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# Good manufacturing practices for active pharmaceutical ingredients



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Canada

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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.

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



**Important:** Key or cautionary information for people to know.



**Information:** Supplementary information like quotes and legal references.



**Tip:** Things for people to do or understand.

# About this document

## 1. Purpose

This guide is for people who work with Active Pharmaceutical Ingredients (APIs) and their intermediates to understand and comply with Part C, Division 2 of the [Food and Drug Regulations](#) (the Regulations), which is about Good Manufacturing Practices (GMP). You can find definitions to terms used in this guide under [Appendix A](#). This guide applies to the following:

- fabricators
- packagers/labellers (including re-packagers/re-labellers)
- testers
- importers
- distributors
- wholesalers

## 2. Scope

These guidelines apply to non-sterile APIs and their intermediates for use in human and veterinary drugs in dosage form:

- pharmaceutical
- radiopharmaceutical

The scope of this document also includes the following:

- The manufacture of sterile APIs up to the point immediately prior to the APIs being rendered sterile.
- Plant-based APIs, such as cannabis APIs (e.g. Cannabidiol, Tetrahydrocannabinol), which are to be used in the fabrication of a health product containing cannabis.
- APIs that are produced using blood or plasma as raw materials intended for use in a pharmaceutical product.
- Particle size processing of APIs (e.g. milling, micronizing).

- Active substances for veterinary use set out on [\*List A: List of Certain Antimicrobial Active Pharmaceutical Ingredients imported or compounded by healthcare professionals.\*](#)



**The scope of this document does not include:**

- Sterile APIs and sterile API intermediates (including the sterilization of APIs and aseptic processing of sterile APIs);
- Drugs in dosage form, dosage form intermediates, heterogeneous API 'Blends', medical gases, biologics and bulk process intermediates (Schedule D to the Act), and radiopharmaceuticals of biological origin (Schedule C to the Act);
- The two items above are subject to the GMP requirements described in [\*Good manufacturing practices guide for drug products \(GUI-0001\)\*](#) and its applicable reference documents (Appendix C);
- Natural health products;
- Ectoparasiticides for veterinary use where other standards than these guidelines that ensure that the material is of appropriate quality are used;
- Materials at steps prior to the introduction of the defined "API Starting Material";
- APIs for use in clinical trials. The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. For information regarding APIs for use in clinical trials, see [\*ICH Q7: Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients\*](#);
- Physical processing such as granulation, coating and heterogeneous API blending. These activities are associated with drugs in dosage form and subject to the GMP requirements described in the [\*Good Manufacturing Practices Guide for Drug Products \(GUI-0001\)\*](#);



### 3. Introduction

These guidelines interpret the requirements for Good Manufacturing Practices (GMP) in Part C, Division 2 of the Regulations. They were developed by Health Canada in consultation with stakeholders.

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

Establishments are inspected by Health Canada inspectors to assess their compliance with the [\*Food and Drugs Act\*](#) (the Act) and associated regulations. When an inspection is conducted, inspectors 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 requirements can be interpreted, and are not intended to cover every possible case. Other ways of complying with GMP requirements will be considered with proper scientific justification. Also, as new technologies emerge, different approaches may be called for.

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

- the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
- the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH)
- the Pharmaceutical Inspection Co-operation Scheme (PIC/S)
- other international regulatory agencies

## Checklist – GMP regulations by API activity

This chart shows which sections of the Regulations apply to which licensable API activities (by type).

**Chart 1.0:** GMP regulations (Part C, Division 2 of the *Food and Drug Regulations*) applicable to licensable API activities

Section of the Regulations		F	P/L	T	I	D	W <sup>1</sup>
Premises	C.02.004	✓	✓	n/a	✓	✓	✓
Equipment	C.02.005	✓	✓	✓	n/a	n/a	n/a
Personnel	C.02.006	✓	✓	✓	✓	✓	✓
Sanitation	C.02.007	✓	✓	n/a	n/a	n/a	n/a
	C.02.008	✓	✓	n/a	n/a	n/a	n/a
Raw material testing	C.02.009	✓	n/a	<sup>2</sup>	n/a	n/a	n/a
	C.02.010	✓	n/a	<sup>2</sup>	n/a	n/a	n/a
Manufacturing control	C.02.011	✓	✓	n/a	✓	n/a	n/a
	C.02.012	✓	✓	n/a	✓	✓	✓
Quality control	C.02.013	✓	✓	n/a	✓	✓	✓
	C.02.014	✓	✓	n/a	✓	✓	✓
	C.02.015	✓	✓	✓	✓	✓	✓
Packaging material testing	C.02.016	✓	✓	n/a	n/a	n/a	n/a
	C.02.017	✓	✓	n/a	n/a	n/a	n/a
Finished product testing	C.02.018	✓	✓	<sup>2</sup>	✓	✓	✓
	C.02.019	n/a	✓	n/a	n/a	n/a	n/a
Records	C.02.020	✓	✓	✓	✓	n/a	n/a
	C.02.021	✓	✓	✓	✓	✓	✓
	C.02.022	n/a	n/a	n/a	✓	✓	✓
	C.02.023	✓	✓	n/a	✓	✓	✓
	C.02.024	✓	✓	n/a	✓	✓	✓
Samples	C.02.025	✓	n/a	n/a	n/a	n/a	n/a

	C.02.026	✓	n/a	n/a	n/a	n/a	n/a
Stability	C.02.027	✓	<sup>2</sup>	<sup>2</sup>	✓	n/a	n/a
	C.02.028	✓	<sup>2</sup>	<sup>2</sup>	✓	n/a	n/a

<sup>1</sup> Although the wholesale of APIs is not defined as a licensable activity in [Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees \(GUI-0002\)](#), agents and brokers will be considered wholesalers and must follow Health Canada's GMP requirements.

<sup>2</sup> Where applicable depending on the nature of the activities.

F = Fabricator, P/L = Packager/Labeller, T = Tester, I = Importer, D = Distributor, W = Wholesaler

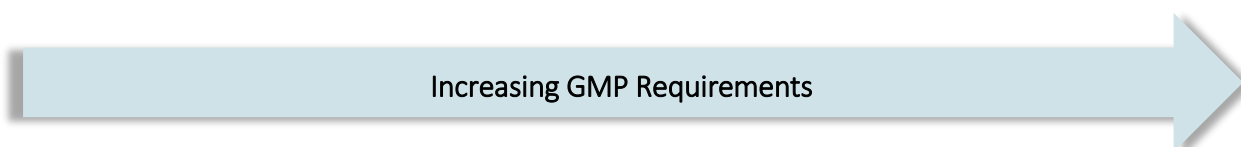
## API manufacturing steps and GMP requirements

The chart included below shows various types of API manufacturing and their related manufacturing steps. The point at which production of the API begins and from which compliance to GMPs should be implemented should be based on the application filed with Health Canada, where applicable, and/or other criteria including the Chart 2.0 below. This guide applies to the manufacturing steps shaded in blue.

Chart 2.0<sup>3</sup>: GMP requirements applicable to different API manufacturing steps

Type of manufacturing	Manufacturing steps				
	1	2	3	4	5
<b>Chemical manufacturing</b>	Production of API starting material	Introduction of API starting material into process	Production of intermediate(s)	Isolation and purification	Physical processing and packaging
<b>APIs derived from animal sources</b>	Collection of organ, fluid or tissue	Cutting, mixing and/or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing and packaging
<b>APIs extracted from plant sources</b>	Collection of plants	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing and packaging
<b>Herbal extracts used as APIs</b>	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing and packaging

APIs made of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting or comminuting			Physical processing and packaging
Biotechnology: fermentation or cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing and packaging
“Classical” fermentation to produce APIs	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing and packaging



<sup>3</sup>Source: [\*ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients\*](#)

This diagram shows at which steps during the API manufacturing process the good manufacturing practices defined in the guidance document would normally be applied.

**Chemical manufacturing:** GMP requirements are normally applied at the introduction of the API starting material into the process and continue during production of intermediate(s), isolation and purification, and physical processing and packaging.

**APIs derived from animal sources:** GMP requirements are normally applied at the introduction of the API starting material into the process and continue during isolation and purification and physical processing and packaging.

**APIs extracted from plant sources:** GMP requirements are normally applied at the introduction of the API starting material into the process and continue during isolation and purification and physical processing and packaging.

**Herbal extracts used as APIs:** GMP requirements are normally applied at further extraction and continue during physical processing and packaging.

**APIs made of comminuted or powdered herbs:** GMP requirements are normally applied at physical processing and packaging.

**Biotechnology manufacturing through fermentation or cell culture:** GMP requirements are normally applied at the maintenance of the working cell bank and continue during cell culture and/or fermentation, isolation and purification, and physical processing and packaging.

**APIs produced through classical fermentation:** GMP requirements are normally applied at the introduction of the cells into fermentation and continue during isolation and purification and physical processing and packaging.

The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps.



The manufacturer should state and document their rationale for the point at which the API production begins since this is the point when GMP requirements will apply. For synthetic processes, this is usually the point when the API starting material is introduced into the process, but for other processes (fermentation, extraction, etc.) a rationale should be established on a case-by-case basis. Chart 2.0 above provides more guidance on where GMPs outlined in this guide start to apply.



For information regarding APIs manufactured by fermentation or cell culture, see [\*ICH Q7: Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients\*](#).

# About quality management

## 4. Pharmaceutical quality system

The following section was adapted for Health Canada from [\*PIC/S Guide To Good Manufacturing Practice For Medicinal Products Part II\*](#).

### Guiding principles

Do you hold an establishment licence, or run an operation governed by Part C, Division 2 of the *Food and Drug Regulations* (the Regulations)? If you do, you must ensure that you comply with these requirements when you fabricate, package, label, import, distribute, test and wholesale

Active Pharmaceutical Ingredients (API) or API intermediates. You must not place consumers at risk because of poor safety, quality, efficacy, or for not complying with regulations.

You are responsible for meeting the requirements outlined in the Regulations and clarified 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 should consider the following:

- Quality should be the responsibility of all persons involved in manufacturing.
- You should 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.
- Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.
- The system for managing quality should include the organisational structure, procedures, processes and resources, as well as activities necessary to provide assurance that the API will meet its intended specifications for quality and purity. All quality related activities should be defined and documented.
- There should be a quality unit(s) that is independent of production and that fulfills both quality assurance and quality control responsibilities. This can be in the form of separate quality assurance and quality control units or a single individual or group, depending upon the size and structure of the organization.
- The personnel authorised to release APIs and API intermediates should be specified.
- All quality-related activities should be recorded at the time they are performed.
- Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.
- No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine or the use of raw materials or intermediates pending completion of evaluation).
- Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g. quality related complaints, recalls, regulatory actions, etc.).



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 APIs.

## Quality risk management

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

The principles of quality risk management should ensure 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 through communication with the user of the active substance.
- The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.



Information on quality risk management processes and applications can be found in [\*ICH Q9: Quality Risk Management\*](#).

## Responsibilities of the quality unit(s)

The quality unit(s) should be involved in all quality-related matters. It should review and approve all appropriate quality-related documents.

The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include, but are not limited to:

- releasing or rejecting all APIs
- releasing or rejecting API intermediates for use outside the control of the manufacturing company
- establishing a system to release or reject raw materials, API intermediates, packaging and labelling materials
- reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution

- making sure that critical deviations are investigated and resolved
- approving all specifications and master production instructions
- approving all procedures impacting the quality of API or API intermediates
- making sure that self-inspections are performed
- approving API and API intermediate contract manufacturers
- approving changes that potentially impact API or API intermediate quality
- reviewing and approving validation protocols and reports
- making sure that quality related complaints are investigated and resolved
- making sure that effective systems are used for maintaining and calibrating critical equipment
- making sure that materials are appropriately tested and the results are reported
- making sure that there is stability data to support retest or expiry dates and storage conditions on APIs or API intermediates where appropriate
- performing product quality reviews

## Responsibilities for production activities

The responsibility for production activities should be described in writing, and should include, but not be limited to:

- preparing, reviewing, approving and distributing the instructions for the production of APIs or API intermediates according to written procedures
- producing APIs and, when appropriate, API intermediates according to preapproved instructions
- reviewing all batch production records and ensuring that these are completed and signed
- making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded
- making sure that production facilities are clean and when appropriate disinfected;
- making sure that the necessary calibrations are performed and records kept
- making sure that the premises and equipment are maintained and records kept
- making sure that validation protocols and reports are reviewed and approved
- evaluating proposed changes in product, process or equipment



- making sure that new and, when appropriate, modified facilities and equipment are qualified

## Self-inspection

In order to verify compliance with the principles of GMP for APIs, regular self-inspections (i.e. internal audits) should be performed in accordance with an approved schedule. Self-inspection findings and corrective actions should be documented and brought to the attention of responsible management of the establishment. Agreed corrective actions should be completed in a timely and effective manner.

## Product quality review

Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least a review of:

- critical in-process control and critical API test results;
- all batches that failed to meet established specification(s);
- other batches that may have been associated with the specific failure or deviation;
- all critical deviations or non-conformances and related investigations;
- any changes carried out to the processes or analytical methods;
- results of the stability monitoring program;
- all quality-related returns, complaints and recalls;
- adequacy of corrective actions.

The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective actions should be completed in a timely and effective manner.

# Guidance

## 5. Regulations

For each section below, the exact text from Part C, Divisions 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.

### 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 \(GUI-0049\)](#).

## Sale

### 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.

#### 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.

#### 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.



Labelling should not be placed over an existing label or obstruct it in any way. Proper labelling is required to comply with the Act and Division 2 of the Regulations



Even though labelling of information is outlined in [C.02.003.2\(2\)](#), importer are responsible for the required labelling information in Section [C.02.003.2\(2\)](#).

