certificate of analysis contains results of tests performed by subcontractors, these results should be identified as such. A copy of the certificate of analysis from the lab that performed the analysis must be attached with contact information.

The certificate of analysis must show actual numerical results from all individual tests and refer to the product specifications and validated test methods used.

i. For terminally sterilized products, provide documented evidence to show each sterilizer load has been sampled appropriately from the potentially coolest part of the load and tested individually for sterility, unless subject to parametric release

ii. For aseptically filled products, evidence must show that samples tested for sterility included the first container filled, the last container filled, and those filled after any significant intervention or stoppage.

c. Ensure evidence is available to show that each lot or batch received has been transported and stored in a way that maintains the quality of the drug (see requirements described in interpretation 3, section C.02.015 “Quality Control Department”).

d. Conduct complete confirmatory testing periodically to verify that imported products consistently meet their specifications.

i. For products imported from sites in non-MRA countries that are members of the Pharmaceutical Inspection Co-operation Scheme (PIC/S): Perform a complete testing on at least one lot per year for each dosage form from each fabricator.

ii. For products imported from sites in non-MRA countries that are not recognized as members of PIC/S: Perform a complete testing on the first five lots of each product received from a fabricator, and at least one lot per year for each dosage form from each fabricator after that.

iii. For each dosage form, select products on a rotational basis. Where multiple drugs are received from the same fabricator, carry out confirmatory testing for each drug at least once every five years.

iv. Carry out confirmatory testing for each drug within one year of marketing the drug in Canada.

v. Ensure confirmatory testing is performed by an alternate lab. In exceptional circumstances (e.g. biologics), the original lab may perform confirmatory testing if justified.

vi. You do not need to conduct confirmatory testing for sterility, pyrogens, bacterial endotoxins, particulate matter or general safety (abnormal toxicity).

e. You may release for sale a lot or batch of the finished product selected for periodic confirmatory testing before all tests are completed if a specific identity test is performed and your quality control department approves.

5. If a non-MRA site fails to conform to finished product testing requirements, you must conduct an investigation of the extent of the non-compliance for all products received from the fabricator. This investigation may include:
    a. reassessment and re-testing of all dosage forms
    b. re-evaluation of GMP compliance
    c. additional complete confirmatory testing, based on the risk associated with the non-compliance

6. As a packager/labeller or importer, you must carry out positive identification on a sample of each lot or batch in a drug shipment after you receive it on your site. This identity testing requirement applies to lots received from **any** non-MRA site. Lab chemical/biological testing is required unless the dosage form has unique physical characteristics. You must perform all identification tests stated in a compendial monograph. Acceptable identity testing methods include the following:
    a. chemical testing
    b. biological testing
    c. physical verification, in cases where the product has unique identifiers
        i. The unique identifier principle must be applied before the final chemical or biological identity testing is performed by the fabricator or packager. Where only a portion of a lot is packaged/labelled for Canada, the identity testing must be performed after the unique identifier is applied on the Canadian labelled product.
        ii. For each product and each strength, uniqueness must be confirmed in writing by the fabricator or packager to the importer at least once a year, as well as whenever a change occurs. The written documentation must confirm that identity testing for each lot is performed after the unique identifier is applied. When no such confirmation can be obtained, chemical or biological identity testing will be required from the importer.
        iii. The unique identifier must be confirmed on the certificate of analysis for each lot received from the fabricator or packager.

Label review or examination of the shape and size of the container is not generally considered adequate identity testing.

        iv. The following unique identifiers are considered acceptable:
            - tablets and capsules that are engraved, embossed or printed with a unique logo

- permanent identification on the drug's closure system indicating the name and strength of the contents (this marking must be applied as part of a continuous filling process, and only where the closure cannot be removed without being destroyed)
- colour closure systems as part of a continuous filling process, if the fabricator uses a uniquely coloured cap or closure for only one product and strength
- a coloured vial (sometimes used for light-sensitive drugs), if it is unique to one product, strength and fabricator
- a dedicated facility fabricating only one product
- labelling, where pre-printed containers are issued to the filling line and where the lot number is either pre-printed or printed/crimped onto the package in a continuous process
- group 2 (biologic) products subject to Health Canada's lot release program

7. You may use process parametric release if it has been authorized on the product's marketing authorization. For more information, please see Health Canada's adopted *Guidance on Parametric Release – Pharmaceutical Inspection Co-Operation Scheme (PIC/S)*.

# Records

## C.02.020

(1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(*b*) and importer shall maintain all of the following records on their premises in Canada for each drug that they fabricate, package/label, distribute or import:

*(a)* Except in the case of an importer of an active pharmaceutical ingredient, master production documents for the drug;

*(b)* evidence that each lot or batch of the drug has been fabricated, packaged/labelled, tested and stored in accordance with the procedures described in the master production documents;

*(c)* evidence that the conditions under which the drug was fabricated, packaged/labelled, tested and stored are in compliance with the

requirements of this Division;

*(d)* evidence that establishes the period during which the drug in the container in which it is sold or made available for further use in fabrication will meet the specifications for that drug; and

*(e)* evidence that the finished product testing referred to in section C.02.018 was carried out, and the results of that testing.

(2) Every distributor referred to in paragraph C.01A.003(*b*) and importer shall make available to the Director, on request, the results of testing performed on raw materials and packaging/labelling materials for each lot or batch of drug that it distributes or imports.

(3) Every fabricator shall maintain on their premises written specifications for all raw materials and adequate evidence of the testing of those raw materials referred to in section C.02.009 and of the test results.

(4) Every person who packages a drug shall maintain on their premises written specifications for all packaging materials and adequate evidence of the examination or testing of those materials referred to in section C.02.016 and of any test results.

(5) Every fabricator, packager/labeller and tester shall maintain on their premises in Canada detailed plans and specifications of each building in Canada where they fabricate package/label or test drugs and a description of the design and construction of those buildings.

(6) Every fabricator, packager/labeller and tester shall maintain on their premises in Canada personnel records in respect of each person who is employed to supervise the fabrication, packaging/labelling and testing of drugs, including the person's title, responsibilities, qualifications, experience and training.

2029

## C.02.021

(1) All records and evidence on the fabrication, packaging/labelling, finished product testing referred to in section C.02.018 and storage of a drug in dosage form that are required to be maintained under this Division shall be retained for one year after the expiration date of the drug unless the person's establishment licence specifies some other period.

(2) Subject to subsection (4), all records and evidence of the fabrication, packaging/labelling, finished product testing referred to in section C.02.018 and storage of an active ingredient that are required to be maintained under this Division shall be retained in respect of each lot

or batch of the active ingredient for the following period unless the person holds an establishment licence that specifies some other period:

*(a)* in the case of an active ingredient that has a retest date, three years after the lot or batch has been completely distributed; and

*(b)* in any other case, one year after the expiration date of the lot or batch.

(3) Subject to subsection (4), all records and evidence of the raw material testing referred to in section C.02.009 and of the testing of packaging/labelling materials that are required to be maintained under this Division shall be retained for five years after the raw materials and packaging/labelling materials were last used in the fabrication or packaging/labelling of a drug unless the person's establishment licence specifies some other period.

(4) If a fabricator is required to maintain records and evidence in respect of the same active ingredient under subsections (2) and (3), they shall maintain them for the longest period that is applicable.

2030

## C.02.022

(1) Every wholesaler, distributor referred to in C.01A.003 and importer of a drug in dosage form shall retain records of sale of each lot or batch of the drug, which enable them to recall the lot or batch from the market, for one year after the expiration date of that lot or batch, unless their establishment licence specifies some other period.

(2) Every distributor of an active ingredient referred to in paragraph C.01A.003(*a*) and every wholesaler and importer of an active ingredient shall retain records of sale of each lot or batch of the active ingredient, which enable them to recall the lot or batch from the market, for the following period unless the person holds and establishment licence that specifies some other period:

*(a)* in the case an active ingredient that has a retest date, three years after the lot or batch has been completely distributed; or

*(b)* in any other case, one year after the expiration date of the lot or batch.

2031

## C.02.023

(1) On receipt of a complaint or any information respecting the quality of a drug or its deficiencies or hazards, every fabricator, packager/labeller, wholesaler, distributor referred to in paragraph C.01A.003 and importer of the drug shall make a record of the complaint or information that contains the following:

*(a)* the results of any investigation carried out under subsection C.02.015(2) and, if applicable, the corrective action taken; or

*(b)* the name and business address of the person in charge of the quality control department to whom the complaint or information was forwarded under subsection C.02.015(2.1) and the date on which it was forwarded.

(2) Records referred to in subsection (1) shall be retained for the following period unless the person holds an establishment licence that specifies some other period:

*(a)* in the case of a drug in dosage form, one year after the expiration date of the lot or batch of the drug; and

*(b)* in the case of an active ingredient,

(i) if the active ingredient has a retest date, three years after the lot or batch has been completely distributed, or

(ii) in any other case, one year after the expiration date of the lot or batch of the active ingredient.

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## C.02.024

(1) Every fabricator, packager/labeller, distributor referred to in section C.01A.003, importer and wholesaler shall

*(a)* maintain records of the results of the self-inspection program required by section C.02.012 and of any action taken in connection with that program; and

*(b)* retain those records for a period of at least three years.

(2) Every person who fabricates or packages/labels a drug shall

*(a)* maintain records on the operation of the sanitation program required to be implemented under section C.02.007; and

*(b)* retain those records for a period of at least three years.

## C.02.024.1

Every distributor of an active ingredient referred to in paragraph C.01A.003(*a*) and every fabricator, packager/labeller, wholesaler and importer of an active ingredient shall add all of the following information to the documentation that accompanies the active ingredient, immediately after any like information that has been added by another person:

*(a)* their establishment licence number, or if there is none, their name, address, telephone number, fax number and email address;

*(b)* an indication whether they have fabricated, packaged/labelled, wholesaled, distributed or imported the active ingredient and the date on which that activity was carried out;

*(c)* the expiration date; and

*(d)* the lot number.

### Rationale

Good documentation is a key part of a pharmaceutical quality system and promotes compliance with GMP requirements. Documentation may exist in a variety of forms, including paper-based, electronic or photographic media.

The various types of documents and media used should be fully defined in the pharmaceutical quality system. The documentation system's main objective must be to establish, control, monitor and record all activities which directly or indirectly impact all aspects of the quality of drugs. This includes information from all stages of the product lifecycle, and all records related to the quality of drug products.

Records must be reliable, complete, consistent and accurate.

You must establish a data governance plan to ensure controls are in place to prevent and detect data integrity issues throughout the product lifecycle. This includes:

- having policies and standard operating procedures that clearly indicate management's expectations for how data should be acquired, modified, reviewed and stored
- validating and maintaining equipment and associated computer systems

- overseeing the preventative measures put in place, to verify their implementation and effectiveness

These are standard principles under a pharmaceutical quality system, regardless of the media used (e.g. paper records or electronic records).

## Interpretation

1. You must make any documentation requested by Health Canada for evaluation available in one of the official languages.

2. You must have all documents required under Division 2 of the Food and Drug Regulations on site and maintained at the locations in Canada that are identified in your establishment licence.

3. You must have standard operating procedures (SOPs) available that describe all phases of your company's operation and how you will comply with GMP requirements.
    a. Make SOPs readily available to all required personnel.
    b. Keep SOPs up-to-date and ensure they accurately reflect all requirements and practices. Establish a system of regular review to ensure qualified personnel are reviewing SOPs on a regular basis.
    c. Establish a formal system to review and approve changes to SOPs. Document the reasons for SOP revisions.
    d. Put systems in place to ensure only current SOPs are in use.

4. Your quality control department must approve, sign and date all relevant SOPs and GMP documents (such as records of actions taken or conclusions reached). They must also approve, sign and date any changes to documents. Any change to a document must still allow the original information to be read. Where appropriate, record the reason for the change.

5. You should establish a data governance plan to ensure data integrity is maintained for all records required under GMP, including production and lab records. The general principles of good documentation practices are applicable to the management of records regardless of media (e.g. paper records or electronic records), throughout its lifecycle from the time data is first generated and any modifications made thereafter.
    a. Records should be traceable to the source the record was generated from. This can be achieved by using techniques such as initials/signatures, secure user identification, and change history/audit trails to capture relevant information (e.g.

processing parameters, method settings, acquisition details, or reasons for changes/reprocessing).

b. Records should be legible, with no parts of the data obscured or removed. If archived, they must be retrievable in a timely way. Any changes to records must also be documented and traceable.

c. Data should be recorded, documented or saved at the time it is generated, with reliable evidence that this was done.

d. Records must be maintained in an original format as an original record, or as a true copy which has undergone a qualified conversion process that maintains data integrity.

e. Records must be generated and maintained under the oversight of a pharmaceutical quality system that ensures their accuracy.