## Use in fabrication

### 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.

## Premises

### 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 permits 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. Buildings and facilities used in the manufacture of APIs and API intermediates should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination, including cross contamination. Where microbiological specifications have been established for the API or API intermediate, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.
2. Ensure there is enough space in buildings and facilities for your equipment and materials to be placed in an orderly way so you avoid mix-ups and contamination.
3. Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.
4. Design the flow of materials and personnel through your building or facilities to prevent mix-ups or contamination.
5. There should be defined areas or other control systems for the following activities:
  - a. receipt, identification, sampling and quarantine of incoming materials before release or rejection
  - b. quarantine before APIs or API intermediates are released or rejected
  - c. API or API intermediate sampling
  - d. holding rejected materials before they are returned to supplier, reprocessed, or destroyed
  - e. storing released materials
  - f. production
  - g. packaging and labelling
  - h. laboratory operations
6. Provide clean washing and toilet facilities for your personnel, as well as places where they can shower and change clothes, if appropriate. Equip washing facilities with hot and cold water, soap or detergent and air driers or single-service towels. Keep washing

and toilet facilities, showers and changing areas separate from, but easily accessible to, production areas.

7. Separate laboratory areas and operations from production areas when possible. Some laboratory areas—e.g. those used for in-process controls—can be located in production areas if this does not adversely affect laboratory measurements, and the lab's operations do not affect production processes, the APIs themselves or the API intermediates.
8. Qualify and monitor all utilities that impact product quality (e.g. water, steam, gases, compressed air, and heating, ventilation and air conditioning). Actions should be taken when limits are exceeded. A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems) and made available upon request.
9. Provide adequate ventilation, air filtration and exhaust systems. Design and build these systems to minimize contamination and cross-contamination. Give special attention to areas where APIs are exposed to the environment. As appropriate to the stage of production, include equipment for control of:
  - a. air pressure
  - b. microorganisms
  - c. dust
  - d. humidity
  - e. temperature

If air is re-circulated to production areas, take appropriate measures to control risks of contamination and cross-contamination.

10. Identify permanent pipework and ensure that it is located in an area, which avoids risk of contamination. Label fixed pipework clearly to indicate the contents and (where applicable) the direction of flow. This can be done by identifying individual lines, documentation, computer control systems, or alternative means.
11. Ensure drains are the right size and have an air break or way to prevent back-siphonage.
12. Where water is treated to achieve a defined quality, the system should be validated and monitored with appropriate actions limits.
13. Use dedicated production areas—which can include facilities, air handling equipment and/or process equipment—for producing highly sensitizing materials such as penicillins or cephalosporins.

14. You must demonstrate that the premises are designed in such a manner that the risk of cross-contamination between products is minimized. Take into account factors including:

- a. facility/equipment design and use
- b. personnel and material flow
- c. microbiological controls
- d. physical, chemical and toxicological properties of materials used
- e. process characteristics
- f. cleaning processes
- g. analytical capabilities

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.

- a. Use dedicated and self-contained production areas when working with infectious, cytotoxic material, or material with a high pharmacological activity unless validated procedures to inactivate and clean up after these materials are established based on a written risk assessment and maintained.
- b. Ensure no production activities (including weighing, milling and packaging) of highly toxic non-pharmaceutical materials (such as pesticides and herbicides) are conducted using premises and/or equipment used for the production of APIs.
- c. Handle and store highly toxic non-pharmaceutical materials (such as pesticides and herbicides) separately from APIs.

15. The manufacturing facility should be well lit to facilitate operation, maintenance and cleaning.

16. Maintain and repair buildings where APIs are produced. Maintain building cleanliness.

## 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 APIs of consistent quality, you must ensure your equipment is appropriate for the intended use and performs as intended.

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

- a. other APIs
- b. dust and other airborne contaminants
- c. foreign materials, such as:
  - rust
  - lubricant
  - particles coming from the equipment
  - cleaning agents

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 adjacent areas easier and avoids interference with other processing operations. It also minimizes the circulation of personnel and optimizes the flow of materials.

## Interpretation

1. Use equipment of the appropriate design and size. The equipment should be located in a suitable place where it can be used as intended, easily cleaned, sanitized, as appropriate, and maintained.
2. Ensure any equipment surfaces touching raw materials, API or API intermediates do not alter quality beyond the official or other established specifications.



3. Clean, store, and where appropriate, sanitize or sterilize your equipment and utensils to prevent contamination or carry over that would alter the quality of the intermediate or API.
4. Ensure that your records for equipment use, sanitization and/or sterilization, maintenance, and cleaning specify the:
  - a. date and time of use or date and time the activity took place
  - b. product and batch number
  - c. person who cleans and does the maintenance on the equipment used to make the batch
5. If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.
6. Keep substances like lubricants, heating fluids or coolants away from APIs and API intermediates to not alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Use food grade lubricants and oils whenever possible.
7. Use closed or contained equipment whenever possible. If you use open equipment, take measures to reduce the risk of contamination.
8. Ensure procedures and controls are in place to prevent mix-ups. When using non-dedicated equipment, cleaning procedures must be in place and validated to avoid cross-contamination.
9. Identify major equipment (e.g. reactors, storage containers) and permanently installed processing lines used for production.
10. Keep schedules, procedures and logs for the preventative maintenance of equipment. The personnel responsible for equipment maintenance should also be established.
11. Remove any equipment that is not suitable for its intended use from production areas. If you cannot move the equipment, clearly label it to prevent use.
12. Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule. Keep records.
13. Calibrate equipment using standards traceable to certified standards, if they exist. Keep records.

14. The current calibration status of critical equipment should be known and verifiable.
15. Identify and do not use equipment that do not meet calibration criteria.
16. Investigate any deviation from calibration standards to determine if these could have had an impact on the quality of the API or API intermediate manufactured using this equipment since the last successful calibration.
17. Ensure that the devices you use to weigh and measure APIs and API intermediates are suitably accurate for their intended use.
18. Use only equipment within its qualified operating range.
19. Validate GMP related computerized systems. The depth and scope of validation depends on the diversity, complexity, and criticality of the computerized system.
20. Keep written procedures for operating and maintaining computer systems.
21. Use Installation Qualification (IQ) and Operational Qualification (OQ) to show that computer hardware and software are capable of performing the intended tasks.
22. Commercially available software that has been qualified does not need the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available. Documentation should be available anytime you install or validate software.
23. Critical equipment and ancillary systems should be qualified. Qualification is usually done by conducting the following activities, individually or combined:
  - Design Qualification (DQ)
  - Installation Qualification (IQ)
  - Operational Qualification (OQ)
  - Performance Qualification (PQ)



Records maintained in a computer system, must comply with section [C.02.015](#) and sections [C.02.020-C.02.024.1](#).



For supplementary optional guidance for validation activities for APIs, refer to the [Guide to validation – drugs and supporting activities \(GUI-0029\)](#) and [PIC/S Annex 11: Computerised Systems](#).

# 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 that the Minister 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 API quality system.

Who you hire is one of the most important elements in any API operation. Without proper personnel with a quality mindset and training, it is difficult to fabricate, package/label, test, import, distribute or store good quality APIs.

It is essential that only qualified personnel supervise the fabrication of APIs. These operations are highly technical in nature and 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 personnel or a lack of understanding of the importance of production control.

## Interpretation

1. There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the fabrication, packaging/labelling, testing, importation, distribution and storage of APIs and API intermediates.
  - a. Do not place so many responsibilities on any one individual where 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. Appoint, qualified replacements when key personnel are absent to carry out their duties and functions.
  - e. Ensure all personnel conducting GMP activities are able to understand the written procedures for those activities.
- 2. 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 university degree; in Canada this must be a Canadian university degree or a degree recognized as equivalent by a Canadian university or Canadian 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 (e.g., to cover all shifts) to a person qualified by appropriate education, training and relevant experience related to the work being carried out, while remaining accountable for those duties and responsibilities.



For foreign quality control departments, the person in charge 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.

- 3. 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 (SOP).
  - 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. safety data sheets).
  - f. Review the performance of all personnel periodically.
- 4. Consultants and contractors must have the right qualifications, training and related experience to give advice on the subjects for which they are retained.

### **Responsibility for production activities**

- 5. The responsibility for production activities should be described in writing, and should include but not necessarily be limited to:
  - a. preparing, reviewing, approving and distributing written procedures for the production of APIs
  - b. producing APIs and their intermediates according to written procedures
  - c. reviewing batch production records and makes sure they are complete and signed
  - d. reporting and evaluating production deviations, investigating deviations and records the investigations' conclusions
  - e. cleaning and disinfecting production facilities
  - f. performing calibration and keeping records
  - g. maintaining site and equipment, keeping maintenance records
  - h. reviewing and approving validation protocols and reports
  - i. evaluating proposed changes to products, processes or equipment
  - j. making sure new or modified facilities and equipment are qualified

### **Responsibility for quality control**

- 6. Do not delegate the main responsibilities of the quality unit(s). These responsibilities should be described in writing and should include but not necessarily be limited to:
  - releasing or rejecting APIs—in some cases, the quality unit(s) can delegate releasing intermediates to the production unit, except for those shipped outside the control of the manufacturing company
  - creating a system to release or reject raw materials, intermediates and packaging and labelling materials
  - reviewing finished batch production and laboratory records showing critical process steps before the API is released

- making sure critical deviations are investigated and resolved
- approving all specifications and master production documents
- approving any procedure affecting the quality of APIs or API intermediates
- making sure self-inspections are done
- approving API and API intermediate contract fabricators
- approving changes that could affect API quality
- reviewing and approves validation protocols and reports
- making sure complaints about quality are investigated and resolved
- making sure that effective systems are used for maintaining and calibrating critical equipment making sure materials are tested and test results are reported
- making sure stability data supports the retest date or expiry date and storage conditions for APIs and/or API intermediates
- reviewing product quality annually
- making sure that product quality control equipment is appropriate to testing activities undertaken

## 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 an API facility influences the quality of API products. API products must be fabricated and packaged in areas that are free from environmental contamination and contamination by other APIs.

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

Open production systems (e.g. vessels without lids) or processes closer to the end of production (e.g. purification) need a higher level of environmental control to minimize contamination. Your sanitation program must prevent unsanitary conditions within your site.

There is a significant difference between a finished product production environment (physical process) and an API production environment (chemical process), where you may be using aggressive and corrosive reagents to produce APIs. The level of cleanliness needed in your facility varies depending on:

- whether you are using an open or closed production system
- the stage of API production

## Interpretation

1. Write procedures for cleaning equipment and its release for use in the manufacture of APIs and API intermediates. Include enough detail that personnel can easily clean each type of equipment in a reproducible and effective manner. Your documentation should specify:
  - a. the person(s) responsible for cleaning equipment
  - b. the cleaning schedules and, where appropriate, sanitizing schedules
  - c. a complete description of the methods and materials, including dilution of cleaning agents used to clean equipment
  - d. where appropriate, the instructions for how to disassemble and re-assemble each piece of equipment so it can be properly cleaned
  - e. the instructions for the removal or destruction of previous batch identification
  - f. the instructions for keeping clean equipment free from contamination before it is used
  - g. the inspection of equipment for cleanliness immediately before it is used

- h. the maximum time that can pass between the completion of processing and equipment cleaning, when appropriate
- 2. Design your sanitation program using quality risk management principles. Identify and reduce contamination risks in your facility design and operation. Your sanitation program must contain procedures that describe the following:
  - a. cleaning requirements that apply to all production areas of your facility, 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 equipment, APIs, API intermediates, raw materials, and packaging/labelling materials when rodenticides, insecticides, fungicides and fumigation agents are used
  - i. microbial and environmental monitoring procedures (established based on quality risk management principles) that:
    - define limits in areas where susceptible products are fabricated or packaged and take action when limits are exceeded
    - 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. Ensure residues from the cleaning process (such as detergents and solvents) are removed from equipment. Define cleaning procedures and cleaning agents, including acceptance criteria for residues.
  - b. Studies on equipment cleaning and sanitization should address microbiological and endotoxin contamination in processes where there is a need to reduce:
    - microbiological count
    - endotoxins in the API



- other processes where contamination is a concern (e.g. non-sterile APIs used to manufacture sterile products)
  - c. Filter sanitizers and disinfectants (like isopropyl alcohol) to remove spores where needed.
  - d. Campaign or continuous 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.
  - e. Clean non-dedicated equipment between productions of different materials to prevent cross-contamination.
  - f. Get rid of sewage, refuse and other waste (e.g. solids, liquids or gaseous by-products) in a safe, timely and sanitary way. Clearly identify containers and pipes for waste.
4. Validate your cleaning procedures. In general, cleaning validations should focus on situations or process steps where contamination or carryover of materials poses the greatest risk to the API quality. For example, you may not need to validate equipment-cleaning procedures in early production, where the next purification steps take away residues.
5. Validate analytical methods used to detect residues or contaminants. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. Establish the recovery level for each method. Residue limits should be practical, achievable, verifiable and based on the most deleterious residue. Set reasonable limits based on the minimum pharmacological, toxicological or physiological activity of the API or its most harmful part.



To better understand how to limit residue and contamination from API materials, see [Cleaning Validation Guidelines \(GUI-0028\)](#).

6. Monitor your cleaning procedures often to ensure they are working. Use analytical testing and visual inspection to check for equipment cleanliness. Visual inspection can allow detection of gross contamination concentrated in small areas that could go undetected by sampling and/or analysis.
7. Ensure that your equipment use, sanitization and/or sterilization, maintenance, and cleaning records specify the:
- a. date and time of use or date and time the activity took place
  - b. product and batch number

- c. person who cleans and does the maintenance on the equipment used to make the batch
- 8. Where processes contain dusty operations, avoid using unit or portable dust collectors in places where you fabricate, especially in dispensing, unless their exhaust filtration is effective and you regularly maintain them according to a written and approved procedure.

## 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.
- 2. Ensure that personnel and visitors practice good sanitation and health habits.
- 3. Ensure that employees follow rules on cosmetics and jewelry.
- 4. Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

5. Ensure that personnel wear clean clothing suitable for the manufacturing activity and change their clothing when appropriate. When necessary, they should also wear head, face, hand and arm coverings to protect APIs and API intermediates.
6. Keep soiled protective clothing that can be re-used in separate containers until it is laundered, disinfected or sterilized according to a written procedure. It is unacceptable to wash soiled protective clothing at home.
7. Staff should avoid direct contact with APIs.
8. Do not smoke, eat, drink or chew food in manufacturing areas. Store food separate from these areas.

## 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 Minister 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 three objectives:

1. Confirm identity of the raw materials.
2. Prevent raw material defects from affecting API quality (raw material not meeting specifications should not be used for manufacturing APIs).
3. Confirm that the raw materials have the properties that will provide the desired quality, quantity or yield in a given manufacturing process.



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

## Interpretation

1. You should put into place and document specifications for:
  - a. raw materials
  - b. intermediates
  - c. APIs, where necessary
  - d. process aids
  - e. materials used during the production of APIs or API intermediates that can critically impact their quality

Also set out and document the criteria you use for accepting in-process controls.



The person in charge of the quality control department should date and approve these specifications. This person can assign someone else to date and approve raw material specifications. The designated person must meet the requirements described under section [C.02.006](#) of the Regulations, interpretation 1.

2. Establish specifications for raw materials based on process design, as well as your overall control strategy. This ensures that your final product meets quality objectives.
3. Buy raw materials based on agreed upon specifications from suppliers approved by the quality unit(s).

4. Ensure that water used in the manufacture of APIs is suitable for its intended use.
5. Ensure the process water, at a minimum, meets World Health Organization (WHO) guidelines for drinking (potable) water quality.
6. If drinking (potable) water is insufficient to assure API quality and tighter chemical or microbiological specifications are called for then you should have appropriate specifications which include:
  - a. physical and chemical attributes
  - b. total microbial count
  - c. objectionable organisms and/or endotoxins
7. When the fabricator of a non-sterile API intends or claims that the API can be further processed to produce a sterile drug, the fabricator should monitor and control water used in the final isolation and purification steps. Monitor and control for total microbial count, objectionable organisms and endotoxins.
8. 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 analytical method validation in [\*ICH Q2 \(R1\): Validation of Analytical Procedures: Text and Methodology\*](#) or [\*VICH GL2: Validation of analytical procedures: Methodology\*](#) as applicable or any standard listed in Schedule B to the Act.

9. When you are validating your methods, consider the characteristics in the ICH guidelines on how to validate analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.



For guidance on validating different types of methods, read the ICH document [\*ICH Q2 \(R1\): Validation of Analytical Procedures: Text and Methodology\*](#). You can also refer to any standard in Schedule B of the Act.

10. Re-evaluate raw materials where appropriate to determine if they can still be used (e.g. after prolonged storage or exposed to heat or humidity).



It is important for you to understand and control impurities in APIs/API intermediates to avoid contamination (e.g. nitrosamines). For more information on the control of impurities, please see:

- [ICH Q3A: Impurities in New Drug Substances](#)
- [ICH M7: Genotoxic Impurities – Assessment and Control of DNA Reactive \(Mutagenic\) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk](#)
- [VICH GL10 Impurities in New Veterinary Drug Substances](#)

## 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 Minister 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 Minister, 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](#) explains when to carry out the testing described 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 and quality when fabricating APIs. Raw materials should come from reliable fabricators.

## Interpretation

1. API or API intermediate manufacturers need a system to evaluate the suppliers of critical materials.
2. Specific identity testing of each batch of raw material received on the premises of the API fabricator should be conducted, with the exception of the materials described below in interpretation 4. A supplier's Certificate of Analysis (CoA) can be used in place of performing other tests, provided that the fabricator has a system in place to evaluate suppliers.
  - a. Provided that the identity test referred to in interpretation 2 is performed, the lot of raw material selected for confirmatory testing may be used in fabrication prior to completion of all tests with the approval of the quality control department.



If new certificates are issued by or on behalf of re-packers/ re-processors, agents or brokers, these certificates should show the name, address and telephone number of the laboratory that performed the analysis of the raw material.

3. Vendor approval should include a written evaluation that provides evidence that the material you get from a fabricator consistently meets specifications. Complete confirmatory testing should be conducted on at least three batches of raw material before you reduce in-house testing. Keep doing this testing at regular intervals and compare it with the CoA. Regularly check that CoAs are reliable. Also ensure complete testing is done any time significant changes are made.
  - a. Issue a document verifying that your supplier(s) meet certification criteria. Have your quality control department approve the document and review it from time to time.
  - b. Use a written system to track any failures during testing, as well as whether any re-qualification of the supplier was needed.



Generally, due to the nature of their 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.

4. If you have a fabricator's CoA showing that the materials conform to established specifications, the following materials do not need to be tested:

- a. processing aids
- b. hazardous or highly toxic raw materials
- c. other special materials
- d. materials transferred to another unit within your company's control

Visually check containers, labels and batch numbers to establish the identity of the materials. Be aware: you must justify and document anytime you do not conduct full testing of any raw material on-site.

5. Samples should be representative of the batch of material from which they are taken. Sampling plans should specify:

- a. the number of containers you are going to sample
- b. which part of the container to sample
- c. the amount of material to be taken from each container

6. A sampling plan should consider:

- a. the criticality of the material
- b. the variability of the material
- c. the past quality history of the supplier
- d. the amount of material is required for analysis

7. Keep written procedures describing how materials are identified and tested.

8. The API fabricator should always know the name and address of the critical raw material fabricator even if the supplier is not the fabricator.

9. Anytime you change the source of critical raw materials, follow your change control procedure (See section [C.02.015](#)).

10. Where appropriate, obtain a copy of the material's residual solvent profile. Additionally, for APIs, obtain a copy of the impurity profile.



11. Transport and store raw materials so that their quality is not impacted.
12. If a delivery or shipment of raw material is made up of different batches, each batch should be considered separate for sampling, testing and release.
13. Raw materials manufactured from the same batch, but received separately should be considered as separate batches for sampling, testing and release. However, you may not have to do full testing if you meet all of the following conditions:
  - a. you perform a specifically discriminating identity test
  - b. the raw material has not been re-packaged or re-labelled
  - c. the raw material is within the retest date given by its vendor
  - d. you have evidence that the material has been transported and stored according to pre-established transportation and storage conditions

## 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 maintain the integrity of the APIs you produce. This begins from the moment the raw materials enter your facility to the time you release the APIs for further fabrication. These measures should be documented to ensure that all of your processes are clearly defined, monitored, and systematically reviewed. They also demonstrate that your manufacturing processes consistently produce APIs that meet the quality standards set by their established specifications.



See [Chart 2.0](#) in this guide to learn about when API production begins and when in the process you need to use certain GMP.

## Interpretation

1. Restrict production area access to designated personnel.
2. Handle raw materials, products and packaging materials according to written procedures and keep records. Handling includes:
  - a. receipt
  - b. identification
  - c. quarantine
  - d. storage
  - e. sampling
  - f. approval or rejection
  - g. tracking
  - h. labelling
  - i. packaging
  - j. dispensing
  - k. processing
  - l. distribution
3. Validate the operations that are critical to the quality and purity of the API.
  - a. If you propose a change to your operations, you must first evaluate whether that change will affect API quality. Create a classification procedure to help determine the level of testing, validation and documentation needed to justify changes to a validated process.



Changes can be classified as major and minor depending on the type of change and extent of the changes since they may affect the process. The amount of testing, validation and documentation you required before making the change should be scientifically justified.

If no significant changes have been made and a quality review confirms that the system or process is consistently producing materials meeting their specifications then there is not usually a need for revalidation.

4. Create a written validation protocol that explains how the validation of each process will be conducted. The quality unit(s) and any other designated units should review and approve it prior to implementation.
  - a. Your validation protocol should:
    - define critical process steps
    - outline acceptance criteria
    - indicate the type of validation you are doing—e.g. retrospective, prospective, concurrent
    - specify the number of process runs



For further information about validation protocols, review section 12 of [\*ICH Q7: Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients\*](#).

- b. Prepare a validation report that cross-references the validation protocol. The report should include the following:
    - a summary of your results
    - any deviations you found and conclusions you made about why they happened
    - recommended changes to the process to correct deficiencies

Justify and document any variations from your validation protocol.

5. Qualify critical equipment and ancillary systems before starting your process validation studies.
6. Document and explain all deviations. All critical deviations (i.e. one that could affect the quality and/or purity of the API), should be investigated.
7. If time limits are specified in the master production instruction, these time limits should be met to ensure the quality of APIs and API Intermediates. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

8. Compare expected and actual yields at specific stages in your production process. Your expected yields with appropriate ranges should be set based on previous laboratory, pilot scale, or manufacturing data. Deviations in the yield associated with critical process steps should be investigated to determine their impact or potential impact on the quality of the affected batches.
9. Residual materials can be carried over into successive batches of the same API as long as there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants (impurities) or microbial contamination that may adversely alter the established API impurity profile.
10. You can fabricate or package/label non-medicinal products in areas or with equipment that is also used for the production of APIs if you use validated changeover procedures.
11. Inspect your facility immediately before each use to ensure that all materials not needed for the next operation have been removed. Document this inspection in your batch production records, facility log, or other records.
12. Production operations should be conducted in a manner that will prevent contamination of APIs or API intermediates by other materials.
13. Perform in-process sampling in a manner that prevents contamination of the sampled material and other APIs. Have procedures to ensure the integrity of samples after collection.
14. Document the progress and control the performance of processing steps that could cause variability in the quality characteristics of APIs. Define in-process controls and their acceptance criteria based on the information gained during the development stage or historical data.
15. When you are deciding acceptance criteria and type and extent of testing, consider:
  - a. the nature of API being manufactured
  - b. the reaction or process step being conducted
  - c. how much the process introduces variability in the API's quality

Less stringent in-process controls might be justified for early steps, but tighter controls may be appropriate for later processing steps (e.g. isolation and purification).
16. Critical in-process controls and critical process monitoring, including your control points and methods, should be stated in writing and approved by the quality unit(s).

17. Qualified production personnel can perform adjustments to in-process control activities, and this process can be changed without your quality unit's approval if the changes are made within pre-set limits approved by the quality unit(s). Document all tests and their results as part of the batch record.
18. Ensure that in-process control activities performed within production areas do not pose any risk to the quality of the API and API intermediate. Establish procedures to ensure the integrity of samples after collection.
19. Describe in written procedures how you sample in-process materials, intermediates and APIs. Your sampling plans and procedures must be scientifically sound.
20. Take precautions to avoid contamination when handling APIs after purification.
21. You can produce different products in the same area if you have controls in place to prevent mix-up or cross-contamination.
  - a. Take steps to prevent cross-contamination from personnel and materials moving from one area to another.
  - b. Check removable and interchangeable transfer lines, or any equipment used to move materials from one area to another. Ensure they are connected correctly.
22. Equipment and segregated process areas should be appropriately identified as to their contents, including the name of the product and batch number and its cleanliness status.
23. Show the processing status for major units of equipment—either on the individual piece of equipment itself, by computer control systems, written documentation, or alternative means.
24. Identify and quarantine rejected materials. This prevents them from being mistakenly used in manufacturing.
25. Appropriately control materials you intend to reprocess or rework to prevent unauthorized use.
26. When you receive (and before you accept) each container or group of containers that holds materials, visually inspect them for:
  - a. correct labelling (check that the name used by the supplier and your in-house name match up, if they are different)
  - b. damage
  - c. broken seals
  - d. evidence of tampering or contamination

You should quarantine materials until they are sampled, examined or tested as appropriate and released for use.

27. Before you mix new materials with existing stocks—e.g. solvents or stocks in silos—identify them as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.
28. If you get bulk deliveries from non-dedicated tankers, ensure the tanker has not cross-contaminated your materials. To do this, you can do one or more the following:
  - a. get a cleaning certificate
  - b. test for trace impurities
  - c. audit the supplier
29. Store intermediates being held for further processing under the appropriate conditions to ensure they are suitable for use.
30. Transport critical materials in a way that does not negatively affect their quality.
31. State any special transport or storage conditions for an API on its label.
32. Sample at defined locations and use procedures that prevent contaminating your sample, and other materials.
33. When you take a sample from a container, open and re-close it carefully. Mark the container to show you took a sample.
34. Identify large storage containers and their manifolds, as well as filling and discharge lines.
35. Assign a distinctive code, batch or receipt number to each container or grouping of containers (batches) of materials. This number should be used in recording the disposition of each batch. You should have a system in place to identify the status of each batch.
36. Handle and store all materials in a way to prevent degradation, contamination and cross-contamination.
37. Ensure that any material stored in fibre drums, bags or boxes are off the floor. Create space between them to permit cleaning and inspection.
38. Ensure that materials are stored under conditions and for a period of time that have no adverse effect on their quality. You should normally use your oldest stock first.
39. You can store certain materials outdoors, if you use the right containers, the labels remain legible and the containers are cleaned before you open and use them.
40. Weigh or measure raw materials, under appropriate conditions, so that they stay suitable for use.