6. If you use an electronic system to create, modify or store records required under these regulations, you should validate the system for its intended use.

    a. Ensure all access and user rights in electronic systems are properly controlled to prevent system users from compromising data integrity.

    b. Control electronic records in a way that ensures the records:

        i. can only be created and modified by authorized personnel

        ii. are protected against intentional or accidental deletion

        iii. are named and organized in a way that allows for easy traceability

        iv. are tracked through an audit trail when created or modified (the audit trail should include changes made to the record, who made the change, the time and date the record was changed and, if applicable, the reason the record was modified)

        v. are backed up at regular intervals to protect against potential data loss due to system issues or data corruption

        vi. are available for review during an inspection and are readily retrievable in a suitable format

        vii. include all necessary metadata

7. An electronic signature is an acceptable alternative to a handwritten signature. Ensure appropriate controls are in place for electronic signatures, including:

    a. Validate electronic signature systems to show that the systems are suitably secure and reliable (and document this validation).

    b. You should have a procedure for the creation of electronic signatures. Put controls in place to ensure the uniqueness of all electronic signatures.

c. Ensure all electronic signatures include a time and date stamp and are subject to audit trail requirements.

d. Inform users that electronic signatures are considered an equivalent to hand-written signatures. Keep records to show that users are aware of their responsibilities and accountability relating to the use of electronic signatures.

8. If you are a fabricator, packager/labeller, distributor (as described in paragraph C.01A.003*(b)*) or importer of a drug, you must maintain the following documents:

a. master production documents (as defined in Appendix A – Glossary)

i. When the fabricator is located in Canada, specific parts of a master production document considered to be a trade secret or confidential may be held by the fabricator rather than the distributor. When the fabricator is located outside Canada, specific parts of a master production document considered to be a trade secret or confidential may be held on behalf of the distributor or importer by an independent party in Canada. In either case, the distributor or importer must ensure that Health Canada has access to the data in a timely way.

ii. Regardless of whether the fabricator is Canadian or foreign, the master production documents retained by the distributor or importer must describe in general terms whatever information has been deleted as a trade secret or confidential.

It is not considered acceptable to withhold entire pages of master production documents from distributors or importers. You should be able to defend any information withheld as being confidential or a trade secret. Some examples of confidential or trade secret information could include quantities of raw materials, or sensitive parameters associated with a process.

The objective is to allow an importer or distributor to perform a reasonable assessment of the information and to provide assurance of adequate control.

b. evidence that each lot or batch of the drug has been fabricated, packaged/labelled, tested and stored according to the procedures described in the master production documents

i. Fabricators must have complete records of all manufacturing activities, including executed batch documentation and release information (e.g. certificates of analysis and associated records) for raw materials and drugs in dosage form.

ii. Packagers must have complete records of all packaging activities, including executed packaging documentation and release information (e.g. certificates

of analysis and associated records) for packaging materials. Records of finished product checks should also be maintained.

iii. Testing laboratories must maintain records that tests were conducted according to required methods, as well as the certificates of analysis issued.

iv. Distributors and importers must have evidence that batches were fabricated, packaged/labelled and tested according to the master production documents and marketing authorization.

- This evidence may include all executed production documents. Test results for raw materials and packaging materials only need to be made available on request in a timely way.
- For distributors, a certificate of manufacture is considered an acceptable alternative to complete batch documentation, provided that complete documentation is made available in a timely way.
- For MRA importers, a copy of the batch certificate will fulfill requirements for evidence, provided there is confirmation from the MRA fabricator and packager/labeller of the current revision of master production documents.
- For a non-MRA importer, systems involving the release of product based on certificate of manufacture and analysis review will fulfill requirements, provided that complete documentation is obtained and reviewed at least once a year per drug.

A certificate of manufacture alone cannot be used when reworking has taken place.

For any changes to production documents, complete documentation must be provided to the importer or distributor, with indication of any changes made.

c. evidence that the conditions under which the drug was fabricated, packaged/labelled, tested and stored comply with the requirements of Part C, Division 2 of the Regulations

i. Fabricators, packagers/labellers and testers must have full records on site showing that their respective manufacturing, packaging and testing processes have been validated. This includes (but is not limited to) the validation master plan, cleaning validation, test method validation, and the qualification of utilities, support systems and equipment.

ii. Distributors of products fabricated, packaged/labelled and tested in Canada must have a copy on site of the drug establishment licence for the fabricator,

packager/labeller and tester. Distributors must have access to process validation information in 8 (c)(i). When complete process validation information is not available at the fabricator's site, this information must be available at the distributor.

iii. MRA importers must have the fabricator, packager/labeller and testing sites listed on the foreign site annex of their establishment licence.

iv. Non-MRA importers must have:

- the fabricator, packager/labeller and tester identified on the foreign site annex of their establishment licence
- for terminally sterilized products, summaries of re-qualification of sterilization processes
- for aseptically filled products, summaries of ongoing aseptic process simulation studies (media fills)
- product-specific process validation for all critical steps of the manufacturing process, including:
    - the validation approach used by the fabricator (prospective or concurrent)
    - the reference numbers and dates of approval for the master formula (including packaging, the process validation protocol, the process validation study, and the validation of the test methods)
    - the lot number involved and dates of completion of these studies
    - a copy of the approved conclusions from product validation studies

Upon request, copies of complete protocols and related studies for all validation activities must be made available for review on the importer's site.

d. evidence establishing the period of time during which the drug—in the container in which it is sold—will meet the specifications for that drug

i. The documentation to be maintained must include: the written stability program, the data generated according to that program, and the conclusions leading to the establishment of the time period.

ii. Data generated as part of the continuing stability program must also be included.

e. evidence of compliance with finished product specifications for each lot of drug in dosage form

9. If you are a fabricator, packager/labeller, distributor, wholesaler or importer of a drug, you must maintain the following documents (as they relate to all operations in Canada):

    a. distribution records of all drug sales, including professional samples

        i. Keep records of all sales readily accessible in a way that allows a complete and rapid recall of any lot or batch of a drug. (This requirement does not necessarily require tracking by lot number.)

        ii. Keep records to show that all customers who received a recalled drug were notified.

    b. records of the results of your self-inspection program, evaluation and conclusions, and corrective measures implemented

10. If you are a fabricator, packager/labeller, distributor, wholesaler or importer of a drug, you must maintain the following documents:

    a. records of complaints or any information about the quality of a drug or its deficiencies or hazards

    b. follow-up investigations, including corrective actions taken

11. If you are a fabricator, you must maintain the following documents:

    a. the written specifications for the raw materials

    b. the results of raw material testing

    c. the sources of the raw materials supplied

    d. records about the operation of the sanitation program required by section C.02.007 “Sanitation”

    e. detailed plans and specifications for each building where fabrication occurs, including a description of the design and construction

12. If you package or label a drug, you must maintain the following documents:

    a. the written specifications for the packaging materials

    b. the results of packaging material examinations or testing

    c. the sources of the packaging materials supplied

    d. records about the operation of the sanitation program required by section C.02.007 “Sanitation”

13. Maintain records of all personnel employed in GMP activities, including:

    a. organization charts

b. each person's title, job description, responsibilities, qualifications, experience and training

c. the name(s) of each person's designated alternate(s)

14. Retain records required under sections C.02.021(1), C.02.022, and C.02.023 "Records" either:

a. for a period of at least one year past the expiration date of the drug the records apply to, or

b. for records and evidence on the testing of raw materials and packaging/labelling materials – for a period of at least five years after the materials were last used to fabricate or package/label a drug (unless otherwise specified in your establishment licence)

## Samples

### C.02.025

(1) Every distributor referred to in paragraph C.01A.003(b) and importer of a drug in dosage form shall retain in Canada a sample of each lot or batch of the packaged/labelled drug for one year after the expiration date of the drug unless their establishment licence specifies some other period.

(2) Subject to subsection (4), the fabricator of a drug in dosage form shall retain a sample of each lot or batch of raw materials used in the fabrication for two years after the materials were last used in the fabrication unless their establishment licence specifies some other period.

(3) Subject to subsection (4), the fabricator of an active ingredient shall retain a sample of each lot or batch of it for the following period unless their establishment licence specifies some other period:

*(a)* in the case of an active ingredient that has a retest date, three years after the lot or batch has been completely distributed; or

*(b)* in any other case, one year after the expiration date of the lot or batch.

(4) If a fabricator is required to maintain samples in respect of the same active ingredient under subsections (2) and (3), they shall maintain them for the longest period that is applicable.

## C.02.026

The samples referred to in section C.02.025 shall be in an amount that is sufficient to determine whether the drug or raw material complies with the specifications for that drug or raw material.

### Rationale

These requirements help ensure that, if a product quality concern arises, your establishment and Health Canada have ready access to samples for re-examination.

Retention samples serve as a record of the batch of finished product or raw material. They can be assessed in the event that concerns arise with a finished product or raw material batch during the shelf life of a product (e.g. a quality complaint, a query relating to compliance with the marketing authorization, a labelling/packaging query, or a pharmacovigilance report).

In general, retention samples should be available for two reasons:

1. analytical testing samples – samples of a batch of raw material or finished product which are stored for the purpose of being analyzed, should the need arise during the shelf life of the batch concerned

2. specimen samples – samples of fully packaged units from a batch of finished product that are stored for identification and inspection purposes (e.g. for review of labelling, patient information leaflet, batch number, expiry date), should the need arise during the shelf life of the batch concerned

### Interpretation

1. If you are a distributor (as described in paragraph C.01A.003*(b)*) or an importer of a drug, you must retain in Canada a sample of each lot or batch of a finished product.
    a. Keep retention samples in their trade package, or in a container that is equivalent with respect to stability. In the case of large containers of finished products, you may retain a smaller representative sample, as supported by stability data. This allowance does not apply to sterile products.
    b. Store retention samples under the conditions listed on the label.
    c. You may store retention samples at another Canadian site if you have a written agreement clearly describing the respective responsibilities of each party.

2. If you are the fabricator of a drug, you must retain a sample of each lot or batch of a raw material (including both active and inactive ingredients).

    a. Store the sample in the same packaging system the raw material is stored in, or in one that is equivalent to or more protective than the vendor's packaging system of the raw material.

    b. Store the sample under the conditions recommended by the vendor.

    c. Take retention samples of bulk raw materials (i.e. materials stored in bulk tanks) before mixing the raw material lot with other raw material lots in the storage tanks.

3. Manage retention samples according to written procedures. Maintain records of traceability for retention samples and ensure they are available for review.

4. Take enough retention samples to allow duplicate testing according to finished product specifications. This will allow both Health Canada and the fabricator, importer or distributor to conduct testing.

    a. This requirement does not apply to the number of units normally required for sterility and pyrogen testing, or to water, solvents and medical gases.

    b. Where a batch is packaged in two or more distinct packaging operations, at least one retention sample should be taken from each individual packaging operation (to allow an assessment of the actual packaging operation, should the need to inspect specimen samples arise).

    c. If secondary packaging is opened (for example, to replace a carton or patient information leaflet), a minimum of one retention sample per packaging operation containing the product must be taken, since there is a risk of product mix-up during the packaging process.

5. Ensure that required analytical materials and equipment are available or readily attainable in order to carry out all required tests listed in the specifications during the retention period for a raw material, intermediate material or finished product. (This is of special concern in the event of a product discontinuation and/or closure of a fabrication facility or testing lab.)

6. Health Canada will consider alternate sample retention sites outside of Canada for distributors and importers of pharmaceutical, radiopharmaceutical, biological and veterinary drugs (as referred to in sub-section C.02.025(1)) if a product-specific request is submitted. For more information, see *Alternate Sample Retention Site Guidelines (GUI-0014)*.

# Stability

## C.02.027

(1) Every distributor referred to in paragraph C.01A.003(*b*) and importer of a drug in dosage form shall establish the period during which each drug in the package in which it is sold will comply with the specifications for that drug.

(2) Every fabricator and importer of an active ingredient shall establish the period during which each drug in the package in which it is sold will comply with the specifications for that drug.

### Rationale

A written stability program determines the established shelf life of a drug product under recommended storage conditions. Each packaged dosage form and strength must be covered by relevant data to support its shelf life in approved packaging material types and configurations for commercial sale.

The requirements for stability studies (primary and commitment batches) are outlined in various Health Canada, ICH and VICH guidelines. Accelerated and long-term storage conditions are described in:

- *ICH Q1A(R2): Stability Testing of New Drug Substances and Products*
- *Stability Testing of Existing Drug Substances and Products*
- *ICH Q1E: Evaluation for Stability Data.*

### Interpretation

1. You must determine the stability of a drug product before marketing, and before adopting any significant changes in formulation, fabrication procedures or packaging materials that may impact the quality of the drug product over its shelf life. You should make this determination according to Health Canada and ICH or VICH guidelines.

2. Fulfill commitments described in stability protocols—sent in premarket submissions or submissions to support post-NOC (notice of compliance) changes—to establish or confirm the approved shelf life for batches.

3. Enrol at least three commercial-scale batches of each strength and approved packaging material type and configuration in the stability program to confirm shelf life. For new drugs, these would be commitment batches.

4. You may apply bracketing and matrixing designs if justified and if you document the rationale, as described in *ICH Q1D: Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products*.

5. Consider including in your finished product stability program batches that have been stored at the limits of extended hold times (e.g. greater than one month) for intermediates and finished products before packaging.

6. Ensure stability studies include testing of parameters that are prone to change during storage and are likely to influence drug product quality. Testing should cover (as appropriate) potency, impurities, performance indicating tests, and the physical characteristics of the product (see Charts 2.1, 2.2 and 2.3).

For guidance on release, shelf life specifications and qualification of impurities:

- *ICH Q3A (R2): Impurities in New Drug Substances*
- *ICH Q3B (R2): Impurities in New Drug Products*
- *ICH Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- *ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

7. Perform antimicrobial preservative effectiveness testing during the product development phase to establish the minimal effective level of preservatives. Also, test a single commercial-scale stability or regular production batch of the drug for antimicrobial preservative effectiveness at the end of the proposed shelf life. Once you have determined the minimal effective preservative level, you must verify preservative content in the stability program—at minimum—at the initial time point and at the expiry date.