41. Have a witness present (or equivalent control) when you weigh, measure or subdivide critical materials. Before use, personnel should verify that materials are listed in the batch record for the intended API.
42. Have a witness present (or equivalent control) for all critical activities.
43. Record all quality-related activities when they are being done.
44. Prepare, review, approve and distribute all your documents related to the manufacturing of APIs or API intermediates according to written procedures.
45. To ensure uniformity from batch to batch, prepare, date and sign master production instructions for each API or API intermediate and have someone from your quality unit independently check, date and sign the instructions.

### **Manufacturing operations**

46. Ensure the master production documents are complete. They should include:
  - a. the name of the API or API intermediate being manufactured, its batch size, and an identifying document reference code, if applicable
  - b. a list of all raw materials and intermediates by names or codes sufficiently to identify any special characteristics
  - c. the quantity or ratio of each raw material or intermediate, including its unit of measure where the quantity is not fixed
    - The calculation for each batch size or rate of production should be included.
    - Variations to quantities should be included where they are justified.
  - d. the production location and major production equipment
  - e. the procedures, or reference to the procedures to be used in production.
  - f. detailed production instructions, including:
    - sequences you will follow
    - ranges of process parameters
    - sampling instructions and in-process controls with their acceptance criteria
    - time limits for completing individual processing steps and/or the total process, where appropriate
    - expected yield ranges for appropriate times or phases

- g. where appropriate, any special notation or precautions you will follow, or cross-references to these
  - h. the instructions for storing intermediates or APIs to ensure its suitable for use, which include labelling and packaging materials or storing them under special conditions (with time limits for storage), where appropriate
- 47. Create batch production records for each API and API intermediate and include complete information relating to the production and control of each batch. Before issuance for use, check that they are the correct version, readable, and are an accurate copy of the right master production instruction. If your batch production record is made from a separate part of the master document, that document should include a reference to the current master production instruction you are using.
- 48. Number batch production records with a unique batch or identification number. Date and sign them. In continuous production, you can use the product code, date and time as the batch's unique identifier until you have a final batch number.
- 49. Document the completion of each significant step in the batch production records (batch production and control records). Include:
  - a. dates and times you started and finished major intermediate stages in production (e.g. blending and heating)
  - b. identification of the major equipment used (e.g. reactors, driers, mills)
  - c. specific identifications for each batch—with the weights, measures and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing
  - d. actual results for critical process parameters
  - e. sampling performed
  - f. signatures of the people who complete and supervise or check each critical step
  - g. in-process and laboratory test results
  - h. actual yields at different phases or times
  - i. description of the packaging and label for the API or API intermediate
  - j. representative label of the API or API intermediate if made commercially available
  - k. any deviations you noted, the evaluation, and investigation conducted (you may reference the investigation if it is kept separately)
  - l. results of release testing



- m. when processing is done, the signature of the person responsible for that processing operation



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

50. If you subdivide a material for later use, ensure the container receiving the material is suitable. Identify the container with the:
- a. material's name and/or item code
  - b. receiving or control number, or its own code
  - c. weight or measure of material in the new container
  - d. re-evaluation or retest date, if appropriate

## Blending



For the purpose of this guide, “blending” refers to the process of mixing materials within the same specification to make a homogenous API or API intermediate.

In-process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

51. Out-of-specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch in the blend should be manufactured according to your established process and should have been tested individually and found to meet its approved specifications prior to blending.
52. Acceptable blending includes but is not limited to:
- a. blending small batches to increase batch size
  - b. blending “tailings” (i.e. fairly small quantities of isolated material) from batches of the same API to form a single batch
53. Control and document blending processes. Test the blended batch for conformance to established specifications, where appropriate.

54. Ensure the production batch record shows the individual batches that make up the blend, so they can be traced.
55. Validate blending when physical attributes of the API are critical (e.g. for APIs intended for use in solid oral dosage forms or suspensions). You must show the homogeneity of the combined batch. Also show how you tested key qualities (e.g. the distribution of particle size, bulk density, and tap density) that could be affected by blending.
56. If blending could adversely affect stability, perform stability testing of the final blended batches.
57. Base the expiry or retest date of your blended batch on the manufacturing date of the oldest tailings or batch in the blend.

### Recovery

58. You are allowed to recover reactants, intermediates or APIs themselves—for example, from mother liquor or filtrates. Ensure approved procedures exist and are followed. The recovered materials must meet the specifications suitable for their intended use.
59. You can recover solvents and re-use them if the recovery procedures are controlled and monitored. The solvents must meet standards before they are re-used or co-mingle with other approved materials.
60. You can combine new and recovered solvents and reagents if adequate testing shows they are suitable for all the processes you might use them in.
61. Document the use of recovered solvents, mother liquors and other recovered materials.



In organic chemistry a “reagent” is defined as a compound or a mixture. Reagents are usually added to a system to create a chemical reaction, or to see if a reaction happens. They are sometimes also called “reactants.”

### Packaging and labelling operations and control

62. You should individually number the packaging orders.
63. Design packaging and labelling operations to prevent mix-ups and cross contamination between different APIs or API intermediates. There should be physical or spatial separation from operations involving other APIs or API intermediates.
64. Ensure only authorized personnel have access to label storage areas.
65. Inspect your packaging and labelling facilities right before use to ensure that all materials not needed for the next packaging session have been removed. Document your inspection using the batch production records, facility log or other system.

66. Document procedures to ensure you use the correct packaging materials and labels.
67. Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.
68. Examine printed labels issued for a batch for proper identity and conformity to specifications in the master production record. The results of this should be documented.
69. Include a printed label representative of the labels used in the batch production record.
70. Clean containers and, when required, sanitize them to ensure they are suitable for their intended use. Containers should not be chemically reactive, additive or absorptive (this could change the quality of the API or API intermediate beyond the specified limits).
71. If you re-use containers, clean them according to documented procedures and ensure that previous labels are removed or defaced to prevent mix-ups.
72. Ensure labels on containers show the name or identifying code, the batch number and storage conditions of the product, when such information is critical to assure the quality of intermediate or API.
73. If you intend to transfer an API or API intermediate outside the control of from the fabricator's material management system then:

- a. Put the following on the container's label:

- the fabricator's name and address
- the quantity of contents
- any special legal requirements
- any required transportation conditions

If the API has an expiry date, include it on the label and CoA. If the API has a retest date, it should also show on the label and/or the CoA.

- b. Ensure that the containers are sealed in a manner such that, if the seal broken or missing, the recipient will be alerted to the possibility that the quality of the contents may have been affected.
74. Check packaged and labelled APIs or API intermediates to ensure the containers and packages have the correct label. This should be done as part of the packaging procedure and the results of the examinations should be recorded in the batch production or control records.
  75. Ensure procedures exist to track the number of labels issued, used, destroyed and returned to ensure that there are no discrepancies. Any discrepancy between the number of labelled containers and the number of labels issued must be investigated. Your quality unit should approve the investigation and the records retained.

76. Destroy all excess labels bearing batch numbers or other batch-related printing. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.
77. Destroy obsolete and out-dated labels.
78. Quarantine APIs or API intermediates that have been packaged and labelled until your quality control department releases them.
79. Your packaging orders should include the following information (recorded at the time each action was taken):
- a. date(s) and time(s) of packaging
  - b. identification of personnel who supervise or verify packaging operations and the withdrawal of bulk materials
  - c. identification of personnel who complete significant packaging steps
  - d. whether you use the correct products and packaging materials
  - e. whether your on-line printing is correct
  - f. whenever possible, samples of the printed packaging materials with the batch number, expiry date and any overprinting are attached to packaging orders
  - g. whether your line monitors are functioning correctly
  - h. handling precautions for a partly packaged product
  - i. notes on any special problems—including details of any deviation from the packaging instructions with written approval from qualified personnel

### **Product Quality Review**

80. The manufacturer should conduct regular periodic or rolling quality reviews of APIs. These reviews should be conducted annually but longer frequencies are acceptable if suitably justified. Conduct and document the 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 control and critical API test results;
  - b. all batches that failed to meet established specification(s);
  - c. other batches that may have been associated with the specific failure or deviation;
  - d. all critical deviations or non-conformances and related investigations;
  - e. any changes carried out to the processes or analytical methods;

- f. results of the stability monitoring program;
- g. all quality-related returns, complaints and recalls; and
- h. adequacy of corrective actions.

81. Your quality control department should evaluate the results of this review, and assess whether corrective action or revalidation should be undertaken. Document reasons for any corrective actions. Carry out corrective and preventive 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 an API that either:

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

APIs 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 from your direct customers throughout the supply chain.

Subsection [C.02.012\(1\)\(b\)](#) of the Regulations 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 GMP. A self-inspection program is designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective/preventative actions.

APIs offered for sale—whether they are produced in Canada or imported—must meet the requirements of Part C, Division 2 of the Regulations. If production and testing 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.



More information regarding written agreements between parties is described in [Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites \(GUI-0080\)](#).

## Interpretation

1. Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

## Recall

2. You must have a written recall system in place to comply with the Food and Drug Regulations.

3. Notify Health Canada of the recall. This notification may include an assessment of the impact that any recall action may have on the market availability of the API.
4. Notify all Canadian and foreign establishments involved in the manufacture, distribution or importation of the recalled API or API intermediate.
5. Take prompt action to recall an API or API intermediate 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.
6. Identify the person(s) responsible for initiating and coordinating all recall activities.
7. 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.
8. Your recall procedure must outline the way to communicate and implement a recall and decide its extent.
9. Your distribution records must enable tracing of each API product. This includes any products in transit and any samples that have been removed by the quality control department.
10. If you are a wholesaler, you must get API 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. This establishment licence requirement does not apply to wholesalers who receive API products from other wholesalers.
11. A written agreement must clearly describe each party's responsibilities with respect to recall. The written agreement must provide understanding of the API or API intermediate distribution supply chain.
12. Identify recalled products and store them separately in a secure area until their disposition is determined.
13. Assess and record the progress and effectiveness of the recall at intervals. Issue a final report (including a final reconciliation).
14. Verify the adequacy of recall procedures periodically. If a recall has not taken place, 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 and drug shortages, see:

- [Drug Shortages in Canada](#)
- [Guide to reporting drug shortages and discontinuations \(GUI-0120\)](#)
- [Recall Policy for Health Products \(POL-0016\)](#)
- [Drug and natural health products recall guide \(GUI-0039\)](#)

### Self-Inspection

15. You must have a comprehensive written procedure that describes the functions of your self-inspection program. Document your findings, which include any corrective or preventive actions and bring these to the attention of management. Actions should be completed in an effective and timely manner by taking a risk-based approach.
16. In order to ensure you comply with Part C, Division 2 of the Regulations, regular self-inspections should be done according to an approved schedule. Your self-inspection team should include personnel that are suitably trained and qualified in GMP.

### Outsourced activities

17. Evaluate any contract manufacturers (including laboratories) that you use to ensure GMP compliance at those sites. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.
18. To ensure the compliance of contractors manufacturers (including laboratories):
  - a. Make all contract arrangements to ensure that each lot or batch of has been manufactured so it complies with the current regulatory filing for the API.
  - b. Create a written and approved agreement that covers the manufacturing (including laboratories) arrangement among parties. Specify GMP responsibilities that relate to the fabrication or packaging/labelling and quality control of the API.
    - Qualified personnel, who are knowledgeable in pharmaceutical technology and GMP, should write technical parts of the agreement.
    - The agreement should permit the contract giver to audit the facilities of the contractor for compliance with GMP.
    - The agreement should clearly describe who is responsible for:
      - i. buying, sampling, testing and releasing materials
      - ii. production, quality and in-process controls
      - iii. validating processes



- Do not sub-contract work without written authorization and mutual agreement.
  - The agreement should describe how raw materials, packaging materials, intermediates and APIs are handled if they are rejected.
  - The contractor's complaint/recall procedures should specify that the distributor or importer should have access to the contractor's records relevant to assessing the quality of a drug in the event of complaints or suspected defects.
- c. The fabricator, packager/labeller, distributor or importer should provide the contractor with any information needed to carry out contracted duties according to the current regulatory filing and other legal requirements. The fabricator, packager/labeller, distributor or importer should ensure the contractor is fully aware of any problems with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products.
- d. The fabricator, packager/labeller, distributor or importer is responsible for ensuring that the contractor continues to meet the requirements of Division 2.
- If you are a contractor, do not make changes to the established process, equipment, test methods, specifications or other contract requirements unless the contract issuer approves them.
  - If you distribute APIs fabricated, packaged/labelled and tested at Canadian sites, you are required to have only a copy of the establishment licence held by your Canadian fabricator, packager/labeller or tester.

## 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 determined to be satisfactory.

Quality control is not confined to laboratory 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 APIs 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. The quality unit(s) should be involved in all quality-related matters.
2. 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.
3. The quality unit of the manufacturer must be independent from production. The unit(s) must meet its quality assurance and quality control responsibilities. Depending on the

size and structure of your establishment, the unit might be made up of separate quality assurance and quality control units, a single person, or a group.

4. The quality unit should have access to facilities (including a laboratory), trained personnel and equipment in order to do its duties and meet responsibilities.
5. 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.

## 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, intermediates and finished APIs. It is very important for this department to exercise adequate controls to guarantee the quality of the end product.

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

## Interpretation

1. The person in charge of your quality control department (or a designated alternate person who meets the requirements described under section [C.02.006](#) "Personnel") must sign and date all decisions made by the quality control department.
2. Do not release or use materials before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine or the use of raw materials or intermediates pending completion of evaluation).
3. When the quality unit(s) assesses an API or API intermediate for release, consider all relevant factors, including:
  - a. production conditions
  - b. results of in-process testing
  - c. fabrication and packaging documentation
  - d. compliance with the API or API intermediate specifications
  - e. visual inspection of the finished package
  - f. review of its storage and transportation (if applicable)
  - g. all deviation, investigation and Out-of-Specification (OOS) reports



Review electronic records (where used) and relevant audit trails when reviewing records that support product release.

4. Only release APIs or API intermediates for distribution to third parties after they have been released by your quality unit(s). APIs or API intermediates can be transferred under quarantine to another company building when the quality unit(s) approve(s) the transfer, and if you have the appropriate controls and documentation in place.
5. Your quality control department must ensure raw and packaging materials are quarantined, sampled, tested and released before they are used in fabricating or packaging/labelling an API or API intermediate.
6. 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. Investigate critical deviations and document your investigation and conclusions.

7. Identify and quarantine rejected materials (e.g. APIs or API intermediates that fail to meet specifications). These intermediates or APIs can be reprocessed or reworked as described in this guidance. The final disposition of rejected materials should be recorded.
8. Maintain records for returned APIs or API intermediates. For each return, documentation should include:
  - a. name and address of the consignee
  - b. intermediate or API, batch number, and quantity returned
  - c. reason for return
  - d. use or disposal of the returned intermediate or API
9. Destroy APIs or API intermediates returned from the market unless you know their quality is acceptable. Identify and quarantine APIs/API intermediates any time you suspect they were stored, shipped or contained in a way that could affect their quality. If the conditions under which returned APIs or API intermediates have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned APIs should be reprocessed, reworked, or destroyed, as appropriate. Record any action you take. Document your rationale for putting returned goods into a resale inventory.
10. You can only consider reselling returned APIs or API intermediates after they are assessed according to a written procedure. When doing your assessment, document the following:
  - a. name and address of the consignee
  - b. API, lot or batch number, and the amount returned
  - c. reason for the return
  - d. nature of the product
  - e. storage and transportation conditions
  - f. API's condition and history
  - g. amount of time since it was first sold
  - h. stability and expiration date
  - i. use or disposal of the returned API

## **Reworking**

11. Before you decide to rework batches that do not conform to standards or specifications, investigate the reason they do not conform.

12. Subject reworked batches to evaluation, testing (including stability testing if appropriate) and documentation to show that the reworked batch is the same quality as the product made by the original process. Concurrent validation is often the most appropriate validation approach for reworking. This allows for a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.
13. Have procedures in place for comparing the impurity profile of each reworked batch against batches manufactured using your established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

### Reprocessing

14. It is generally acceptable to introduce an API or API intermediate—including one that does not conform to standards or specifications—back into the established manufacturing process. You can reprocess the material by repeating a crystallization step or other chemical or physical manipulation steps, such as:
  - a. distillation
  - b. filtration
  - c. chromatography
  - d. milling

However, if you use this kind of reprocessing in most of your batches, include reprocessing as part of your standard process.



Consider it part of the normal process to continue a process step after an in-process control test has shown that the step is incomplete. This is not reprocessing.

Reprocessing includes introducing chemical material that has not yet reacted—i.e. “unreacted material”—back into a process (unless you perform that step in your normal manufacturing process). If you add in unreacted materials, be extremely careful that product quality is not negatively affected by by-products or over-reacted materials.



Your quality control department should approve all reprocessing and reworking steps.



Recovery is not considered to be either a reprocessing or a reworking operation. Guidance about recovery is found in section [C.02.011](#) of this guide.

## 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

Pharmaceutical 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 laboratory 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

1. Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g., quality related complaints, recalls, regulatory actions, etc.).
2. The quality unit should review and approve quality-related documents. Have written procedures for how to perform the following with raw materials, packaging materials, API intermediates and APIs:
  - a. receiving
  - b. identifying
  - c. quarantining
  - d. storing
  - e. handling
  - f. sampling
  - g. labelling
  - h. dispensing
  - i. processing
  - j. distributing
  - k. inspecting
  - l. testing
  - m. approving
  - n. rejecting



3. Create a formal change control system. Evaluate all changes that may affect the production and control of APIs and API intermediates.
4. Create written procedures for how to identify, document, review and approve changes in:
  - a. raw materials
  - b. specifications
  - c. analytical methods
  - d. facilities
  - e. support systems
  - f. equipment (including computer hardware)
  - g. processing steps
  - h. labelling and packaging materials
  - i. computer software
5. Appropriate departments must draft, review and approve any proposals for GMP-relevant changes. Your quality unit(s) should then review and approve or reject the change.
6. Evaluate the potential impact of the proposed change on the quality of the API or API intermediate.
7. A classification procedure may help to figure out how much testing, validation and documentation you need to justify changes. Changes can be classified (e.g. as minor or major) depending on their nature, extent and possible effects. Use your scientific judgement: what additional testing and validation studies are needed to justify changing a validated process?
8. When putting approved changes into place, ensure all documents affected by the changes are revised.
9. Evaluate whether critical changes may affect retest or expiry dates. If necessary, put samples of the API or API intermediate produced with the modified process on an accelerated stability program, or add them to your stability monitoring program.
10. After you put the change into place, evaluate the first batches produced or tested under the change.
11. When changes have been made to your established processes that may impact the quality of your API or API intermediate you should notify all of your clients that use the API or API intermediate.

12. If your establishment is involved in producing, distributing and importing APIs—including if you are an agent, broker, re-packager or re-labeller—you should have a system for recording and investigating all quality-related complaints.
- a. Importers, distributors, wholesalers, packagers, and labellers (including re-packagers or re-labellers) should review the complaint with the original API fabricator to determine if further action, either with other customers who may have received this API, or with the regulatory authority, or both, should be initiated. The investigation to determine the cause for the complaint or recall should be conducted and documented by the appropriate party.
  - b. If a complaint is referred to the original fabricator, the records maintained by importers, distributors, wholesalers, packagers, and labellers (including re-packagers or re-labellers) should include any reply they get from the fabricator, including the date the response was received.
  - c. Keep records of complaints in order to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective actions. Record all decisions and measures taken as a result of a complaint.
13. Ensure all specifications, sampling plans and tests are scientifically sound and appropriate to ensure that raw materials, APIs, API intermediates, labels and packaging conform to established standards of quality and/or purity. Keep specifications and test procedures consistent with any included in your registration or filing. The appropriate organizational unit should draft sampling plans and test procedures, including any related changes. Your quality unit(s) must review and approve the changes.
14. Have written procedures for recording and storing laboratory data. All laboratory data should be created, maintained, processed and reviewed as outlined by the firm's data governance system.



The data governance system (as it applies to laboratory data) must include enough detail to allow accurate and complete reporting and interpretation of all laboratory test data and ensure data integrity.

Data integrity is an important consideration. For other requirements relating to a data governance system, see sections [C.02.020 to C.02.024](#) "Records."

15. The data governance system (as it applies to laboratory data) must include enough detail to allow accurate and complete reporting and interpretation of all laboratory test data

and ensure data integrity. This system should include (but is not limited to) the following elements:

- a. 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.
  - b. Have systems and procedures in place to ensure that laboratory 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 an API are reported, reviewed and assessed appropriately.
  - c. 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).
  - d. Put controls in place to ensure that 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). Also, put controls on your computer systems to prevent unauthorized access or changes to data.
  - e. Retain data in its original format. Original records (or a true copy), including electronic records, are subject to review by qualified personnel.
  - f. Protect and back up data for all computerized systems.
  - g. Keep written procedures for operating and maintaining computer systems.
16. Make changes to your computer system according to a change procedure and formally authorize, document, and test the changes made. This includes modifications or enhancements to hardware, software, or any other key part of the system. Keep records to show that you maintain your system in a validated state.
17. When you are entering critical data into a computer system manually, do an additional check on the entry's accuracy using a second operator or the system itself.
18. Record and investigate incidents related to computer systems that could affect the quality of APIs or API intermediates or the reliability of records or test results.
19. Follow laboratory procedures and document the results while the testing is happening. Any deviation from an approved procedure should be explained and documented.
20. You should include complete data from all tests in the laboratory control records to ensure compliance with established specifications and standards, including examinations and assays. Include the following:
- a. a description of samples you receive for testing:

- the sample's name or source
  - its batch number or other identifying code
  - the date it was taken
  - the sample quantity (when appropriate)
  - the date the sample was received for testing
- b. a reference to all test methods used
  - c. the weight or measure of the sample used for each test as described by an approved method
  - d. data or cross reference to data regarding the preparation and testing of reference standards, reagents and standard solutions
  - e. a record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested
  - f. a record of all calculations performed in connection with the test (including, for example, units of measure, conversion factors and equivalency factors)
  - g. the test results and how they compare with established criteria
  - h. the signature of the person who did each test, and the date(s) the tests were done, as appropriate
  - i. the date and signature of a second person showing that they reviewed original records for accuracy, completeness and compliance with established specifications

21. Complete records should also be kept for:

- a. any changes to an established analytical method
- b. the calibration of laboratory instruments, apparatus, gauges and recording devices
- c. all stability testing done on APIs
- d. the OOS and Out-of-Trend (OOT) investigations

22. Prepare and label reagents and standard solutions by following your written procedures. Apply "use-by" dates for analytical reagents or standard solutions. Data should be available to support expiry or retest dates.

23. Conduct testing in a laboratory that meets all relevant GMP.

- a. Laboratory facilities should be designed, equipped and maintained to do the required testing:
  - In a microbiology lab, environmental monitoring should be done periodically. Handle microbiological cultures and test samples in an environment that prevents contamination.
- b. The person in charge of the laboratory should meet requirements in section [C.02.006](#) of this guide or report to a person who has these qualifications.
- c. There are enough laboratory personnel qualified to carry out the work they undertake.
- d. Laboratory control equipment and instruments are suited to the testing procedures carried out. Equipment and records are maintained as per the interpretations under section [C.02.005](#) of this guide.
- e. Ensure water used for microbial and analytical tests meets the requirements of the test or assay in which it is used.
- f. Record all reagents and culture media when they are received or prepared. Reagents made up in the laboratory should be prepared according to written procedures and properly labelled.
  - Sterilize prepared media using validated procedures and store under controlled temperatures.
  - Properly label prepared media with lot numbers, expiration dates and identification. Support the expiration date of media by growth-promotion testing results that show that the performance of the media still meets acceptance criteria up to the expiration date.
  - Do sterility and growth-promotion testing to verify that culture media is suitable.
  - Ensure that all purchased, ready-to-use media come with a CoA. The CoA must show the media's expiry date, recommended storage conditions, and any quality control organisms used in its growth-promotion and selectivity testing.
    - 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.

- Do sterility and growth-promotion tests on lots you receive unless the vendor is certified. Perform periodic confirmatory testing on ready-to-use media received from each certified vendor.
  - Keep records.
  - g. Ensure out of specification (OOS) and out of trend (OOT) test results are investigated in accordance with a defined procedure:
    - The first phase of investigation should be to determine if the OOS results were caused by a clearly identifiable laboratory error.
    - In the case where the OOS result was caused by a clearly identified laboratory 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. The source of the error should be determined with corrective action implemented to prevent recurrence.
    - When a clearly identifiable laboratory error is not present then a second phase of investigation should be conducted. This phase should include a review of the manufacturing process and any other factors that could have impacted the testing. This may include laboratory retesting.
    - Any retesting performed must be specified and approved in advance with the number of retests to be performed on the original sample and/or a new sample, and the statistical treatment of the resulting data.
    - Hypothesis testing may be required to demonstrate the presumptive root cause in either phase.
    - Report all valid test results (both passing and suspect) and fully consider them in batch release decisions.
  - h. The root cause of confirmed OOS results should be investigated. 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. You do not normally need OOS investigations for in-process tests that are done to monitor or adjust your process.
24. Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognised source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

25. Prepare, identify, test, approve and store secondary reference standards appropriately. To find out if each batch of secondary reference standard is suitable before you first use it, compare it against a primary reference standard. Periodically re-qualify each batch of secondary reference standard according to a written protocol.
26. If a primary reference standard is not available from an officially recognized source, establish an “in-house primary standard.” Do the appropriate testing to establish fully the identity and purity of your in-house primary standard. Document the testing.
27. To ensure the compliance of contractors conducting testing required under Part C, Division 2 of the Regulations:
- a. A Canadian contract laboratory must have a relevant valid establishment licence. A foreign building providing testing must be listed on a Canadian establishment licence, as described in [\*How to demonstrate foreign building compliance with drug good manufacturing practices \(GUI-0080\)\*](#) and [\*Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees \(GUI-0002\)\*](#).
  - b. All arrangements for external testing must comply with the marketing authorization for the API concerned (including the testing of API intermediates, raw materials, packaging materials, and all other testing required by Part C, Division 2 of the Regulations).
  - c. There must be a written agreement covering all testing activities between the contract laboratory 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.
  - d. Technical aspects of the agreement must be drawn up by qualified personnel knowledgeable in the relevant laboratory testing and GMP. The agreement must:
    - permit audit of the external lab's facilities and operations
    - clearly describe (at a minimum) who is responsible for:
      - overseeing collection, transportation and storage conditions of samples before testing
      - keeping stability samples at predetermined temperatures and humidity, if applicable
      - testing methods to be used, limits and test method validation

- retaining analytical results and supporting documentation (see additional guidance under section [C.02.021](#))
- e. Ensure no subcontracting of any work happens without written authorization.



To learn more about how to keep good records of analytical results, refer to section [C.02.021](#) of this guide.

28. The manufacturer should ensure that the transportation contractor knows and follows proper transport and storage conditions.



For more guidance on storage and transportation, see [\*Guidelines for Temperature Control of Drug Products during Storage and Transportation \(GUI-0069\)\*](#).

## 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 Minister 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.





- (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 Minister 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 Minister,
    - (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

Whether APIs are suitable for their intended use depends not only on production process but also on how well they are protected from contamination or breakdown. API packaging materials must be tested or examined before they are used. As the filling of solid APIs is often a dusty

operation, you should consider the choice of container as how the container is filled and closed will affect the quality of the API and API intermediates.