8. Ensure stability data are available for drug products before and after constitution, reconstitution or dilution (if applicable).

9. Ensure analytical test procedures used to evaluate stability are validated according to ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology. Assays must be stability-indicating (i.e. specific enough to detect and quantify degradation products and

distinguish between degraded and non-degraded materials). Include limits for individual specified, unspecified and total degradation products.

10. Ensure shelf life is assigned according to ICH Q1E: Evaluation of Stability Data. Verify shelf life using additional long-term stability data, as these data become available.

11. Establish the shelf life based on the drug product stability data. Assign shelf life from the date of fabrication, unless the marketing authorization says otherwise.

12. For imported products, stability studies from foreign sites are acceptable if the data meet Health Canada, ICH and VICH guidelines for stability, and if the site can show GMP compliance. The importer/distributor's responsible quality function should ensure study protocols comply with the marketing authorization. They must also review, update and maintain the stability results.

13. Ensure initial stability data and justification is available for reworked lots before their release for sale. Enrol reworked lots into the continuing stability program.

## Checklists – Stability

Use these stability charts to help you choose parameters to study in your stability program. They should be used as a guide only. Examine each product separately.

Chart 2.1: Potency

| | Tablets | Capsules | Liquids & Gels | Ointments & Creams | Powders | Parenterals | Suppositories | Aerosols |
|---|---|---|---|---|---|---|---|---|
| Assay all active ingredients | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Preservative content (antimicrobial, antioxidant agents) | | | ✔ | ✔ | | ✔ | | |
| Complete testing data on reconstituted forms | | | | | ✔ | | | |
| Quantity delivered per spray for metered dose products | | | | | | | | ✔ |

2370 This chart will help you choose potency parameters to study in your stability program.

Chart 2.2: Physical characteristics

| | Tablets | Capsules | Liquids & Gels | Ointments & Creams | Powders | Parenterals | Suppositories | Aerosols |
|---|---|---|---|---|---|---|---|---|
| Containers | | | | | | | | |
| Appearance of inner walls and cap interiors colour | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Integrity of seals | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Appearance and adhesion of label | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Finished products | | | | | | | | |
| Appearance | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Colour | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Dissolution | ✔ | ✔ | | | | | | |
| Disintegration | ✔ | ✔ | | | | | | |
| Odour | ✔ | | ✔ | ✔ | ✔ | | | |
| Hardness | ✔ | | | | | | | |

Chart 2.2: Physical characteristics

| | Tablets | Capsules | Liquids & Gels | Ointments & Creams | Powders | Parenterals | Suppositories | Aerosols |
|---|---|---|---|---|---|---|---|---|
| Condition of shells | | ✔ | | | | | | |
| Clarity/clarity of solution | | | ✔ | | ✔ | ✔ | | |
| Viscosity | | | ✔ | ✔ | | ✔ | | |
| Specific gravity | | | ✔ | | | ✔ | | |
| pH | | | ✔ | ✔ | | ✔ | | |
| Precipitation of ingredients | | | ✔ | ✔ | | ✔ | | |
| Non-homogeneity of suspensions | | | ✔ | | | | | |
| Homogeneity | | | ✔ | ✔ | ✔ | | ✔ | |
| Texture | | | | ✔ | ✔ | | | |
| pH (after reconstitution) | | | | | ✔ | | | |
| Particle size | | | | | ✔ | | | |
| Flow characteristics (inhalation powder) | | | | | ✔ | | | |
| Particulate matter | | | | | | ✔ | | |
| Optical rotation | | | | | | ✔ | | |
| Multiple dose vial: product integrity after maximum number of punctures | | | | | | ✔ | | |
| Melting point | | | | | | | ✔ | |
| Net weight | | | | | | | | ✔ |
| Delivery weight/volume | | | | | | ✔ | | ✔ |
| Delivery pressure | | | | | | | | ✔ |
| Delivery effectiveness (e.g. spray pattern & droplet size) | | | | | | | | ✔ |
| Number of doses or sprays per package | | | | | | | | ✔ |

2371 This chart will help you choose physical characteristics to study in your stability program.

2372

Chart 2.3: Purity

| | Tablets | Capsules | Liquids & Gels | Ointments & Creams | Powders | Parenterals | Suppositories | Aerosols |
|---|---|---|---|---|---|---|---|---|
| Containers | | | | | | | | |
| Migration of drug into plastic | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Migration of plasticisers into drug | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Corrosion (if applicable) | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Finished Products | | | | | | | | |
| Microbial test | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Endotoxins | | | | | | ✔ | | |
| Degradation products | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Moisture content | ✔ | ✔ | | | ✔ | | | |
| Sterility for ophthalmics | | | ✔ | ✔ | | | | |
| Particulate matter for ophthalmics | | | ✔ | ✔ | | | | |
| Sterility | | | | | | ✔ | | |

2373 This chart will help you choose purity parameters to study in your stability program.

2374 ## C.02.028

(1) Every distributor referred to in paragraph C.01A.003(*b*) and importer of a drug in dosage form shall monitor, by means of a continuing program, the stability of the drug in the package in which it is sold.

(2) Every fabricator and importer of an active ingredient shall monitor, by means of a continuing program, the stability of the drug in the package in which it is sold.

2375 ### Rationale

2376 A written continuing stability program monitors a drug product over its shelf life and provides
2377 evidence that the product will remain within specifications under the recommended storage

conditions. Each strength and packaged dosage form must be covered by relevant data to support its labelled expiry date in its trade package.

## Interpretation

1. Implement a continuing stability program to ensure drug products comply with approved shelf life specifications. Ensure a protocol is available and implemented for each drug marketed in Canada. Prepare a summary of all the data generated, including the evaluation and conclusions of the study.

   Your stability study protocol should include (but is not limited to) the following parameters:

   a. reference to the manufacturing master formula and packaging master formula
   b. number of batch(es) per strength and batch sizes
   c. packaging size (i.e. container format, fill volume or configurations)
   d. relevant physical, chemical, microbiological or biological test methods
   e. test method and acceptance criteria
   f. container closure system(s)
   g. testing frequency
   h. storage conditions (and tolerances) of samples
   i. orientation of samples (e.g. upright, inverted, horizontal), reflective of the worst-case scenario
   j. other applicable parameters specific to the drug

2. Scientifically justify any differences in the continuing stability program protocol and the commitment stability protocol.

3. Enrol a minimum of one batch of every drug strength and container closure system into your continuing stability program each year the drug is produced. Consider packaging size in your choice of batches to be enrolled. You may apply the principle of bracketing and matrixing designs if justified according to ICH Q1A(R2): Stability Testing of New Drug Substances and Products.

4. For long-term stability studies, ensure testing is performed often enough to establish the stability profile of the drug product. Ensure testing frequency complies with the marketing authorization.

5. For drugs with an established shelf life and consistent historical stability profile, conduct testing at least every year, with a minimum of five time points (including the initial and final time points).

6. Address worst-case scenarios (e.g. reworked or reprocessed lots), and include these lots in the continuing stability program.

7. Assess any confirmed out-of-specification (OOS) result, borderline result or significant atypical trend that may have an impact on the quality of the product. Such cases may require further actions (e.g. further stability studies, an increase in testing frequency or change in shelf life). Consider the impact on all batches available on the market.

8. For imported products, you may use stability studies from foreign sites if the data and protocol fulfill requirements of the marketing authorization and Health Canada/ICH/VICH guidelines for stability, and if the site can show GMP compliance.

It is your responsibility as an importer or distributor to obtain, maintain and review up-to-date records related to the continuing stability program.

9. For sterile products, include in your stability protocol confirmation of sterility at the initial time point and at expiry. Demonstration of container closure integrity at end of shelf life is an acceptable alternative to sterility testing.

10. Ensure stability protocols for multi-dose sterile products include an evaluation of stability during the in-use period.

11. Ensure stability protocols consider evaluation of stability for drug products before and after constitution, reconstitution or dilution (if applicable).

12. For drugs with a preservative, you must verify preservative content in the continuing stability program—at minimum—at the initial time point and at the expiry date.

# Sterile products

## C.02.029

In addition to the other requirements of this Division, a drug that is intended to be sterile shall be fabricated and packaged/labelled

*(a)* in separate and enclosed areas;

*(b)* under the supervision of personnel trained in microbiology; and

*(c)* by a method scientifically proven to ensure sterility.

### Rationale

The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination and particulate and pyrogen contamination. A lot depends on the skill, training and attitudes of the personnel involved. Quality assurance is particularly important. This type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. You must not rely only on a terminal process or finished product test for sterility or other quality aspects.

Health Canada is an active participating member of the Pharmaceutical Inspection Cooperation Scheme (PIC/S). In working towards international harmonization, Health Canada has adopted interpretations to support the manufacture of sterile drugs from those published by PIC/S. Expectations aligned with PIC/S are described in Health Canada's guidance document *Annex 1 to the* Good manufacturing practices guide – *Manufacture of sterile drugs (GUI-0119)*. Future revisions adopted by PIC/S will be reflected by Health Canada in that guidance document.

### Interpretation

Interpretations to fulfill expectations under C.02.029 are described in a separate guidance document: *Annex 1 to the* Good manufacturing practices guide – *Manufacture of sterile drugs (GUI-0119)*.

# Medical gases

## C.02.030

The provisions of C.02.025, C.02.027, and C.02.028 do not apply to medical gases.

Sections C.02.026 and C.02.029 also do not apply to medical gases.

For more on GMP requirements for medical gases, please see: *Good Manufacturing Practices Guidelines for Medical Gases (GUI-0031)*.

# Appendices

## Appendix A – Glossary

The former Appendix A: “Content of Fabricator’s/Manufacturer’s Batch Certificate for Drug/Medicinal Products Exported to Countries under the Scope of a Mutual Recognition Agreement” has been removed. It has been delinked from this guidance.

Only the definition of “batch certificate” still references the *International Harmonized Requirements for Batch Certification* (which replaces Appendix A).

### Acronyms

API: Active pharmaceutical ingredient

GMP: Good manufacturing practices

ICH: International Council for Harmonisation

MRA: Mutual recognition agreement

NOC: Notice of compliance

OOS: Out of specification

PIC/S: Pharmaceutical Inspection Cooperation/Scheme

SOP: Standard operating procedure

VICH: Veterinary International Council on Harmonisation

WHO: World Health Organization

# Terms

These definitions explain how terms are used in this document, as well as in the annexes (unless otherwise specified). Definitions cited directly from other documents are noted in brackets at the end of the definition.

If there is a conflict with a definition in the *Food and Drugs Act* or Food and Drug Regulations, the definition in the Act/Regulations prevails.

**Active ingredient –** "A drug that, when used as a raw material in the fabrication of a drug in dosage form, provides its intended effect." (C01A.001 (1))

**Active pharmaceutical ingredient** – "An active ingredient that is used in the fabrication of a pharmaceutical." (C.01A.001(1))

**Airlock** – An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods. (PIC/S)

**Alternate sample retention (ASR) site** – An alternate site specified on a Drug Establishment Licence for the storage of samples pursuant to section C.02.025 (1) of the Food and Drug Regulations.

**Aseptic process** – A process for compounding and assembling sterile bulk drugs or raw materials with sterile packaging components under Grade A or B conditions to produce a sterile product (see table in *Annex 1 to the* Good manufacturing practices guide – *Manufacture of sterile drugs (GUI-0119*).

**Audit trail –** GMP audit trails are metadata that are a record of GMP critical information (for example the change or deletion of GMP relevant data), which permit the reconstruction of GMP activities. (MHRA)

An audit trail is a process that captures details such as additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or over-writing the original record. An audit trail facilitates the reconstruction of the history of such events relating to the record regardless of its media, including the "who, what, when and why" of the action. For example, in a paper record, an audit trail of a change would be documented via a single-line cross-out that allows the original entry to be legible and documents the initials of the person making the change, the date of the change and the reason for the change, as required to

substantiate and justify the change. Whereas, in electronic records, secure, computer-generated, time-stamped audit trails at both the system and record level should allow for reconstruction of the course of events relating to the creation, modification and deletion of electronic data. Computer-generated audit trails shall retain the original entry and document the user ID, time/date stamp of the action, as well as a reason for the action, as required to substantiate and justify the action. Computer-generated audit trails may include discrete event logs, history files, database queries or reports or other mechanisms that display events related to the computerized system, specific electronic records or specific data contained within the record. (WHO draft)

**Batch** (or lot) – A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. (ICH Q7)

**Batch certificate** – "A certificate issued by the fabricator of a lot or batch of a drug that is exported within the framework of a mutual recognition agreement and in which the fabricator

*(a)* identifies the master production document for the drug and certifies that the lot or batch has been fabricated, packaged/labelled and tested in accordance with the procedures described in that document;

*(b)* provides a detailed description of the drug, including

(i) a statement of all properties and qualities of the drug, including the identity, potency and purity of the drug, and

(ii) a statement of tolerances for the properties and qualities of the drug;

*(c)* identifies the analytical methods used in testing the lot or batch and provides details of the analytical results obtained;

*(d)* sets out the addresses of the buildings at which the lot or batch was fabricated, packaged/labelled and tested; and

*(e)* certifies that the lot or batch was fabricated, packaged/labelled and tested in accordance with the good manufacturing practices of the regulatory authority that has recognized those buildings as meeting its good manufacturing practices standard." (C.01A.001)

A batch certificate's content is also described in Health Canada's *International Harmonized Requirements for Batch Certification*.