Labelling, storage, and distribution contribute to final suitability for use in the manufacture of APIs and API intermediates. To ensure identity and traceability, the inner packaging should be controlled by the establishment.

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 personnel 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 receipt on the API packager's premises.

## Interpretation

1. You must have written procedures describing how to receive, identify, quarantine, sample, examine and/or test and release, and handle packaging and labels.
2. Ensure that each packaging material used in the packaging/labelling of an API is covered by specifications (as defined under 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 interpretation 2.d) of section [C.02.006](#) "Personnel".
  - a. Packaging material that does not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.
  - b. Where applicable, you should use pharmacopeial specifications or a scientifically justified equivalent and comply with the specifications in the marketing authorization for the drug in finished dosage form.
  - c. Test methods that are not considered pharmacopeial or equivalent should be shown to be scientifically adequate. Document the adequacy of the test method.
  - d. Only use recycled or reprocessed primary packaging material after you have fully evaluated the risks involved, including any impact on product quality. Specifications should include considerations for these situations.
  - e. Ensure that the containers are not reactive, additive or absorptive, as this may change the quality of the API or API intermediates beyond the specified limits.

- f. Ensure that any packaging material in direct contact with the API should be at minimum, food grade quality and appropriate for the API being packaged.
- 3. Sample in an appropriate environment and take measures to prevent contamination.
- 4. Conduct positive identification of all packaging materials, labels and printed packaging material following their receipt 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. Keep master labels for comparison with issued labels.
- 5. Use only packaging components released by the quality control department for packaging/labelling operations.
- 6. Ensure that containers provide enough protection against any deterioration or contamination that may happen while transporting and storing the API or API intermediates.
- 7. Clean and, where indicated by the nature of the API or API intermediate, sanitize containers to ensure they are suitable for their intended use.
- 8. Clearly identify any out-dated or obsolete packaging. Keep it separate from other packaging until it is disposed.
- 9. The testing or examination of the packaging material should be performed on a sample taken after their receipt on the premises of the person that packages the drug unless the vendor is certified. A packaging material vendor certification program, if employed, should be documented in a standard operating procedure. Such a program should include the following:
  - a. A written evaluation providing evidence (e.g. of past quality history or evidence of a quality system) that the fabricator can consistently provide material that meets specifications.
  - b. Complete confirmatory testing on at least three batches before reducing your in-house testing.
  - c. As a minimum, confirmatory testing should be performed at appropriate intervals, at least one lot per year, and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.

## 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 API 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 API sold is safe and meets the relevant standard.

### Interpretation

1. For each batch of API or API Intermediate, conduct appropriate laboratory tests to determine that the API meets specifications.
2. Keep specifications and tests consistent with those in the registration/filing (but note that you can have specifications in addition to these). Document specifications, sampling plans and test procedures and have them approved by the appropriate organizational unit. They must also be reviewed and approved by your quality unit(s). All specifications, sampling plans and tests must be scientifically sound and designed to ensure APIs meet standards of quality and/or purity.
  - a. Specifications should be equal to or exceed a recognized standard (as listed in Schedule B to the Act) and must comply with the marketing authorization.
  - b. If a recognized pharmacopoeia (see Schedule B to the Act) contains a specification for microbial content, include that requirement. Set and meet limits for total microbial counts and objectionable organisms.

- c. Your API or API intermediate specifications must align with accepted standards and your manufacturing process. The specifications should include a limit for impurities—e.g. organic impurities, inorganic impurities and residual solvents. Also set and meet limits for endotoxins, if applicable to the API or API intermediate.
3. Validate your analytical methods unless they are included in a pharmacopoeia or other recognized standard reference. You should verify, under actual conditions of use, and document that your testing methods are suitable for use.



For guidance on validating particular types of methods, see ICH and VICH guidance including [\*ICH Q2 \(R1\): Validation of Analytical Procedures: Text and Methodology\*](#) and [\*VICH GL2 Validation of analytical procedures : Methodology\*](#).

4. The degree of analytical method validation you do should reflect the purpose of the analysis and the stage of the API production process.
5. Perform all tests according to the approved specifications. These tests may be carried out by the fabricator or by their contracted testing laboratory when a written agreement specifies the responsibility of each party.
6. Create an impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process for each API. The impurity profile should include:
  - a. the identity or some qualitative measurement such as retention time
  - b. the classification of each identified impurity (e.g. inorganic, organic or solvent)
  - c. the range of each impurity observed

The impurity profile normally depends on your production process and the API's origin.



For additional guidance on impurities, see ICH guidance [\*ICH Q3A \(R\): Impurities in New Drug Substances\*](#).

7. At regular intervals, compare the API's impurity profile against the profile in the regulatory submission or historical data. This helps to detect changes to the API resulting from changes to raw materials, equipment operating parameters or the production process.
8. Issue authentic CoAs for each batch of API or API intermediate with the following:

- a. grade, where appropriate
- b. batch number
- c. date of release

List the expiry date on the label and CoA. List the retest date on the label and/or CoA, as applicable.

9. CoAs should list each test performed in accordance with pharmacopoeial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).
10. CoAs should show the name, address and telephone number of the original fabricator. If a repackager or reprocessor did the analysis, the CoA should show the name, address and telephone number of the repackager/reprocessor, and reference the original fabricator's name and address. CoAs should be dated and signed by quality unit(s) personnel.
11. If new CoAs are issued by or on behalf of repackagers/reprocessors, agents or brokers, show the name, address and telephone number of the laboratory that did the analysis on the CoA. Also reference the name and address of the original fabricator and the original batch CoA. Attach a copy of the original certificate.
12. Quarantine any lot or batch of an API that does not comply with specifications until final disposition. You should:
  - a. investigate and document the issue according to a procedure
  - b. not make the lot or batch 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 Minister 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 Minister, 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 the conditions and exemptions as to when the finished product (API or API intermediate) testing is to be performed. Section [C.02.019\(1\)\(b\)](#) outlines requirements you must meet if the finished product (API or API intermediate) testing is done before receipt on the premises of the packager/labeller of the drug. Sections [C.02.019\(3\)](#) and [C.02.019\(4\)](#) set out when finished product (API or API intermediate) testing is not required.

## Interpretation

1. If you are a packager/labeler, you must confirm identity on a sample taken after the lot or batch is packaged.



Identity testing is not required for multiple shipments of the same API/API intermediate lot providing that the primary packaging/labelling and secondary packaging/labelling of the entire batch has been completely processed as a single batch and not as partial packaging of the same bulk. Storage and transportation conditions must be evaluated for each shipment.

2. Packagers/labellers who do not themselves fabricate the API or API intermediate (i.e. re-packagers/re-labellers) must confirm the identity of the API through one of the following methods:
  - a. Test each lot or batch upon receipt to positively identify the API or API intermediate in a shipment and employ a packaging process with adequate controls to prevent mix-up and provide assurance that the correct lot of API or API intermediate has been packaged.
  - b. Test a sample taken from each packaging lot to positively identify the packaged API or API intermediate.
3. Ensure that each lot has an authentic certificate of analysis (or an electronic copy with an electronic signature). The CoA should show actual numerical results and reference product specifications and validated test methods.
4. 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 API.



To learn more about how to transport and store APIs, refer to the [\*Guidelines for Temperature Control of Drug Products during Storage and Transportation \(GUI-0069\)\*](#).

## 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 Minister, 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.

## 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.

## 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.

## 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.

## 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 APIs/API Intermediates.

Records must be reliable, complete, consistent and accurate.

You must establish a data governance system to ensure controls are in place to prevent and detect data integrity issues. 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.
- Checking the preventative measures put in place periodically 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. If Health Canada requires any documentation for evaluation, you must provide it in one of Canada's official languages (English or French).
2. If you fabricate, package/label, test, import, distribute or wholesale APIs or API intermediates, you are responsible for getting all quality or regulatory information, as applicable, related to API or API intermediate production from any party that provides related services, such as:
  - a. agents
  - b. brokers
  - c. distributors
  - d. re-packagers
  - e. re-labellers
3. You should establish a data governance system to ensure data integrity is maintained for all records required under GMP. 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.



Cloud computing services are to be treated as a contracted service and responsibilities clearly outlined in a contract or service agreement.

- 4. If you use an electronic system to create, modify or store records required under these regulations, the system should be qualified and tested for security, validity, and reliability, and records of those qualifications and tests should be maintained.
  - 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:
    - can only be created and modified by authorized personnel
    - are protected against intentional or accidental deletion
    - are named and organized in a way that allows for easy traceability
    - 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)
    - are backed up at regular intervals to protect against potential data loss due to system issues or data corruption
    - are available for review during an inspection and are readily retrievable in a suitable format

- include all necessary metadata.
5. 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 handwritten signatures. Keep records to show that users are aware of their responsibilities and accountability relating to the use of electronic signatures.
  6. Establish and keep standard operating procedures (SOPs) for all GMP requirements outlined in this guide. Regularly review these SOPs and keep them up to date. They are important as reference documents and for inspection purposes. Document any revisions and ensure only current SOPs are in use.
    - a. Have a system to control the lifecycle of documents (ie. when you issue, revise, replace or stop using them). Keep revision histories.
    - b. Ensure you have procedures to cover what types of documents must be kept and for how long. You should keep:
      - development history reports
      - scale-up reports
      - technical transfer reports
      - process validation reports
      - training records
      - production records
      - control records
      - distribution records
  7. You can keep records such as, specifications, instructions, procedures and records either as originals or true copies—e.g. photocopies. You can also keep these documents in electronic format, but be sure to have backups. Where reduction techniques such as microfilm or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available (e.g. electronic records are readily

retrievable in a printed format). During the period that you retain these records, the fabricator, packager/labeller or importer should be able to access them upon an inspector's request. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

- a. Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.

8. When making entries in your records, you should:

- a. document them clearly in the space provided
- b. make entries immediately after doing an activity
- c. identify the person who made the entries
- d. sign and date any changes to documents and ensure that the original information can be read.

Where appropriate, record the reason for the change.

9. If you fabricate and/or package/label APIs or API intermediates, you should keep master production documents for each API or API intermediate. A qualified person must sign and date these documents, after which they should be independently checked, dated and signed by a person in the quality unit. They should include:

- a. the name of the API or API intermediate and a document reference code, if applicable.
- b. the list of raw materials used, shown by names or codes specific enough to identify any special quality characteristics
- c. the accurate quantity with a unit of measure or ratio of each raw material used, including any variations (and, if quantity is not set, the amount for each batch size or rate of production)
- d. the location and equipment used
- e. detailed production instructions: sequences, ranges of process parameters, sampling instructions, in-process controls with their acceptance criteria, time limits and expected yield ranges
- f. any special notes or precautions, or cross-references to these
- g. instructions for storing the API or API intermediate, including any labelling and packaging materials and special storage conditions with time limits

10. If you fabricate, package/label, or import an API or API intermediate:



- a. Maintain evidence that each lot or batch has been fabricated, packaged/labelled, tested, and stored according to the master production documents. This evidence should include, but is not limited to:
- Any records created under sub-section [C.02.012\(2\)](#) of the Regulations and evidence that manufacturing and packaging processes and analytical methods are validated.
  - Written procedures you followed to review and approve batch production and laboratory control records—including packaging and labelling—to confirm that the API or API intermediate complies with specifications.
  - Manufacturing records, packaging records, test methods and test results for raw materials, packaging materials and APIs or API intermediates.
  - Records of storage conditions for all materials used in the fabrication and packaging/labelling of APIs or API intermediates (e.g. controlled temperatures and humidity) when necessary.



For importers of APIs or API intermediates, test results for raw materials and packaging materials only need to be made available to Health Canada upon request in a timely way.

- b. Keep evidence that the conditions under which the API or API intermediate was fabricated, packaged/labelled, tested and stored comply with the Regulations.
- c. You should have evidence establishing the period of time that the API or API intermediate, where appropriate, meets the required specifications. This period of time is specific to the container and conditions in which it is stored or sold. The documentation to be maintained should include the following:
- the written stability program
  - the data generated in accordance with that program
  - conclusions of the stability program that support the expiry or retest date
  - data generated as part of the continuing stability program



Stability studies to justify assigned retest or expiry dates should be conducted if the API is repackaged in a different type of container than that used by the API fabricator.

11. If you fabricate an API or API intermediate, you must maintain the following documents:

- a. the written specifications for the raw materials
  - b. the results of raw material testing
    - how the materials were examined and/or tested to ensure they conform to established specifications
    - whether the batches were accepted or rejected
    - records showing how the materials were used
  - c. the sources of the raw materials supplied, including:
    - name of the fabricator
    - date of receipt and the number given on receipt
    - identity and quantity of each batch shipment
    - name of the supplier
    - supplier's control number(s), if you know them, or other identification number
  - d. records about the operation of the sanitation program required by section [C.02.007](#) "Sanitation" for a period of at least 3 years
12. If you package or label an API or API intermediate, you must maintain the following documents:
- a. the written specifications for the packaging materials
  - b. the results of packaging material examinations or testing:
    - how the materials were examined and/or tested to ensure they conform to established specifications
    - whether the batches were accepted or rejected
    - records showing how the materials were used
  - c. the sources of the packaging materials supplied, including:
    - name of the fabricator
    - date of receipt and the number given on receipt
    - identity and quantity of each batch shipment
    - name of the supplier
    - supplier's control number(s), if you know them, or other identification number

- d. records about the operation of the sanitation program required by section [C.02.007](#) "Sanitation" for a period of at least 3 years



Save all records and evidence of raw material testing and packaging/labelling material testing, as applicable, for at least **five years** after the materials are last used to fabricate or package/label an API, unless your establishment licence specifies another amount of time.