**Batch number** – (See lot number)

**Biological drug** – As defined in Division 4 of the FDR "drug" means a drug that is listed in Schedule D to the Act that is in dosage form or a drug that is an active ingredient that can be used in the preparation of a drug listed in that Schedule. (C.04.001)

**Bracketing** – "The design of a stability schedule such that only samples on the extremes of certain design factors (e.g. strength, package size) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g. for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different sized capsule shells). Bracketing can be applied to different container sizes or to different fills in the same container closure system." (ICH, Q1AR)

**Bulk drug** – A drug in dosage form that is not in its final packaging, usually in quantities larger than the largest commercially available package size.

**Bulk process intermediate** – "An active ingredient that is used in the fabrication of either a drug of biological origin that is listed in Schedule C to the Act or a drug that is listed in Schedule D to the Act." (C01A.001(1))

**Campaign production** "Manufacturing a series of batches of the same product in sequence in a given period of time and/or maximum number of batches followed by an appropriate (validated) cleaning procedure." (TGA, Q&As)

**Certificate of analysis (C of A)** – A document containing the name and address of the lab performing the test(s), name and specifications of the material(s), test(s) performed, test method(s) used, actual numerical results, approval date(s), signature of approver, and any other technical information deemed necessary for its proper use.

**Certificate of manufacture** – A document issued by a vendor to a distributor or importer that attests that a specific lot or batch of drug has been produced in accordance with its master production documents. Such certificates include a detailed summary of current batch documentation, with reference to respective dates of revision, manufacture, and packaging, and are signed and dated by the vendor's quality control department. For drugs that are fabricated, packaged/labelled and tested in MRA countries, the batch certificate is considered to be equivalent.

**Change control** – A written procedure that describes the action to be taken if a change is proposed *(a)* to facilities, materials, equipment, and/or processes used in the fabrication, packaging, and testing of drugs, or *(b)* that may affect the operation of the quality or support system.

**Changeover procedure** – A logical series of validated steps that ensures the proper cleaning of suites and equipment before the processing of a different product begins.

**Clean area** – "An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area." (PIC/S)

**Commitment batches** – "Production batches of a drug product for which the stability studies are initiated or completed post approval through a commitment made in the registration application." (ICH Q1A (R2))

**Computerized systems** – All the components necessary to capture, process, transfer, store, display and manage information, including (but not limited to) hardware, software, personnel and documentation.

**Containment** – The action of confining a chemical or biological agent or other entity within a defined space.

Primary containment: A system of containment which prevents the escape of a substance into the immediate working environment. It involves the use of closed containers or safety biological cabinets along with secure operating procedures.

Secondary containment: A system of containment which prevents the escape of a substance into the external environment or into other working areas. It involves the use of rooms with specially designed air handling, the existence of airlocks and/or sterilizers for the exit of materials and secure operating procedures. In many cases it may add to the effectiveness of primary containment. (Adapted from PIC/S)

**Contractor** – A legal entity that carries out activities on behalf of a company according to a written agreement. This includes other sites within the same corporate structure.

**Critical process** – A process that if not properly controlled may cause significant variation in the quality of the finished product.

**Data** – Data means all original records and certified true copies of original records, including source data and metadata and all subsequent transformations and reports of this data, which are recorded at the time of the activity and allow full and complete reconstruction and evaluation of the activity. (Adapted from WHO draft)

**Data governance plan** – A plan that outlines the sum total of arrangements to ensure that data, irrespective of the format in which it is generated, is recorded, processed, retained and used to

ensure a complete, consistent and accurate record throughout the data lifecycle. (MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015)

**Data integrity** – The extent to which all data are complete, consistent and accurate throughout the data lifecycle. (MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015)

**Date of fabrication** – The date when any active ingredient, excipient, anti-oxidant, preservative or air/oxygen scavenger is first added to the lot being processed, unless otherwise defined in the Food and Drug Regulations.

**Dilute drug premix** – "A drug for veterinary use that results from mixing a drug premix with a feed as defined in Section 2 of the *Feeds Act*, to such a level that at least 10 kg of the resulting mixture is required to medicate one tonne of complete feed, as defined in Section 2 of the Feeds Regulations, 1983, with the lowest approved dosage level of the drug." (C.01A.001)

**Director** – "The Assistant Deputy Minister, Health Products and Food Branch, of the Department of Health." (A.01.010)

**Distributor** or **manufacturer** – "A person, including an association or partnership, who under their own name, or under a trade, design or word mark, trade name or other name, word, or mark controlled by them, sells a food or drug." (A.01.010)

"Divisions 1A and 2 to 4 apply to the following distributors:

*(a)* a distributor of an active ingredient or a drug in dosage form that is listed in Schedule C to the Act; and

*(b)* a distributor of a drug for which that distributor holds the drug identification number." (C.01A.003)

**Dosage form** – A drug product that has been processed to the point where it is now in a form in which it may be administered in individual doses, unless otherwise defined in the Food and Drug Regulations.

**Drug** – "drug" includes any substance or mixture of substances manufactured, sold or represented for use in:

*(a)* the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,

*(b)* restoring, correcting or modifying organic functions in human beings or animals, or

*(c)* disinfection in premises in which food is manufactured, prepared or kept;

(Section 2 of the *Food and Drugs Act*)

In Division 1A and Division 2 of the Food and Drug Regulations, “drug” does not include a dilute drug premix, a medicated feed as defined in subsection 2(1) of the Feeds Regulations, 1983, an active ingredient that is for veterinary use or a drug that is used only for the purposes of an experimental study in accordance with a certificate issued under section C.08.015. (C.01A.001(2))

Drug establishment licence – A licence issued to a person in Canada to conduct licensable activities in a building which has been inspected and assessed as being in compliance with the requirements of Divisions 2 to 4 of the Food and Drug Regulations.

Drug identification number – A drug identification number (DIN) is an eight (8)-digit numerical code assigned by Health Canada to each drug product marketed under the *Food and Drugs Act* and Regulations. A DIN uniquely identifies the following product characteristics: manufacturer, brand name, medicinal ingredient(s), strength of medicinal ingredients(s), pharmaceutical form, route of administration.

Drug premix – “A drug for veterinary use to which a drug identification number has been assigned, where the directions on its label specify that it is to be mixed with feed as defined in Section 2 of the *Feeds Act*.” (C.01A.001)

Expiry date (or expiration date): "means:

*(a)* in the case of a drug in dosage form, the earlier of the following dates, expressed at minimum as a year and month:

(i) the date up to and including which the drug maintains its labelled potency, purity and physical characteristics, and

(ii) the date after which the manufacturer recommends that the drug not be used; and

*(b)* in the case of an active ingredient, whichever of the following dates is applicable, expressed at minimum as a year and month:

(i) the retest date, or

(ii) the date after which the manufacturer recommends that the active ingredient not be used.” (C.01.001)

Fabricate – “To prepare and preserve a drug for the purpose of sale.” (C.01A.001)

Filling – The transfer and enclosure of a bulk drug into its final container.

Finished product – A product that has undergone all stages of production, including packaging in its final container and labelling.

**Formulating** – Preparing components and combining raw materials into a bulk drug.

**Grade A air supply** – A supply of air which is HEPA filtered, and at the point of supply meets when tested, the non-viable particulate requirements of a Grade A area. (PIC/S)

**Group 2 products** – Drugs listed in Schedule D to the *Act* and subject to Health Canada's lot release program, which require the highest level assessment after the notice of compliance (NOC) has been issued. This assessment includes targeted testing, protocol review, and written approval for sale of each lot in Canada in the form of a release letter.

**Import** – "To import into Canada a drug for the purpose of sale." (C.01A.001)

**In-process control** – Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the finished product conforms to its specifications. The control of the production environment or equipment may also be regarded as a part of in-process control.

**In-process drug** – Any material or mixture of materials that must undergo further processing to become a drug in dosage form.

**In-process testing** – The examination or testing of any material or mixture of materials during the manufacturing process.

**Installation qualification** – Documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements. (ICH Q7)

**Label** – "Includes any legend, word, or mark attached to, included in, belonging to, or accompanying any food, drug, cosmetic, device, or package (section 2 of the *Act*). As described in package/label, the action of labelling refers to affixing the inner or outer label to the drug." (C.01A.001)

**Lot** – See Batch.

**Lot number** – "Any combination of letters, figures, or both, by which any food or drug can be traced in manufacture and identified in distribution." (A.01.010)

**Manufacturer** or **distributor** – See Distributor.

**Manufacturing batch record** – Records demonstrating that the batch of a drug was fabricated in accordance with the approved master production documents.

**Marketing authorization** – A legal document issued by Health Canada, authorizing the sale of a drug or a device based on the health and safety requirements of the *Food and Drugs Act* and its associated Regulations. The marketing authorization may be in the form of a Notice of Compliance (NOC), Drug Identification Number (DIN), a device licence for classes II, III and IV medical devices, or a natural product number (NPN) or homeopathic DIN (DIN-HM).

**Mass balance** – "The process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical error." (ICH, Q1AR)

**Master formula** – A document or set of documents specifying the raw materials with their quantities and the packaging materials, together with a detailed description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

**Master production documents (MPD)** – Documents that include specifications for raw material, for packaging material and for packaged dosage form; master formula (including composition and instructions as described in the definition above), sampling procedures, and critical processing related standard operating procedures (SOPs), whether or not these SOPs are specifically referenced in the master formula.

**Matrixing** – "The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and possibly in some cases, different container closure systems." (ICH, Q1A(R)) The concept of matrixing may also apply in other areas such as validation.

**Medical gas** – "Any gas or mixture of gases manufactured, sold or represented for use as a drug." (C.02.002)

**Medicinal ingredient** – See Active pharmaceutical ingredient.

**Metadata** – "Metadata is the data that describe the attributes of other data, and provide context or meaning. Typically, these are data that describe the structure, data elements, inter-relationships and other characteristics of data. It also permits data to be attributable to an individual." (MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015)

**Method transfer study** – "The systematic process that qualifies a laboratory to use an analytical method through the documented and demonstrated ability of the destination laboratory to

effectively perform the critical elements of the transferred technology to the satisfaction of all parties, including applicable regulatory bodies." (Schwenkea & O'Connor, 2008)

**MRA country** – A country that is a participant to a mutual recognition agreement with Canada. (C.01A.001)

**Mutual recognition agreement (MRA)** – "An international agreement that provides for the mutual recognition of compliance certification for Good Manufacturing Practices for drugs." (C.01A.001)

**Operational qualification** – "Documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges." (ICH Q7)

**Original record** – "Data as the file or format in which it was originally generated, preserving the integrity (accuracy, completeness, content and meaning) of the record, e.g. original paper record of manual observation, or electronic raw data file from a computerised system." *(MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015)*

**Package** – "As described in 'package/label,' the action of packaging refers to putting a drug in its immediate container." (Adapted from C.01A.001.)

**Package/label** – "To put a drug in its immediate container or to affix the inner or outer label to the drug." (C.01A.001) This includes the repackaging and relabeling of previously packaged and labelled drugs.

**Packaging material** – Includes a label. (C.02.002)

Note: For the purpose of these guidelines, this definition also includes: labels, printed packaging materials, any material intended to protect the intermediate or API or drug during storage and transport, and those components in direct contact with the final API or drug.

**Pharmaceutical** – "A drug other than a drug listed in Schedule C or D to the *Act*." (C.01A.001)

**Potency** – The activity or amount of active moiety, or any form thereof, indicated by label claim to be present.

**Process aids** – Materials, excluding solvents, used as an aid in the manufacture of an in-process drug or final product that do not themselves participate in a chemical or biological reaction (e.g. filter aid, activated carbon, etc.). (Adapted from ICH Q7.)

**Process validation** – Establishing documented evidence with a high degree of assurance, that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. Process validation may take the form of prospective, concurrent or retrospective validation and process qualification or re-validation.

**Production** – All operations involved in preparing a finished product—from receipt of materials to processing, packaging, completion of the finished product and storage.

**Purified water** – As defined in any standard listed in Schedule B to the *Food and Drugs Act*.

**Purity** – The extent to which a raw material or a drug in dosage form is free from undesirable or adulterating chemical, biological, or physical entities as defined by specifications.

**Qualified authority** – A member of the Pharmaceutical Inspection Cooperation/Scheme (PIC/S).

**Quality control department** – A unit maintained by an establishment that monitors the quality of production operations and exercises control over the quality of materials required for and resulting from those operations.

**Quality risk management** – A systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively (ICH, Q9).

**Quarantine** – "The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection." (ICH Q7)

**Radiopharmaceutical** – "A drug that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons." (C.03.201)

**Raw data** – Original records and documentation, retained in the format in which they were originally generated (i.e. paper or electronic), or as a 'true copy.' Raw data must be contemporaneously and accurately recorded by permanent means. In the case of basic electronic equipment which does not store electronic data, or provides only a printed data output (e.g. balance or pH meter), the printout constitutes raw data. *(MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015)*

**Raw material** – Any substance other than packaging material or an in-process drug that is intended for use in drug manufacture, including substances that appear in the master formula but not in the drug, such as solvents and processing aids.