13. If you fabricate, package/label, or test an API or API intermediate, you must maintain the following documents:

- a. Detailed plans for each building in Canada where APIs or API intermediates are fabricated, packaged/labelled or tested. Keep these records on each site. Include a description of the design and construction of those buildings.
- b. Records of each person who supervises the fabrication, packaging/labelling, and testing of APIs or API intermediates, including:
  - organization charts
  - titles
  - job descriptions
  - responsibilities
  - qualifications
  - experience
  - training
  - name(s) of each person's designated alternate(s)
- c. Records of the names, qualifications and experience of consultants employed for GMP purposes, along with the services that each provides.



If you fabricate, package/label, test, import or store APIs, the following applies to you, unless you hold an establishment licence that specifies some other period:

- If the API has a retest date, keep these records for **three years** after the lot or batch has been completely distributed. In any other cases, keep these records for **one year** after the expiration of the lot or batch.

14. If you are a fabricator, packager/labeller, wholesaler (including agents, brokers and traders), distributor or importer of an API or API intermediate, you must maintain the following documents (as they relate to all operations in Canada):

a. Distribution records of all API or API intermediate sales:

- 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.

b. Keep records to show that all customers who received a recalled API were notified.



If you are a wholesaler (including agents, brokers and traders), distributor or importer of an API, the following applies to you, unless you hold an establishment licence that specifies some other period:

- If the API has a retest date, keep these records for **three years** after the lot or batch has been completely distributed. In any other cases, keep these records for **one year** after the expiration of the lot or batch.

15. If you are a fabricator, packager/labeller, wholesaler (including agents, brokers and traders), distributor or importer of an API or API intermediate, you must maintain the following documents (as they relate to all operations in Canada):

a. Records of any complaints—whether oral or in writing—about API defects or hazards (include how you investigated and took actions to correct the issue). Complaint records should include the:

- name and address of the complainant (if available)
- name and phone number of the person submitting the complaint (if available)
- nature of the complaint (including the name and batch number of the API)
- date on which the complaint was received
- initial action taken (including the dates and identity of the person taking the action)
- actions taken, if any
- response given to the complainant, where possible (including the date on which the response was sent)
- final decision on the API batch or lot



If you are a fabricator, packager/labeller, wholesaler (including agents, brokers and traders), distributor or importer of an API or API intermediate, the following applies to you, unless you hold an establishment licence that specifies some other period:

- If the API or API intermediate has a retest date, keep these records for **three years** after the lot or batch has been completely distributed. In any other cases, keep these records for **one year** after the expiration of the lot or batch.

- Records of the results of your self-inspection program, evaluation and conclusions, and corrective measures implemented. These records must be retained for a period of at least three years.

16. If you are a fabricator, packager/labeller, wholesaler or distributor, referred to in section C.01A.003(a) of the Regulations, or you import APIs or API intermediates —and this includes anyone other than the original fabricator who might trade or possess, repackage, re-label, manipulate, or store an API or API intermediate —you should add the following information to the documentation that accompanies the API or API intermediate:

- the establishment licence number (or, if you do not have an establishment licence, your name, address, telephone number, fax number and email address)
- the activity (fabrication, packaging/labelling, wholesaling, distributing or importing) and the date it occurred
- the expiration date and/or retest date
- the lot number of the API or API intermediate

17. If you are a packager/labeller, re-packager/re-labeller, importer, agent, broker, trader, distributor or wholesaler, you should be able to completely trace any API or API intermediate you distribute. To do so, document the following:

- name and identity of original fabricator and packager/labeller
- address of original fabricator and packager/labeller
- purchase orders
- bills of lading (transportation documentation)
- receipt documents
- name of the API or API intermediate
- fabricator's or packager/labeller's batch number

- h. transportation and distribution records
- i. all certificates of analysis (CoAs), including those of the original fabricator
- j. retest or expiry date



[C.02.020 \(5\)](#) requires every fabricator, packager/labeller and tester to have 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. You should have a site master file available on-site to help satisfy this and other record keeping requirements. You can find out more about how to prepare a site master file in Health Canada's [\*Explanatory notes for drug establishments on the preparation of a site master file \(GUI-0005\)\*](#).

### Required validation documentation

The required validation documents should be available for the purpose of inspection and evaluation. The information required depends on your role in the manufacturing process and it is explained below.

18. Fabricators, packagers/labellers and testers must have the following full records on site showing that their respective manufacturing, packaging and testing processes have been validated. This includes (but is not limited to) the:
  - a. validation master plan
  - b. cleaning validation
  - c. test method validation
  - d. qualification of utilities (e.g. support systems and equipment)
19. Importers of APIs or API intermediates fabricated, packaged/labelled and tested outside of Canada must have the following:
  - a. a certificate of manufacture with a certificate of analysis
  - b. the valid importer's Establishment Licence identifying the foreign building
20. Upon request, copies of complete protocols and related studies for all validation activities must be made available for review.
  - a. product specific process validation documentation showing:
    - the validation approach utilized by the fabricator (prospective, concurrent or retrospective)

- the reference numbers and dates of approval for:
  - the master formula including packaging
  - the process validation protocol
  - the process validation studies
  - the validation of the test methods
- the lot numbers involved and the dates of completion of these studies
- a certified copy of the approved conclusions of the 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.

## 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 can be assessed in the event that concerns arise with an API batch during the shelf life of a product (e.g. a quality complaint or a labelling/packaging query).

### Interpretation

1. Take a representative sample for the purpose of performing a retest.
2. Package and hold retention samples for any future evaluation of API batch quality—not for future stability testing.
3. Keep samples of each API batch for one year after the expiry date of the batch, or for three years after distribution of the batch (whichever is longer). For APIs with retest dates, keep similar samples for three years after the batch is completely distributed by the fabricator.
4. You may store retention samples at another site if you have a written agreement clearly describing the respective responsibilities of each party.



To learn more about alternate sample retention sites, refer to the [Guidance Document Alternate Sample Retention Site Guidelines \(GUI-0014\)](#).

5. Store the sample in the same packaging system the API is stored in, or in one that is equivalent to or more protective than the marketed packaging system of the API. Take sufficient quantities of retention samples to allow duplicate testing according to API specifications.



6. Store retention samples under the conditions listed on the label, if applicable.

## 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 retest or expiry date of an API under recommended storage conditions. Each packaged API must be covered by relevant data to support its retest or expiry date in approved packaging material types. An API's expiry and/or re-test date should be based on well-designed stability studies.



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: Stability Testing of New Drug Substances and Products\*](#)
- [\*ICH Q1E: Evaluation for Stability Data\*](#)
- [\*VICH GL3\(R\): Stability Testing of New Veterinary Drug Substances and Medicinal Products\*](#)
- [\*VICH GL51: Statistical evaluation of stability data\*](#)

### Interpretation

1. Ensure that supporting stability information is available (e.g. published data and test results) when an intermediate is transferred outside of the control of the fabricator's material management system and an expiry or retest date is assigned.
2. Base API expiry or retest dates on data from stability studies. Common practice is to use a re-test date instead of an expiration date.

3. You can base preliminary API expiry or retest dates on pilot scale batches if:
  - a. Pilot batches are manufactured in a way that simulates the final commercial manufacturing process (e.g. linear scale-up using like for like materials and equipment).
  - b. The quality of the API represents the material to be made on a commercial scale.
4. You can obtain preliminary information from accelerated stability studies. The retest or expiry date may initially be based on accelerated data and extrapolated long-term data. In such a case, it should be verified with the long-term stability data as they become available.
5. Store stability samples in containers that simulate the market container. For example, if the API is marketed in bags within fibre drums, you can package stability samples in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.
6. Enrol or continue monitoring at least three commercial-scale batches in the stability program to confirm the retest or expiry date. However, when data from previous studies show that the API should maintain stability for at least two years, you can use fewer than three batches.
7. For imported APIs, stability studies from foreign buildings are acceptable if the data meet Health Canada, ICH and VICH guidelines for stability, and if the site can show GMP compliance. The importer or distributor's responsible quality unit should review and maintain the stability data.
8. Ensure analytical test procedures used to evaluate stability (including accelerated stability studies) are validated according to [\*ICH Q2 \(R1\): Validation of Analytical Procedures: Text and Methodology\*](#) or [\*VICH GL2 Validation of analytical procedures: Methodology as applicable\*](#). 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.



“Degradation” means the chemical breakdown of a pharmaceutical product. Degradation can be affected by various factors, such as exposure to light, oxygen or moisture.



- (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.

## Rationale

A documented, on-going testing program should be designed to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.

## Interpretation

1. Design and document an ongoing testing program to verify the stability of APIs at the specified storage conditions.
2. Store stability samples in containers that simulate the market container. For example, if the API is marketed in bags within fibre drums, you can package stability samples in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.
3. Following the enrollment of the first three commercial batches, at least one batch per year of any API you manufacture should be added to the stability monitoring program and tested annually to confirm stability.
4. Do testing more often for APIs with short shelf lives. For example: APIs with a shelf-life of one year or less need stability samples taken and tested each month for the first three months, and then at three-month intervals. When data confirm that the API's stability is not compromised, you can consider eliminating specific test intervals.
5. Stability storage conditions should follow ICH guidelines on stability, where appropriate.
6. Include "worst-case" situations—e.g. including reworked or reprocessed lots—in your ongoing 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. additional stability studies, an increase in testing frequency or change in the retest or expiry date). Consider the impact on all batches available on

the market. Report such cases to Health Canada in accordance with C.01A.013 (b) where it may affect the quality, safety or efficacy of a drug.

8. For imported APIs, stability studies from foreign buildings are acceptable if the data meet Health Canada, ICH and VICH guidelines for stability, and if the site can show GMP compliance. It is the importer's responsibility to have records associated with the ongoing stability program made available upon request.

# Appendices

## Appendix A – Glossary

### Acronyms

AI:	Active ingredient
API:	Active pharmaceutical ingredient
ASR:	Alternate Sample Retention
CoA:	Certificate of analysis
DIN:	Drug identification number
DQ:	Design Qualification
GMP:	Good manufacturing practices
ICH:	International Council for Harmonisation
IQ:	Installation Qualification
MRA:	Mutual recognition agreement
NOC:	Notice of compliance
OOS:	Out of specification
OOT:	Out of trend
OQ:	Operational Qualification
PIC/S:	Pharmaceutical Inspection Cooperation/Scheme
PQ:	Performance Qualification
SOP:	Standard operating procedure
TGA:	Therapeutic Goods Administration

VICH: International Cooperation on Harmonisation of Technical Requirements for  
Registration of Veterinary Medicinal Products

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. Any reference to Sections are to the Regulations.

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.

**Acceptance criteria** – Numerical limits, ranges, or other suitable measures for acceptance of test results ([ICH Q7](#)).

**Active ingredient** – A drug that, when used as a raw material in the fabrication of a drug in dosage form, provides its intended effect (C.01A.001(1)).

**Active pharmaceutical ingredient** – An active ingredient that is used in the fabrication of a pharmaceutical (C.01A.001(1)).

**Active pharmaceutical ingredient blends** – The homogenous mixture of the same APIs within the same specification

**Active pharmaceutical ingredient intermediate** – A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated ([ICH Q7](#)).

or

an “active pharmaceutical ingredient intermediate” is any intermediate substance after the API starting material, but prior to the final API (no excipients or additives)

**Alternate Sample Retention (ASR) site** – An alternate site specified on a Drug Establishment Licence for the storage of samples pursuant to [subsection C.02.025 \(1\)](#) of the *Food and Drug Regulations*.

**Antimicrobial agent** – Antimicrobial agent means a drug that is capable of destroying pathogenic micro-organisms and that is labelled as being for use in the disinfection of environmental surfaces or medical devices, as defined in the *Medical Devices Regulations*, that

- (a) are not invasive devices as defined in those Regulations; and
- (b) are intended to come into contact with intact skin only (C.01A.001(1)).

Antimicrobial agents include environmental hard surfaces disinfectants used to clean surfaces such as desks and benches.

**API starting material** – A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure. ([ICH Q7](#))

**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. A packaging lot or batch refers to a lot packaged in a continuous process.

**Batch number** – A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. ([ICH Q7](#))

**Batch production record** – Records that demonstrate that the batch of a final API was fabricated according to the approved master production documents.



**Bulk API** – An API 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. (C.01A.001(1))

**Calibration** – The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. ([ICH Q7](#))

**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)

**Cannabis API** – The active ingredient that is the starting material for the manufacturing process of the finished product, which could be an extracted and purified active component of the cannabis plant (for example, a cannabinoid), an extract of specified parts of the cannabis plant, or powdered specified parts of the cannabis plant. (TGA)

**Certificate of analysis (CoA)** – A document containing the name and address of the laboratory 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 or API 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/APIs, or (*b*) that may affect the operation of the quality or support system.

**Changeover procedure** – A logical series of validated steps that ensure the proper cleaning of suites and equipment before the processing of a different product begins.

**Computerized system** – All the components necessary to capture, process, transfer, store, display and manage information, including (but not limited to) hardware, software, personnel and documentation.

**Concurrent validation** – A process where current production batches are used to monitor processing parameters. It gives assurance of the present batch being studied, and offers limited assurance regarding consistency of quality from batch to batch.

**Containment** – The action of confining a chemical or biological agent or other entity within a defined space.

**Contamination** – The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport. ([ICH Q7](#))

**Contractor** – A legal entity carrying out activities on behalf of a company pursuant to a written agreement. This includes other sites within the same corporate structure.

**Critical** - Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification. ([ICH Q7](#))

**Critical process** – A process that if not properly controlled may cause significant variation in the quality of the finished product.