**Recognized building** – "In respect of the fabrication, packaging/labelling or testing of a drug, a building that a regulatory authority that is designated under subsection C.01A.019(1) in respect of that activity has recognized as meeting its Good Manufacturing Practices standards in respect of that activity for that drug." (C.01A.001)

**Reconciliation** – A comparison between the amount of product or materials theoretically produced/used and the amount actually produced/used, with allowance for normal variation.

**Recovery** – The introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.

**Regulatory authority** – A government agency or other entity in an MRA country that has a legal right to control the use or sale of drugs within that country and that may take enforcement action to ensure that drugs marketed within its jurisdiction comply with legal requirements. (C.01A.001)

**Reprocessing** – Subjecting all or part of a batch or lot of an in-process drug, a bulk process intermediate (final biological bulk intermediate), bulk drug, or a finished product of a single batch/lot to a previous step in the validated manufacturing process due to quality concerns with the batch. Reprocessing procedures are foreseen as occasionally necessary and are validated and pre-approved by the quality control department and as part of the marketing authorization, where applicable.

**Re-test date** – "The date when a material should be re-examined to ensure that it is still suitable for use." (ICH Q7)

**Re-test period** – "The period of time during which a drug substance can be considered to remain within the specifications and therefore acceptable for use in the fabrication of a given drug product, provided that it has been stored under defined conditions; after this period, the batch is re-tested for compliance with specifications and then used immediately." (ICH, Q1AR)

**Reworking** – "Subjecting an in-process drug, a bulk process intermediate (final biological bulk intermediate), or final product of a single batch/lot to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization." (WHO GMP)

**Secondary labelling** – The process of affixing an inner or outer label to a previously labelled container to fulfill the regulatory requirements of Part C of the Food and Drug Regulations.

**Self-contained facility** – Means a premise that provides complete and total separation of all aspects of the operation, including personnel and equipment movement, with well established procedures, controls and monitoring. This includes physical barriers and separate utilities such as air handling systems. A self-contained facility does not necessarily imply a distinct and separate building.

**Sell** – "Offer for sale, expose for sale, have in possession for sale, and distribute, regardless of whether the distribution is made for consideration." (section 2 of the *Food and Drugs Act*)

**Shelf life** – The time interval during which a drug product is expected to remain within the approved specification provided that it is stored under the conditions defined on the label and in the proposed containers and closure.

**Specifications** – "Means a detailed description of a drug, the raw material used in a drug, or the packaging material for a drug and includes:

*(a)* a statement of all properties and qualities of the drug, raw material or packaging material that are relevant to the manufacture, packaging, and use of the drug, including the identity, potency, and purity of the drug, raw material, or packaging material,

*(b)* a detailed description of the methods used for testing and examining the drug, raw material, or packaging material, and

*(c)* a statement of tolerances for the properties and qualities of the drug, raw material, or packaging material." (C.02.002)

**Stability studies** – "Stability studies under the recommended storage condition, for the re-test period or shelf life proposed (or approved) for labelling." (ICH, Q1AR)

**Standard operating procedure (SOP)** – A written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documents.

**Sterile** – Free from viable microorganisms.

**System** – A regulated pattern of interacting activities and techniques that are combined to form an organized whole.

**Terminal sterilization** – The sterilizing of a drug in its final closed container.

**Test** – To perform the tests, including any examinations, evaluations and assessments, as specified in the Division 2 of the Food and Drug Regulations.

**True copy** – An exact verified copy of an original record. Data may be static (e.g. a "fixed" record such as paper or pdf) or dynamic (e.g. an electronic record which the user/reviewer can interact with).

Example 1: A group of still images (photographs – the static "paper copy" example) may not provide the full content and meaning of the same event as a recorded moving image (video – the dynamic "electronic record" example).

Example 2: Once printed or converted to static .pdfs, chromatography records lose the capability of being reprocessed and do not enable more detailed viewing of baselines or any hidden fields. By comparison, the same dynamic electronic records in database format provides the ability to track, trend, and query data, allowing the reviewer (with proper access permissions) to reprocess, view hidden fields, and expand the baseline to view the integration more clearly. (MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015)

Validation – A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria. (ICH Q7)

Vendor – Person who is the fabricator of the item (raw material, packaging material, medicinal ingredients, reagents).

Veterinary drugs – Drugs that are administered to food-producing and companion animals.

Wholesaler – "A person who is not a distributor described in section C.01A.003 and who sells any of the following drugs other than at retail sale: (a) a drug in dosage form that is listed in Schedule C or D to the Act, a drug that is a prescription drug or a controlled drug as defined in subsection G.01.001(1); (b) an active ingredient; or (c) a narcotic as defined in the Narcotic Control Regulations." (C.01A.001(1)).

# Appendix B – Questions and answers

## Premises – C.02.004

1. **Are firms required to use high-efficiency particulate air (HEPA) filters for air supply in areas used for the manufacture of non-sterile dosage forms?**

   Division 2 "Good Manufacturing Practices" of the Food and Drug Regulations does not specifically require manufacturing facilities for non-sterile drugs to maintain HEPA-filtered air.

   The Regulations do require you to use equipment for proper control over air pressure, microorganisms, dust, humidity and temperature (when needed). Also, you must use air filtration systems (including prefilters and particulate matter air filters) on air supplies to production areas (when needed). These provisions are meant to prevent cross-contamination, and the key phrase is "when needed."

   Despite the lack of an explicit GMP requirement, you may choose to use HEPA-filtered air systems as part of your dust control procedures. For example, you may perform dust containment assessments and decide that filters are needed to prevent cross-contamination of highly potent drugs that, even in small quantities, could pose a significant health hazard when carried over into other products.

2. **Is there an acceptable substitute for dioctyl phthalate (DOP) for integrity testing of high-efficiency particulate air (HEPA) filters?**

   Yes. Dioctyl phthalate aerosols (also called Di (2-ethylhexyl) phthalate, di-sec octyl phthalate, DOP or DEHP) have long been used to test the integrity of HEPA filters. But concern about the potential health effects to personnel working with DOP test aerosols has led to a search for a safer yet equal replacement.

   The product of choice from US Army testing (with help from various private companies) was a Henkel Corporation (Emery Group) product called Emery 3004 PAO. This product is a polyalphaolefin (POA) in the 4 centistoke (4 cSt) viscosity grade, used mainly as a lubricant base stock for oils, lubricants and electrical/hydraulic fluids.

   Emery 3004 (POA) can replace DOP in HEPA filter integrity testing.

3. What is the acceptable limit for dew point of the compressed air used in pneumatic equipment and to dry the manufacturing tanks after cleaning?

There is no limit specified in this document for the relative humidity percentage of the air used for pneumatic equipment and to dry manufacturing tanks.

From a general perspective, based on interpretation 4 in section C.02.004 "Premises," humidity must be controlled where required to safeguard sensitive materials. So it is the fabricator's and packager/labeller's responsibility to determine the need for such control.

If the humidity percentage of the compressed air used at the last step of drying a reservoir is too high, micro-droplets of water could be generated on internal surfaces from condensation, contributing to the possibility of microbial growth following storage. Similarly, it is important to make sure that residual water has been completely eliminated from hard-to-reach surfaces of the equipment after cleaning operations.

4. What are the requirements for quality control and engineering personnel who travel many times daily between self-contained facilities and regular facilities?

Movement of personnel between self-contained and other facilities must be subject to procedures that will prevent cross-contamination. This may include (but is not limited to) decontamination procedures, such as showering and changing clothes.

5. What should be the standard of compressed air used in the manufacture of a drug?

You should monitor air that comes into direct contact with primary contact surfaces and/or the product to control the level of particulates and microbial contamination and ensure the absence of hydrocarbons. The limits you use should take into consideration the stage of manufacture and the product. More tests might be needed depending on the nature of the product.

Ensure gas used in aseptic processes is sterile. Check filters for integrity.

6. Does the concept of self-contained facilities apply equally to research and development labs (susceptible to contain highly sensitizing, highly potent or potentially pathogenic material in the analytical scale) that may be in the same building as the manufacturing facilities? Or is this concept limited to actual manufacturing operations?

Manufacturers must ensure that their premises and operations have been designed to minimize the risk of contamination between products. This includes research and development areas within facilities where marketed drug products are fabricated and packaged. For more information, see interpretation 11, section C.02.004 "Premises."

## Equipment – C.02.005

1. **Should equipment be labelled with calibration dates?**

You should identify major equipment with a distinctive number or code that is recorded in batch records. This identification requirement is intended to help identify which equipment was used to manufacture batches of drug product.

Division 2 of the Food and Drug Regulations does not require that each piece of equipment have labelling showing its state of calibration or maintenance. But you must calibrate and/or maintain your equipment according to an established schedule, and keep records documenting these activities.

The Regulations do not distinguish critical from non-critical equipment for calibration and maintenance purposes. The need for calibrating a given piece of equipment depends on its function. In general, equipment that measures materials and operating parameters should be calibrated.

You do not need to track or include equipment that does not require calibration/maintenance in your calibration/maintenance program. But you do need to be able to support your decision to exclude a particular piece of equipment from your program.

During an inspection, you should be able to show through your documents:

- when a specific piece of equipment was last calibrated/maintained
- the results or action
- when the next calibration/maintenance is scheduled

Not having this documentation is considered a GMP deviation.

## Personnel – C.02.006

1. **Is a company required to notify Health Canada of a change in key personnel, such as the person in charge of quality control or manufacturing?**

No. But it is your responsibility to make sure the new person meets the requirements of interpretations 1, 2, 3 or 4 under section C.02.006 “Personnel” (depending on the activities performed).

## Sanitation – C.02.007, C.02.008

1. **Is fumigation a requirement under sanitation?**

   Your written sanitation program should include procedures for pest control and precautions to prevent contamination of a drug when fumigating agents are used.

   Fumigation is not a requirement per se. You should monitor and control infestation. If you use fumigation, you should take proper precautions.

   Methods of sanitary control that satisfy the requirements of sections 8 “Prohibited sales of drugs” and 11 “Unsanitary manufacture etc., of drug” of the Food and Drugs Act are considered acceptable.

2. **Are gowning rooms required even in pilot plant operations?**

   Assuming the pilot plant will produce drugs for sale (including clinical studies), the same principles and considerations that apply to full-scale production operations must also be applied in pilot plant facilities.

   Even in a pilot plant consisting of a small laminar flow area where the apparatus for filter sterilization of solutions are set up, it is unacceptable to gown in there. You must make a change room available beside your sterile pilot plant production area.

3. **In terms of cleaning, what would be the frequency and type of cleaning required for equipment and premises for successive manufacturing of batches of the same product? And for different strengths of the same product?**

   A cleaning procedure requiring complete product removal may not be necessary between batches of the same drug. The frequency and type of cleaning for equipment and premises must address the length of time between consecutive lots. The ultimate goal is that a particular lot will not be contaminated by the previous lot or the environment.

   You must ensure that residual quantities of the previous lot do not impact on the quality of the following lot. So a partial cleaning is required between two lots of the same product regardless of strength (especially for forms such as liquids or suspensions). This will prevent a few units at the beginning of a new lot from being filled with residual quantities from the previous lot (which may be located in hoses or pumps).

   You should establish a procedure to ensure adequate removal of residual quantities from the previous lot. You should also validate the maximum period of time between two successive lots to avoid problems such as microbial contamination, accumulation of residue, or

degradation of product. You need to determine the number of lots of the same product that could be manufactured before a complete/full cleaning.

4. **Is it acceptable to have two levels of clothing in non-sterile manufacturing areas? (For example: one level for operators with full gowning and coveralls, and another level for quality assurance auditors and visitors.) What environmental monitoring data is required?**

   Yes. There are basic clothing requirements for any person entering the manufacturing areas (such as protective garments and hair, mustache and beard covering). But you may decide to apply more stringent requirements for operators (such as dedicated shoes and garments that provide a higher level of protection).

   There are no specific environmental monitoring requirements for clothing worn in non-sterile manufacturing areas.

5. **Can sampling for the microbial monitoring of air in non-sterile areas where susceptible products are produced be conducted when there are no manufacturing packaging activities?**

   You should take samples during actual manufacturing or packaging, to reflect the conditions the products being produced are really exposed to. You should also monitor between production runs, to detect potential problems before they arise.

6. **Do written procedures have to be available to prevent objectionable microorganisms in drug products not required to be sterile?**

   Yes. You should establish and follow proper written procedures to prevent objectionable microorganisms in drug products not required to be sterile. This means that, even though a drug product is not sterile, you must follow written procedures to pro-actively prevent contamination and proliferation of microorganisms that are objectionable.

7. **Can industrial grade nitrogen be used as a blanketing agent during the manufacture of a drug product?**

   No. Any gas used as a blanketing agent should be of compendial standard.

8. **If nitrogen is used as a blanket in the manufacturing/filling of parenteral drugs, and if the nitrogen supplier has been audited, do we need to test the identity of all the cylinders?**

   Interpretation 11 under section C.02.009 “Raw Material Testing” specifies that you must test each container of a lot of a raw material for the identity of its contents using a specifically discriminating identity test. Interpretation 11.b allows for testing only a proportion of the containers, but interpretation 11.b.iv specifies that interpretation 11.b does not apply when the raw material is used in parenterals.

So in response to the question, yes, you must test the identity of all the cylinders of nitrogen used as a blanket agent in the manufacturing/filling of parenteral drugs.

## Raw material testing – C.02.009, C.02.010

1. **What are the requirements of maintaining an impurity profile?**

The United States Pharmacopeia (USP) defines an impurity profile as "a description of the impurities present in a typical lot of drug substance produced by a given manufacturing process" (USP <1086>). This standard release profile must be developed early on and maintained for each pharmaceutical chemical. Each commercial lot should be comparable in purity to this profile.

We can also call this profile a "reference profile" because the quality control unit refers to it

- when assessing the purity of each batch of active pharmaceutical ingredients (API)
- when evaluating the viability of proposed process changes

For more information on the control of impurities, please see:

- *ICH Q3A(R2): Impurities in New Drug Substances*
- *ICH Q3B(R2): Impurities in New Drug Products*

2. **Does every individual container of a raw material need to be sampled for identification (ID) purposes, regardless of the number of containers of the same lot available? Or are composite samples acceptable if they are obtained from a maximum of 10 containers?**

According to interpretation 10, section C.02.009 "Raw Material Testing," you must test each container of a lot of a raw material for the identity of its contents. So you must open and sample each container of all raw materials (including excipients and active pharmaceutical ingredients).

Then, you have two options:

a. Test every sample for ID using a discriminating method. You do not have to perform all ID tests in the specifications (for example, United States Pharmacopeia), but the test must be specific.

b. Mix and pool individual samples taken from each container in a composite sample (if the raw material can be tested for potency). You may not have more than 10 individual samples in a composite. You must then perform a specific ID test on each composite. You must also perform a potency test to ensure the mass

balance of the composite. (You must weigh an equal quantity of each individual sample in the composite to ensure the mass balance is representative.)

As an example, say 72 containers of the same lot of a raw material are received. Each and all containers must be opened and a sample taken from each container. After that, the first option is to test each sample for ID (which implies 72 ID tests).

The second option is to combine equal quantities of those individual samples, ensuring the number of samples in any composite does not exceed 10. Then you would test those composites for ID and potency.

In this case, the easiest way to combine the samples would be 8 composites of 9 individual samples. For a given composite, a potency result of 88.8% or so would indicate that one of the containers does not contain the right material, as each individual sample contributes 1/9 or 11.11% of the total mass of the composite (similarly, a result of 77.7% would indicate 2 containers with the wrong material). In this case, you would have to test each container selected for this particular composite for ID to pinpoint the one (or more) containers with the wrong material.

You cannot use a composite sample to establish the ID of a raw material when the potency limits are too wide or when the precision of the assay method is not sufficient to properly establish the mass balance.

3. **An active pharmaceutical ingredient (API) can be used after the retest date assigned by the API fabricator if a re-analysis done immediately before use shows that it still meets its specifications. Can the new data generated be used by the drug fabricator to assign a longer retest date to future lots of this API obtained from the same fabricator?**

No. Any extension of the retest date originally assigned to the API should be supported by data generated through a formal stability protocol. This may require the filing of a notifiable change submission. Please refer to the appropriate Health Canada review directorate.

### 3.b What about inactive ingredients?

Normally, any inactive raw material should have an expiry date. If an inactive raw material is received without an expiry date, the fabricator should assign either an expiry date or a re-test date based on stability data (or other documented evidence that this raw material is not subject to chemical/physical modifications or is not susceptible to microbial contamination).

4. For the re-test date of drug substances, we have stability data for a drug substance for up to 24 months at real-time stability conditions. The re-test period is assigned up to 24 months. According to the "Evaluation of Stability Data – ICH Q1E," 2.4.1.1, the retest period can be assigned up to 36 months ("…the proposed retest period or shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data").

   Can we assign the retest period up to 36 months? If yes, does this require retesting the active pharmaceutical ingredient (API) at 24 months?

   The retest period and expiry date for APIs should be based on stability data. If an expiry date has been assigned to an API, then its batches cannot be used after the expiry period. However, if a retest period has been assigned to the API, then after the retest period is over, the API batch can be tested and used immediately (for example, within one month of the testing).

   In the scenario presented above, any extrapolation of the expiry date beyond 24 months should be based on stability data, both at long-term and accelerated storage conditions. If the test results are satisfactory, the retest period can be extended to a period not exceeding 36 months. Once the retest period of the API has been extended to 36 months, testing batches at the 24-month time point would be part of the continuing stability protocol (it would not be considered *retest*).

   For more guidance on retest and expiry periods, please see:

   - *ICH Q1A(R2): Stability Testing of New Drug Substances and Products*
   - *ICH Q1E: Evaluation of Stability Data*

5. We are a subsidiary of a United States (US) corporation. This US corporation supplies us with active pharmaceutical ingredients (APIs) that are fully tested after receipt on its premises. Can the US site be certified for the purpose of testing exemptions for the Canadian site?

   The US parent company cannot be considered the vendor. To be certified, the vendor must be the original source of the API. In this instance, the US company would be acting as a contract lab and should meet the requirements under interpretation 8.k, section C.02.015 "Quality Control Department."

   When received by the Canadian site, a specific identity test must be performed. For an API, the testing must be as per interpretation 10, section C.02.009 "Raw Material Testing" (for example, each container must be sampled and tested). This is assuming that no repackaging is done by the US site. In other words, the materials must be supplied in their original containers with the original labels and certificate of analysis received from the vendor.

6. **Is a sampling plan based on the ($\sqrt{}$n+1) acceptable for identifying the number of containers of raw material to be sampled?**

   Sampling plans and procedures must be statistically valid. They should be based on scientifically sound sampling practices. They should also take into account the risk associated with accepting defective product (based on predetermined classification of defects, criticality of the material, and past quality history of the vendor).

   In some circumstances (such as for a large number of containers), a sampling plan based on ($\sqrt{}$n+1) may be acceptable. But a sampling plan based on ($\sqrt{}$n+1) may present a significant risk of accepting defective goods in some instances (such as when sampling a small number of containers). As with all sampling plans, you must have documented justification available.

7. **If we already test each batch of our finished product for the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*, do we also have to test it for the purified water?**

   Yes. You must test the purified water for the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. It is the general expectation that raw material testing support finished product testing.

8. **Interpretation 11 under section C.02.009 "Raw Material Testing" specifies that "you must test each container of a lot of raw material for the identity of its contents using a specifically discriminating identity test." Does this requirement apply to raw materials used to fabricate finished products imported from non-mutual recognition agreement (non-MRA) countries?**

   Any drug imported into Canada must meet the requirements in Part C, Division 2 of the Food and Drug Regulations. Any sampling and testing requirements for raw materials used in finished products imported from non-MRA countries should be equivalent to the requirements in the Regulations, as described in sections C.02.009 and C.02.010 of this document. Importers should have evidence (such as technical agreements) that their suppliers in non-MRA countries have equivalent requirements for sampling and testing raw materials used in finished products.

## Manufacturing control – C.02.011, C.02.012

1. **Can a single lot number be assigned to two or more co-mingled lots of bulk finished drug products packaged during the same run?**

   This document requires that you:

   - identify each batch using an individually numbered manufacturing batch document
   - test each lot or batch of the finished product fully against the specification

- keep retained samples for each lot or batch

You may use one lot number to package multiple lots of bulk finished drug product in a single packaging run only in exceptional circumstances. If you do this, you must properly justify and document why. You must indicate the shortest expiry date of all the lots packaged on the label. In case of a product recall, you must recall the entire lot, including all the sub-lots.

### 2. What is the acceptable deviation in physical counts of finished product stock?

The allowable deviation between physical counts versus counts noted in records (including computer records) should be zero. You must fully account for all finished product stock and maintain records of distribution and disposition. You should investigate any deviations from physical counts versus expected counts as per the records and document the results of such investigations.

### 3. May firms omit the second-person component weight check if scales are connected to a computer system?

You must do the second-person component weight check if you have an automated system that does not include:

- checks on component quality control release status
- proper identification of containers

You may omit the check if you have a validated automated system that:

- has a bar code reader that registers each raw material's identification, lot number and expiry date
- is integrated with the recorded accurate weight data

### 4. When are independent checks by another operator necessary?

This document outlines a number of measures to maintain the integrity of a drug product from the moment the raw materials enter your plant to the time you release the finished dosage form for sale. These measures seek to eliminate as many sources of error as possible so that you only distribute drugs that have met established specifications.

One of the measures is to have written procedures to ensure each ingredient added to a batch is subjected to one or more checks for identity and quantity by qualified personnel. These checks may require independent checks by a second individual.

However, if you can ensure that the design, construction, operation and security features of the procedure make it impossible to make an error, an independent check by another operator may not be needed. You may use alternative approaches in the case of validated automated processes.

Independent checks that materials have been added to the batch are usually assumed to take place at the time of actual addition of the materials. You may also verify the addition of materials using these steps:

a. Check staged materials in the immediate compounding area before starting processing.
b. Afterwards, verify the empty containers before clearing the compounding area.

### 5. Is verification of empty containers an acceptable check for addition of ingredients?

Yes. It is acceptable to check staged materials by verifying empty containers before and after processing as a method of checks for addition of ingredients.

That said, the preferred way to conduct addition checks is to have the verifier directly observe. Verifying empty containers is an acceptable alternative, but only where stringent controls are in place for handling dispensed raw materials. Such controls include:

- assurance that a dispensed raw material does not end up in the wrong batch (locked portable cages are being used by some firms, and only relevant cages are allowed in the room at the same time)
- good operator awareness, training and motivation (the operator has to ensure that additions are performed in the right sequence and report any spillage of raw materials promptly)
- pre- and post-checks performed by qualified personnel (and whenever possible, by the same person)
- post-processing checks performed before removing any material from the area

### 6. What are the expectations on label accountability?

You must have proper controls in place to ensure that during a labelling operation, correct labels are applied and printed packaging materials are accounted for.

One acceptable way to meet this requirement is to issue an accurately counted number of labels. This number should be reconciled with the number of labels used, damaged and returned to stock.

In theory, you should set a target in your procedure of "0" deviation for labels and other printed packaging materials. You must investigate and account for any significant or unusual discrepancy before release when reconciling the amount of bulk product and printed packaging materials with the number of units packaged.

If you validate electronic verification of all printed packaging materials on the packaging line, you may not need a full reconciliation.

7. Are quarantine and release stickers required on all containers of raw materials and packaging materials?

Quarantine and release stickers are required on all containers of raw materials and packaging components to identify status if you use a physical quarantine/release system.

But such stickers are not required if you use a validated electronic quarantine system that effectively prevents the possibility of inadvertent use of unreleased material. If you use fully computerized storage systems, you should have backup systems in case of system failure.

8. For recalls, do we need to document quantities by lot numbers of finished stock destroyed?

For products returned following a recall, you must document the returns by lot number in order to perform a final reconciliation. If an establishment's recall procedures depend on dates of first and last sale of a given lot, records of destruction by lot numbers may provide necessary information about accountability per lot.

9. For a contract fabricator, is it required to test the raw materials provided by clients?

Yes. Testing of raw materials is the fabricator's responsibility. An observation will be made to you (the fabricator) for not testing a particular raw material even when it is provided by your client. The exception is if you are excluded by your client in a contract and requirements under section C.02.009 to C.02.010 have been fulfilled.

For more information on contracts, see:

- interpretation 3 under section C.02.012 "Manufacturing Control" (covers written agreements with respect to fabrication and packaging/labelling activities between parties)
- interpretation 8.k.iii under section C.02.015 "Quality Control Department" (covers written agreements with respect to the testing among the parties involved)

### 10. If the customer asks a contract fabricator not to test a finished product, is it necessary for the contract fabricator to test the product?

Yes. Testing of finished products is the fabricator's responsibility. An observation will be made to you (the fabricator) for not testing a particular finished product, unless you are excluded by your client in a contract and requirements under sections C.02.018 to C.02.019 have been fulfilled.

### 11. Is a contract fabricator or packager responsible for qualification of utilities and systems and cleaning validation, or is this the distributor's responsibility? And what about the validation of the manufacturing/packaging process and test methods?

The contract fabricator is primarily responsible for the qualification of utilities and systems and cleaning validation. In certain cases, the distributor may have information relevant to support cleaning validation activities.

For process and test method validation, the main responsibility rests with the distributor (according to section C.02.003 "Sale" of the Regulations). But the contract fabricator, packager or tester is also responsible for process or test method validation, unless a written agreement is signed by both parties that excludes the contract fabricator, packager or tester from performing validation activities.

### 12. How long in advance can the raw materials be weighed?

You have to have data to support the timeframe you establish.

You may weigh raw materials before the scheduled production date if you:

- show that the materials and design of the containers the raw materials are weighed and kept in will not alter their quality
- consider the characteristics of the raw materials (see interpretation 2 of section C.02.026 "Samples")
- ensure re-weighed material is properly labelled to allow traceability
- have a system in place to ensure the material is still suitable for use on the date of manufacturing

### 13. A Canadian firm does business with a foreign company, and that foreign company contracts out the fabrication, packaging and testing of a product. Is it acceptable to only have a written agreement between the Canadian firm and the foreign company, and not with the contract company?

No subcontracting of any work should happen without written authorization from the Canadian firm. In the event of subcontracting, there should be a written agreement between the contracting and subcontracting parties (for example, contracts between the Canadian firm and foreign company, and the foreign company and subcontractor). The Canadian firm should assess the relevant agreements to verify compliance with Canadian requirements. Copies should be available at the Canadian firm's site.

All establishments conducting licensable activities must hold an establishment licence or be listed on an importer's licence. All arrangements for external fabrication, packaging/labelling and testing must comply with the marketing authorization for the drug product concerned. (See interpretation 3 under section C.02.012 "Manufacturing Control" and interpretation 8.k under section C.02.015 "Quality Control Department.")There must also be a written agreement covering all activities between the parties involved.

### 14. What are the expectations for a firm's management review of the Annual Product Quality Review (APQR)?

Senior management should be aware of the major outcomes from the APQR process and dedicate the resources needed to address the identified concerns.

Evidence to show that senior management has been made aware could include:

- meeting agendas and/or minutes
- quarterly reports
- management sign-off of APQR reports

### 15. Do "all products" as described in interpretation 57 (regular periodic or rolling quality reviews of all drugs) include low-risk Category IV drug products?

Yes. You must complete Annual Product Quality Reviews for Category IV products.

### 16. For biologics, where annual reports are already being prepared by fabricators, is a separate APQR required?

There are some gaps between the information required by the Yearly Biologic Product Reports (YBPR) (as described in section 5.1 of *Guidance for Sponsors: Lot Release Program for*

*Schedule D (Biologic) Drugs* and the APQR. For example, these elements are required for the APQR, but not the YBPR:

- review of the adequacy of any equipment corrective actions
- qualification status of relevant equipment and systems (such as heating, ventilation and air conditioning, water, compressed gases)
- contractual agreements
- roles/responsibilities of the quality control department in APQR

The YBPR is acceptable if an addendum is available to address those aspects not covered.

17. In section C.02.011 "Manufacturing Control," interpretation 58.j states: "…a review of agreements to ensure that they are up-to-date" and interpretation 61 states: "Where required, you should have an agreement in place between the various parties involved in a review (e.g. importer, distributor, fabricator). This agreement should define each party's responsibilities in producing and assessing the quality review and taking any corrective and preventative actions."

    Do these statements mean that an importer should have a quality agreement with the fabricator and that this agreement should be reviewed yearly?

    Yes. The importer should have a quality agreement with the fabricator (outlining responsibilities related to APQR, etc.). That agreement should be reviewed at least once a year, and updated as needed.

## Quality control department– C.02.013, C.02.014, C.02015

1. If a product fails its particulate matter specifications, can it be released for sale?

    No. The particulate matter requirement is treated the same way as any other specification. Failure means non-compliance with the labelled standard.

2. Are the *United States Pharmacopeia* (USP) general notices enforceable?

    Yes, they are also enforceable in Canada. The USP general notices provide summaries of the basic guidelines for interpreting and applying the standards, tests, assays and other USP specifications. This way, these general statements do not need to be repeated in the various monographs and chapters throughout the book. Where exceptions to the general notices exist, the wording in an individual monograph or general test chapter takes precedence.

3. If a lot meets USP specifications but fails the firm's internal specifications, can it be released?

No. If a lot does not meet its declared release specifications or marketing authorization, it should not be released. If more stringent internal specifications act as an alert limit and not as the basis for release, the lot may be released after investigation and justification if it meets its release specifications.

4. Is it acceptable for firms to export expired drugs for charity?

No. We recognize the dire need for drugs in distressed parts of the world. Once the expiration date has passed, there is no assurance that the drugs have the safety, identity, strength, quality and purity characteristics they are said to have. So expired drugs are considered adulterated, and their introduction or delivery for introduction into commerce is prohibited.

5. Can an older version of an official method be used, or must the most updated version always be used?

You must use the most up-to-date version of the analytical method to determine compliance.

6. What is Health Canada's position on the use of secondary reference standards? What are the conditions for the use of secondary reference standards?

You may use a secondary reference standard if you determine each lot's suitability before use by qualifying it against a Schedule B reference standard or primary standard. You must also requalify each lot periodically according to a written protocol. The protocol should clearly address the receipt, storage, handling and use of the Schedule B reference standard or primary reference standard,, the purification of secondary standards, and their qualification against official reference standards.

7. What is Health Canada's position on the use of loose work sheets as opposed to bound notebooks to record lab data?

We recommend using a bound book to record lab data. But you may use loose work sheets as long as it is controlled by a system or procedure. You must ensure that all raw data are true and accurate, properly recorded and captured, well maintained and easily retrievable. The system you use should also provide accountability and traceability of work sheets.

### 8. How does Health Canada view validation when reworking is required (for example, when three consecutive incidents will never happen)?

Reworking of a batch should happen very rarely. Instead of having validation in place, you should carry out any reworking according to a defined procedure approved by Quality Control, and meet the conditions described in interpretation 6 of section C.02.014 “Quality control department.” This procedure should include extra measures and testing during the reworking operations to ensure that the quality of the final product is not compromised.

You must fully investigate rework proposals and reworked product to determine impact on release characteristics and potential impact on bio-availability. Certain changes, including the incorporation of additional lubricant, dissolution aid or critical processes may require comparative bio-availability studies. Furthermore, you must undertake continuing stability studies on reworked batches to ensure that critical characteristics are not compromised over time (during product shelf life) due to the rework.

### 9. Is it mandatory when approving a procedure to sign each page, or is it acceptable to only sign the first page?

The approvers do not need to sign each page of the procedure. It is acceptable to only sign the first page or the last page, provided that there is a way to ensure all pages are accounted for and that the package is complete.

### 10. If we perform a Total Aerobic Count (TAC) of purified water and we identify each species found (if any) during the TAC (showing the absence of the two pathogens), is it required to perform a specific test to show the absence of Staphylococcus aureus and Pseudomonas aeruginosa?

Yes, specific tests are required to show the absence of these two pathogens if the specific tests are in the purified water specification to support finished product quality. The species-specific tests should follow a compendial method.

### 11. Will an inspector observe and question a technician’s analytical work?

Yes, an inspector may verify if lab staff are qualified to carry out the work they undertake. This could occasionally include observing what lab technicians are doing and questioning their actual analytical work with respect to the standard operating procedures, methods or equipment used.

Also, inspectors will often examine testing data from the lab for format, accuracy, completeness, adherence to written procedures and integrity of data. These matters would usually be seen as requirements under section C.02.015 “Quality Control Department.”

## Packaging material testing – C.02.016, C.02.017

1. **Is it necessary to include a chemical identification test in a specification for a packaging component (such as a plastic bottle)? Must this chemical identification (ID) be conducted for each lot received? Would vendor certification be considered an acceptable substitution for testing upon receipt?**

   You do not have to repeat the chemical ID (such as Infra-Red) if the type of material is described on the certificate of analysis and if a specific test has been performed by the fabricator of the packaging materials confirming the identity of the starting polymer used to manufacture a specific lot. But you should visually examine each lot of packaging materials to confirm identity.

## Finished product testing – C.02.018, C.02.019

1. **Do bacteriostasis and fungistasis testing have to be performed for each lot of product in reference to the United States Pharmacopeia (USP) sterility test?**

   No. This needs to be established only once for a specific formulation, to determine the suitable level of inoculate for that product. If the formulation has not changed for a number of years, you can simply do periodic verification (as microorganisms become resistant to preservatives in a formulation).

2. **Does Health Canada encourage the use of environmental isolates for preservative effectiveness testing?**

   You may use environmental isolates in addition to the specified compendia cultures. But using environmental isolates alone is not acceptable.

3. **What are Health Canada's expectations for process parametric release for foreign and Canadian manufacturers?**

   For more information, see: *PIC/S Annex 17: Guidance on Parametric Release*.

   Please note that we will only consider requests:

   - for terminally sterilized drugs in their immediate containers
   - following submission and approval of acceptable evidence according to this guidance

### 4. Does DO-25 (the official method for determining tablet disintegration times) apply to tablets labelled as being professed or as manufacturer's standard?

Section C.01.015 "Tablet Disintegration Times" in the Food and Drug Regulations requires that all drugs in tablet form that are intended to be swallowed whole must disintegrate in not more than 60 minutes when tested by the official method (DO-25). The regulations also prescribe a specific disintegration requirement and test for tablets that are enteric coated.

Subsection (2) outlines conditions where subsection (1) requirements for DO-25 are not required:

- a drug demonstrated by an acceptable method to be available to the body
- a drug where representations are made about the site, rate or extent of release to the body of a medicinal ingredient (e.g. extended release tablets)

See C.01.011 and C.01.012 "General" for more information.

You may use an alternate disintegration or dissolution method to show compliance with the prescribed release requirements as long as you properly validate the method. DO-25 is not generally used for new drugs.

### 5. Are solid dosage drugs exempted from dissolution testing if sold under a manufacturer's standard?

No. Solid dosage drugs should include a routine test for monitoring release characteristics (such as dissolution).

### 6. Do tests for impurities have to be repeated for finished products if they have been done on the raw materials?

Testing of impurities must be performed at the appropriate stage to satisfy the conditions of the marketing authorization.

For more information about controlling impurities, please see:

- *Impurities in New Drug Substances – ICH Q3A(R)*
- *Impurities in New Drug Products – ICH Q3B(R)*

### 7. What are the standards—other than the United States Pharmacopeia (USP)—that have official status in Canada?

The acceptable standards are described in Schedule B of the Food and Drugs Act:

- European Pharmacopoeia (Ph.Eur.)
- Pharmacopée française (Ph.F.)
- Pharmacopoeia Internationalis (Ph.I.)
- The British Pharmacopoeia (BP)
- The Canadian Formulary (C.F.)
- The National Formulary (N.F.)
- The Pharmaceutical Codex: Principles and Practices of Pharmaceuticals
- The United States Pharmacopeia (USP)

Trade standards are also acceptable under certain conditions.

### 8. Should compendial test methods be validated?

Compendial methods cannot include all possible formulations of a drug product. So you must prove a compendial method applies to your company's particular formulation of a drug product. You must show that there is nothing in the product that interferes with the compendial method or affects the performance of the method. You must also establish that the impurities that would be expected from the route of synthesis or formulation are controlled by the compendial method.

The main objective of validation of an analytical procedure is to demonstrate that the procedure is suitable for its intended purpose.

For guidance on validation of analytical procedures, please see:

- *Validation of Analytical Procedures: Text and Methodology – ICH Q2 (R1)*

### 9. Do we have to perform all identification tests stated in a compendial monograph?

Yes. You must perform all tests stated in the monograph.

### 10. Do products labelled as United States Pharmacopeia (USP) have to be tested as per the USP test methods?

No. an alternate method can be used. If an alternate method is used, it must be fully validated and results from a correlation study should be available showing it to be equal to or better than a USP method. It is important that USP states "Only those results obtained by the methods and procedures given in the compendium are conclusive." You can refer to USP General Notices for more information.

### 11. What should be the calibration frequency for a dissolution apparatus used with both baskets and paddles?

We do not outline specific time periods in this document. You should calibrate equipment at suitable intervals to ensure reliable and reproducible results. This should be covered in your firm's standard operating procedures. You may consult the apparatus manufacturer's manual for guidance. You may also use historical or validation data to support an appropriate calibration frequency.

You should also calibrate equipment as required if there is any event that might change operating characteristics of the equipment (such as maintaining or moving it).

### 12. In performing system suitability as per United States Pharmacopeia (USP) <621>, do all replicate injections have to be completed before any analyte sample injections are made?

No.

### 13. Is routine product pH testing required for endotoxin (*limulus amebocyte lysate* – LAL) testing?

No, provided that you have validated the method and have not committed to such testing in a new drug submission.

### 14. Is the use of recycled solvents for high performance liquid chromatography (HPLC) columns acceptable?

Yes, provided that you have performed appropriate validation studies.

### 15. If one lot of a product made in a mutual recognition agreement (MRA) country is split into two separate shipments, is it mandatory for the importer to obtain separate manufacturer's batch certificate for each shipment?

No. However, the importer should demonstrate that the conditions of transportation and storage applicable to this product have been met for each shipment.

16. **Is it acceptable to perform release testing (including for potency) before packaging? Or is it mandatory to perform this testing after packaging?**

Only identity testing must be performed after packaging.

Otherwise, there is no specific requirement to perform the other tests after packaging (including potency). However, you must validate the manufacturing process to demonstrate that the packaging/filling operation does not change the quality of the product (including potency). Your validation data must also show that the homogeneity of a product is maintained by appropriate means throughout the entire filling process for dosage forms such as lotions, creams or other suspensions.

For parenteral, ophthalmic and other sterile products, you must at least perform identity and sterility testing on the product in the immediate final container.

17. **A product is manufactured in a non-MRA country, then shipped in bulk to an MRA country, where it is packaged and tested before being released and exported to Canada. Would the testing exemption provided by subsection 4 under regulation C.02.019 "Finished Product Testing" apply?**

No.

18. **With respect to the Health Canada document *Annex 1 to the Current Edition of the Good Manufacturing Practices Guidelines – Selected Category IV Monograph Drugs (GUI-0066)*, how are firms required to demonstrate that "all test methods have been shown to provide accurate and consistent results"?**

To demonstrate consistency, include a satisfactory analytical evaluation of parameters such as accuracy, precision, specificity and linearity. Ensure this evaluation covers multiple tests of samples with known properties.

## Records – C.02.020, C.02.021, C.02.022, C.02.023, C.02.024, C.02.024.1

1. **If an importer's master production documents refer to standard operating procedures (SOPs), do these SOPS have to be available at the importer's premises?**

Yes. Procedures related to critical processes must be available on site, regardless of whether they are referenced in the master product documents or not.

2. According to section C.02.020 “Records,” documents to be kept by the fabricator, packager/labeller, distributor and importer must be stored on their premises in Canada. In the case of a distributor or importer particularly, these documents are sometimes kept only on the premises of a consultant hired to provide quality control services. Therefore they are not available on the premises of the distributor or importer at the time of the inspection. Is this practice acceptable?

No. All documents required under Division 2 of the Food and Drug Regulations must be available on the premises of the distributor or importer. Exceptionally, the consultant may bring a file home for a short time to review it. But if at the time of the inspection, required documents are not available on the premises of the distributor or importer, an observation to this effect will be made in the report. In some cases, this could also lead to a non-compliant rating.

3. Do wholesalers need to validate their computerized systems used for good manufacturing practice (GMP) activities (for example, recall)?

Yes, wholesalers need to validate their computerized systems used for GMP activities. See interpretation 6 under sections C.02.020 to C.02.024 “Records.”

Also, wholesaling operations must carry out routine quality system functions, as outlined in sections C.02.004 “Premises,” C.02.006 “Personnel,” C.02.012 “Manufacturing Control,” and C02.013 to C.02.015 “Quality Control Department.” This includes ensuring:

- customer orders and product distribution are tracked (to be able to carry out an effective and timely recall)
- material status control is maintained (for example: released, rejected, quarantined, returned and recalled products)
- accountability of stock/inventory control (related to recall capability)
- expiry date control (to ensure expired or soon-to-be expired products are not distributed)
- proper storage/environmental control of drug products (for example: temperature mapping, monitoring of storage temperature to ensure drug label storage conditions are met)
- deviation handling (for example: temperature excursion, temperature alarm and notification, procedure deviation, etc.)
- processing of returned drugs
- complaint handling (product- or operation-related)

- self-inspection

You may choose to control these functions using a computerized system. There is no specific regulation requiring computer validation. However, this requirement is implied. When computer or automated systems are used to control and maintain quality system functions, the system must be able to provide and maintain data integrity in order to maintain records properly and comply with regulatory requirements for records.

So, you should validate your system for its intended use. Document validation activities and results.

## Samples – C.02.025, C.02.026

1. **What is considered an adequate sample when a tank load of a raw material is received?**

The retained sample should represent at least twice the amount needed to complete all required tests (see interpretation 4, sections C.02.025 to C.02.026 "Samples"). For bulk materials received in tankers, take the retained sample before mixing it with unused quantities still present in the storage tank.

2. **A pressurized tanker of hydrocarbon raw materials (isobutan, propane, etc.) is normally sampled and approved before pumping. What is the current Health Canada policy for sample retention, given the inherent risks generated by these flammable gases under pressure?**

Manufacturers are not expected to retain samples of pressurized raw materials. The intent of section C.02.030 "Medical Gases" is applied to these cases.

3. **If a product is fabricated in Canada and exported outside of Canada (i.e. the product is not sold on the Canadian market), are samples of this finished product to be retained in Canada?**

No. In this case, the Canadian site is a contract fabricator and not a distributor.

Subsection C.02.025 (1) "Samples" of the Food and Drug Regulations requires that the distributor and importer (not the fabricator) keep a sample of each lot of the packaged/labelled drug. This also applies if the Canadian fabricator manufactures a product for a Canadian distributor (a Drug Identification Number owner).

On the other hand, subsection C.02.025 (2) "Samples" of the Regulations for retained samples of raw materials applies to the fabricator (the person who transforms the raw material into a finished product), not the distributor.

4. **If a product is fabricated in Canada, packaged by another company in Canada, and then exported outside of Canada (i.e. the product is not sold on the Canadian market), who is responsible for retaining samples of finished products?**

The Canadian fabricator and the Canadian packager/labeller are not responsible for retaining samples of the finished product. Instead, subsection C.02.025 (1) "Samples" of the Regulations requires that the distributor and importer keep a sample of each lot of the packaged/labelled drug. Similarly, if a Canadian fabricator manufactures a product for a Canadian distributor (a Drug Identification Number owner), the distributor is responsible.

This requirement could vary depending on the health authority, as each country could have their own regulatory requirement. The Canadian fabricator or packager/labeller may want to negotiate a written contract or agreement with the foreign client (the distributor/owner of the product) to clearly mention who will be responsible to keep the retained samples of the finished product, as long as this is acceptable to the health authority of that country.

## Stability – C.02.027, C.02.028

1. **Do batches have to be tested for preservatives at initial release and then in the continuing stability program?**

For finished products where antimicrobial agents are added to preparations (such as multiple dose injections, topical creams and oral liquids), include an assay with limits in the specifications.

You must perform a test for antimicrobial preservative effectiveness during the development phase of the product to establish the minimal effective level of preservatives that will be available up to the stated expiry date. This is also the level that a single regular production batch of the drug is to be tested against for antimicrobial preservative content at the end of the proposed shelf life. Once the minimal effective preservative level has been determined, you must test all lots of any preservative-containing dosage form included in your stability program at least once at the expiry date for preservative content.

For sterile drugs, you must have a declaration of preservatives on the label and treat them the same as active ingredients (i.e. test them for preservative content at pre-established control points for those batches enrolled in your continuing stability program). Where the lower limit of the preservative is less than 90% of label claim, you should perform a challenge test on samples at or below the lower limit. The challenge test does not need to be included in your specifications, as long as you include an assay for the preservative.

2. Can it be assumed that *United States Pharmacopeia* (USP) chromatographic assay methods are stability indicating?

No.

3. Is it acceptable to place an expiry date on a bottle cap instead of on the bottle label?

No. The expiration date must appear on any panel of the inner and outer label. Please refer to section C.01.004 (c) (v) "General" of the Food and Drug Regulations.

4. When the labelled expiration date states only the month and year, does it mean the end of the month?

Yes. The product should meet approved specifications up to the last day of the specified month.

5. Can accelerated stability data of less than three months be used to determine expiry date?

Accelerated stability studies of any length are considered as preliminary information only and should be supported by long-term stability testing. The assignment of expiry dates should be based on long-term stability testing.

6. Should drugs packaged into kits and later sterilized be tested for stability?

Yes. These operations are part of manufacturing. For drugs that are packaged into trays or kits, with the resulting package sterilized before being marketed, you should have data available to show that the sterilization process does not adversely affect the physical and chemical properties of the drug. The testing should be sensitive enough to detect any potential chemical reactions and/or degradation. You should compare test results with test values obtained before sterilization.

7. What are the required storage conditions with respect to stability drug samples of drug products, including Category IV monograph products?

Store stability drug samples for all drug products within the acceptable temperature range defined on the approved labelling of the product. Also, stability samples for all drugs—including Category IV monograph drug products—must be stored under conditions described in *Stability Testing of Existing Drug Substances and Products*.

You must assign expiry dates for Category IV monograph drug products based on stability studies, as described in *Evaluation for Stability Data – ICH Topic Q1E*. Storage conditions on labels should reflect current ICH guidance.

## Sterile products – C.02.029

Questions and answers about sterile products are covered in a separate guidance document: *Annex 1 to the* Good manufacturing practices guide – *Manufacture of sterile drugs (GUI-0119)*.

# Appendix C – References

## Laws and regulations

*Food and Drugs Act*
laws.justice.gc.ca/en/F-27

Food and Drug Regulations
laws.justice.gc.ca/en/F-27/C.R.C.-C.870

*Controlled Drugs and Substances Act*
laws.justice.gc.ca/en/C-38.8

## Annexes to GUI-0001

Annex numbers and titles have been updated to match those used by the European Union (EU) and the Pharmaceutical Inspection Cooperation/Scheme PIC/S. This helps us work towards the global harmonization of technical standards and procedures related to GMP and prepare for future revisions.

URLs to these documents (active at the time of this GUI-0001 posting) are provided. Annexes are also available on Health Canada's website under Good Manufacturing Practices/Guidance Documents.

*Annex 1 to the* Good manufacturing practices guide – *Manufacture of sterile drugs (GUI-0119)*
* URL not available at time of posting

*Annex 1 to the Current Edition of the Good Manufacturing Practices Guidelines – Selected Category IV Monograph Drugs (GUI-0066)* ** To be renamed Annex 7 at next revision.
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0066_annex_1-eng.php

*Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines – Schedule D Drugs, Biological Drugs (GUI-0027)*
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0027_annexe_d-eng.php

*Annex 3 to the Current Edition of the Good Manufacturing Practices Guidelines – Schedule C Drugs (GUI-0026)*
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0026_annexe_c-eng.php

*Annex 4 to the Current Edition of the Good Manufacturing Practices Guidelines – Veterinary Drugs (GUI-0012)*
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0012_annex_4-eng.php

*Annex 5 to the Current Edition of the Good Manufacturing Practices Guidelines – Positron Emitting Radiopharmaceuticals (PER's) (GUI-0071)*
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui_0071_tc-tm-eng.php

*PIC/S Annex 11: Computerised Systems*
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/comput-inform-eng.php

*Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines – Drugs Used in Clinical Trials (GUI-0036)*
hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/docs/cln_trials-essais_cln-eng.php

*PIC/S Annex 17: Guidance on Parametric Release*
hc-sc.gc.ca/dhp-mps/compli-conform/int/part/gui_0046_tc-tm-eng.php

## Good manufacturing practices

*Good Manufacturing Practices Guidelines for Active Pharmaceutical Ingredients (GUI-0104)*
hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugs-drogues/actingre-gui-0104-eng.php

*Good Manufacturing Practices Guidelines for Medical Gases (GUI-0031)*
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui_0031_tc-tm-eng.php

*Guidelines for Temperature Control of Drug Products during Storage and Transportation (GUI-0069)*
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0069-eng.php

## Validation guidelines

*Cleaning Validation Guidelines (GUI-0028)*
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/gui_0028_tc-tm-eng.php

*Process Validation: Aseptic Processes for Pharmaceuticals (GUI-0006)*
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/app-papp-eng.php

*Process Validation: Terminal Sterilization Processes for Pharmaceutical Products (GUI-0074)*
http://www.hc-sc.gc.ca/dhp-mps/consultation/compli-conform/2011-gui-0074_ltr-eng.php

*Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)*
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/gui_29-eng.php

## Recall procedures

*Product Recall Procedures*
hc-sc.gc.ca/dhp-mps/compli-conform/recall-retrait/proces-eng.php

*Recall Policy (POL-0016)*
hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugs-drogues/pol_0016_tc-tm-eng.php

## Other related documents

*Alternate Sample Retention Site Guidelines (GUI-0014)*
hc-sc.gc.ca/dhp-mps/compli-conform/licences/form/gui-0014_doc-eng.php

*Guidance Document: Blood Regulations (GUI-0113)*
hc-sc.gc.ca/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/blood-reg-sang/blood-guid-sang-ligne-2014-10-23-eng.pdf

*Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees (GUI-0002)*
hc-sc.gc.ca/dhp-mps/compli-conform/licences/directives/gui-0002-eng.php

*Guidance on Evidence to Demonstrate Drug Good Manufacturing Practices Compliance of Foreign Sites (GUI-0080)*
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0080-eng.php

*International Harmonized Requirements for Batch Certification*
hc-sc.gc.ca/dhp-mps/compli-conform/int/mra-arm/ihrbc-eihd_tc-tm-eng.php

*Risk Classification of Good Manufacturing Practices Observations (GUI-0023)*
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0023-eng.php

*Stability Testing of Existing Drug Substances and Products*
hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/stabt_stabe-eng.php

*Standard for the Fabrication, Control and Distribution of Antimicrobial Agents for Use on Environmental Surfaces and Certain Medical Devices (GUI-0049)*
hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/gui_49-eng.php

J.R. Schwenkea & D.K. O'Connor (2008), “Design and Analysis of Analytical Method Transfer Studies,” Journal of Biopharmaceutical Statistics 18(5), 1013-33

# International guidance documents

These guidance documents were developed by the International Council on Harmonisation (ICH) and adopted (and translated) by Health Canada. They can be found on the Health Canada website under ICH.

*ICH Q1A(R2): Stability Testing of New Drug Substances and Products*
hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q1a(r2)-eng.php

*ICH Q1B: Stability Testing: Photostability Testing of New Drug Substances and Products*
hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q1b-eng.php

*ICH Q1C: Stability Testing: Requirements for New Dosage Forms*
hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q1c-eng.php

*ICH Q1D: Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products*
hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q1d-eng.php

*ICH Q1E: Evaluation for Stability Data*
hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q1e-eng.php

*ICH Q2 (R1): Validation of Analytical Procedures: Text and Methodology*
hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q2r1-eng.php

*ICH Q3A (R2): Impurities in New Drug Substances*
hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q3ar2-eng.php

*ICH Q3B(R2): Impurities in New Drug Products*
hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q3br2-eng.php

*ICH Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q6a-step4etape-eng.php

*ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q6b-eng.php

*ICH Q7: Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients*
hc-sc.gc.ca/dhp-mps/compli-conform/legislation/gazette1-q7a-eng.php

*ICH Q9: Quality Risk Management*
hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q9-step4etape-eng.php

*ICH Q10: Pharmaceutical Quality System*
hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q10-step4etape-eng.php