**Cross-contamination** – Contamination of a material or product with another material or product. ([ICH Q7](#))

**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** - 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. ([2016 Draft PIC/S Guidance: Good practices for data management and integrity in regulated GMP/GDP environments](#))

**Data integrity** – The extent to which all data are complete, consistent and accurate throughout the data lifecycle. ([MHRA Guidance on GxP data integrity March 2018](#))

**Design qualification (DQ)** – Documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose. ([ICH Q7](#))

**Deviation** – Departure from an approved instruction or established standard. ([ICH Q7](#))

**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 Regulations.

**Drug** – 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*)

For the purpose of this guidance, drug does not include any of the following:

- (a) a dilute drug premix;
- (b) a medicated feed as defined in subsection 2(1) of the Feeds Regulations, 1983;
- (c) an active ingredient that is for veterinary use and that is not an active pharmaceutical ingredient;
- (d) an active pharmaceutical ingredient for veterinary use that is not required to be sold pursuant to a prescription and that is also a natural health product as defined in subsection 1(1) of the Natural Health Products Regulations;
- (e) 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 by the Minister pursuant to subsection

C.01A.008(1) of the Regulations that authorizes a person to conduct licensable activities in a building in Canada.

**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.

**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
- (c) the date after which the manufacturer recommends that the active ingredient not be used. (C.01.001 (1))

**Fabricate** –To prepare and preserve a drug for the purpose of sale. (C.01A.001)

**Filling** – The transfer and enclosure of a bulk drug or API into its final container.

**Finished Dosage Form (FDF) Intermediate** - Any physical mix, starting when any 2 ingredients (e.g., active ingredient, anti-oxidant, preservative, filler, binder, solvent, etc.) are first added to the drug lot being manufactured, and before it becomes a drug in dosage form. Partially processed drug product intermediate, in-process drugs or bulk drug are examples of drug in dosage form intermediates.

**Finished product** – A product that has undergone all stages of production, including packaging in its final container and labelling.

**Import** –To import into Canada a drug for the purpose of sale.” (C.01A.001(1))

**Impurity** – Any component present in the intermediate or API that is not the desired entity. ([ICH Q7](#))

**Impurity profile** – A description of the identified and unidentified impurities present in an API. ([ICH Q7](#))

**In-process control** – Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the intermediate or API 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 testing** – The examination or testing of any material or mixture of materials during the manufacturing process.

**Installation qualification (IQ)** – 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](#))

**Intermediate** – See Active pharmaceutical ingredient intermediate.

**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(1))

**Lot** – See Batch.

**Lot number** – See Batch number.

**Manufacture** – All operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage, and distribution of APIs and related controls. ([ICH Q7](#))

**Manufacturer or distributor** – See Distributor.

**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).

**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.

**Material** – A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs and packaging and labelling materials. ([ICH Q7](#))

**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 Guidance on GxP data integrity March 2018](#))

**Mother liquor** – The residual liquid which remains after the crystallization or isolation processes. The mother liquor may contain unreacted materials, intermediates, levels of the API and/or impurities. It may be used for further processing. ([ICH Q7](#))

**MRA country** – A country that is a participant in a mutual recognition agreement with Canada (C.01A.001 (1)).

**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(1)).

**Operational qualification (OQ)** – Documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges. ([ICH Q7](#))

**Package/label** – To put a drug or API in its immediate container or to affix the inner or outer label to the drug. (C.01A.001(1)). This includes the repackaging and relabelling 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.

**Performance qualification (PQ)** – Documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications. ([ICH Q7](#))

**Pharmaceutical** – A drug other than a drug listed in Schedule C or D to the Act. (C.01A.001(1))

**Potency** – The activity or amount of active moiety, or any form thereof, indicated by label claim to be present.

**Procedure** – A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of an intermediate or API. ([ICH Q7](#))

**Process aids** – Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid, activated carbon, etc). ([ICH Q7](#))

**Process validation**– The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a drug meeting its predetermined specifications and quality attributes. (Adapted from [ICH Q7](#))

**Production** – All operations involved in preparing an API—from receipt of materials to processing, packaging, completion of the finished product and storage.

**Purity** – The extent to which a raw material or a final API is free from undesirable or adulterating chemical, biological or physical entities as defined by specifications.

**Qualification** – Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation. ([ICH Q7](#))

**Quality assurance**– The sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained. ([ICH Q7](#))

**Quality control**– Checking or testing that specifications are met. ([ICH Q7](#))

**Quality manual** - Document specifying the quality management system of an organization. (ISO 9000:2015)

**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](#)).

**Quality unit** – An organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate quality assurance and quality control units or a single individual or group, depending upon the size and structure of the organization. ([ICH Q7](#))

**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 material** – A general term used to denote starting materials, reagents, and solvents intended for use in the productions of APIs and API intermediates. ([ICH Q7](#))

**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.

**Reference standard, primary** – A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognised source, or (2) prepared by independent synthesis, or (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material. ([ICH Q7](#))

**Reference standard, secondary** – A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis. ([ICH Q7](#))

**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(1))

**Reprocessing** – Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration,



chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process, and not reprocessing. ([ICH Q7](#))

**Retest date** – The date when a material should be re-examined to ensure that it is still suitable for use. ([ICH Q7](#))

**Reworking** – Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent). ([ICH Q7](#))

**Sell** – Offer for sale, expose for sale, have in possession for sale, and distribute, whether or not the distribution is made for consideration. (Section 2 of the *Food and Drugs Act*)

**Senior Management** - Person(s) who direct and control a company or site at the highest levels with the authority and responsibility to mobilize resources within the company or site. ([ICH Q10](#))

**Shelf life** – The time interval during which an API 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.

**Signed** – The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature. ([ICH Q7](#))

**Solvent** – An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API. ([ICH Q7](#))

**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](#))

**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.

**System** – A regulated pattern of interacting activities and techniques that are united to form an organized whole.

**Test** – To perform the tests, including any examinations, evaluations, and assessments, as specified in the Part C, 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 Guidance on GxP data integrity March 2018](#))

**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 C.01A.001(1);

(b) an active ingredient; or

(c) a narcotic as defined in the *Narcotic Control Regulations* (C.01A.001(1)).

**Yield, expected** – The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data. ([ICH Q7](#))

**Yield, theoretical** – The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production. ([ICH Q7](#))

# Appendix B – References

## Laws and regulations

### *Food and Drugs Act*

<https://laws-lois.justice.gc.ca/eng/acts/f-27/>

### *Food and Drug Regulations*

[https://laws-lois.justice.gc.ca/eng/regulations/c.r.c.,\\_c.\\_870/index.html](https://laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/index.html)

## Annexes to GUI-0104

## Good manufacturing practices

### *Good Manufacturing Practices Guide for Drug Products (GUI-0001)*

<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-0001.html>

### *ICH Q7: Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients*

<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/legislation-regulatory-amendments/guidance-industry-good-manufacturing-practice-guidance-active-pharmaceutical-ingredients-topic.html>

### *PIC/S Guide To Good Manufacturing Practice For Medicinal Products Part II*

<https://www.picscheme.org/en/publications?tri=gmp>

## Validation guidelines

### *Q2A: Text on Validation of Analytical Procedures*

<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/texte-concernant-validation-methodes-analyse.html>

### *VICH GL2 Validation of Analytical Procedures: Methodology*

<https://vichsec.org/guidelines/pharmaceuticals/pharma-quality/analytical-validation.html>

### *Cleaning Validation Guidelines (GUI-0028)*

<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/validation/cleaning-validation-guidelines-guide-0028.html>

[ICH Q2 \(R1\): Validation of Analytical Procedures: Text and Methodology](#)

<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/validation-analytical-procedures-text-methodology.html>

[Recall Policy for Health Products \(POL-0016\)](#)

<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/recall-policy-0016.html>

## Other related documents

[Policy on Manufacturing and Compounding Drug Products in Canada \(POL-0051\)](#)

<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/policy-manufacturing-compounding-drug-products.html>

[Risk Classification of Good Manufacturing Practices \(GMP\) Observations \(GUI-0023\)](#)

<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/risk-classification-drug-gmp-observations-0023.html>

[Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites \(GUI-0080\)](#)

<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/guidance-evidence-demonstrate-drug-compliance-foreign-sites-0080.html>

[Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees \(GUI-0002\)](#)

<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/establishment-licences/directives-guidance-documents-policies/guidance-drug-establishment-licences-drug-establishment-licensing-fees-0002.html>

[Guidelines for Temperature Control of Drug Products during Storage and Transportation \(GUI-0069\)](#)

<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/guidelines-temperature-control-drug-products-storage-transportation-0069.html>

*Standard for the Fabrication, Control and Distribution of Antimicrobial Agents for Use on Environmental Surfaces and Certain Medical Devices (GUI-0049)*

<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/policies-standards/standard-fabrication-control-distribution-antimicrobial.html>

*Guidance Document Alternate Sample Retention Site Guidelines (GUI-0014)*

<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/establishment-licences/forms/alternate-sample-retention-site-guidelines-0014.html>

*Guide to reporting drug shortages and discontinuations (GUI-0120)*

<https://www.canada.ca/en/public-health/services/publications/drugs-health-products/reporting-drug-shortages-discontinuations.html>

## International guidance documents

*ICH Q10: Pharmaceutical Quality System*

<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/adoption-international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use-guidance-pharmaceutical-quality-system.html>

*PIC/S Good Practices for Data Management and Integrity in Regulated GMP/GDP environments*

<https://picscheme.org/en/news/draft-pic-s-good-practices-for-data-management-and-integrity-in-regulated-gmp-gdp-environments>

*ICH Q9: Quality Risk Management*

<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/adoption-international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use.html>

*ICH Q3A (R): Impurities in New Drug Substances*

<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/impurities-new-drug-substances-topic.html>

[Guidance on Parametric Release - Pharmaceutical Inspection Co-Operation Scheme \(PIC/S\)](https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/international/partnerships/guidance-parametric-release-pharmaceutical-inspection-operation-scheme.html)

<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/international/partnerships/guidance-parametric-release-pharmaceutical-inspection-operation-scheme.html>

[EudraLex: The Rules Governing Medicinal Products in the European Union: Volume 4: Part II: Basic Requirements for Active Substances used as Starting Materials](https://ec.europa.eu/health/documents/eudralex/vol-4_en)

[https://ec.europa.eu/health/documents/eudralex/vol-4\\_en](https://ec.europa.eu/health/documents/eudralex/vol-4_en)

## Appendix C – Crosswalk between GUI-0104 and ICH Q7 documents

Table 1: Crosswalk between GUI-0104 and ICH Q7 documents

Interpretations of GUI-0104	Section of ICH Q7
<b>C.02.003 - Sale and Use in Fabrication</b>	
All	Not applicable
<b>C.02.004 - Premises</b>	
1	4.10
2	4.11
3	4.12
4	4.13
5	4.14
6	4.15
7	4.16
8	4.20
9	4.21, 4.22
10	4.23
11	4.24
12	4.33
13	4.40
14	4.42 (partial), 4.41 (partial), 4.43
15	4.50
16	4.70
<b>C.02.005 - Equipment</b>	
1	5.10

2	5.11
3	5.22
4	6.20
5	6.21
6	5.14
7	5.15
8	5.24 (partial)
9	5.13
10	5.20
11	Not applicable
12	5.30, 5.32
13	5.31, 5.32
14	5.33
15	5.34
16	5.35
17	8.1 (partial)
18	5.12
19	5.40
20	5.44
21	5.41
22	5.42 (partial)
23	12.30
<b>C.02.006 - Personnel</b>	
1	3.10, 3.11 (partial), 3.12 (partial)
2	Not applicable
3	3.12 (partial)
4	3.30
5	3.11 (partial)
6	2.22
<b>C.02.007 - Sanitation</b>	
1	5.21
2	Not applicable
3	5.25 (partial), 12.75 (partial), 12.74 (partial), 5.24 (partial), 4.60 (partial)
4	12.70
5	12.76
6	6.20
7	Not applicable
<b>C.02.008 - Raw Material Testing</b>	



1	Not applicable
2	3.20
3	Not applicable
4	3.24
5	3.21
6	Not applicable
7	3.22
8	3.23
<b>C.02.009 - Raw Material Testing</b>	
1	6.17
2	Not applicable
3	7.12
4	4.3
5	4.31
6	4.32
7	4.34
8	12.80
9	12.81
10	7.50
<b>C.02.010 - Raw Material Testing</b>	
1	7.11
2	7.30 (partial)
3	7.31 (partial)
4	7.32
5	7.33
6	7.33
7	7.10 (partial)
8	7.13
9	7.14
10	Not applicable
11	10.21 (partial)
12	Not applicable
13	Not applicable
<b>C.02.011 - Manufacturing Control</b>	
1	Not applicable
2	7.10 (partial)
3	12.12, 13.13 (partial), 12.60
4	12.20, 12.21, 12.22
5	12.3

6	2.16
7	8.20
8	8.14
9	8.5
10	Not applicable
11	9.44 (partial)
12	8.51
13	8.35
14	8.30
15	8.31
16	8.32
17	8.33
18	4.16 (partial)
19	8.34
20	8.52
21	4.13 (partial)
22	5.26 (partial)
23	8.16
24	7.44
25	8.17
26	7.20
27	7.21
28	7.22
29	8.21
30	10.21 (partial)
31	10.22
32	7.34
33	7.35
34	7.23
35	7.24
36	7.40
37	7.41
38	7.42
39	7.43
40	8.10
41	8.12
42	8.13
43	2.15
44	6.10

45	6.40
46	6.41
47	6.50
48	6.51
49	6.52
50	8.11
51	8.41
52	8.42
53	8.43
54	8.44
55	8.45
56	8.46
57	8.47
58	14.40
59	14.41
60	14.42
61	14.43
62	Not applicable
63	9.41
64	9.30
65	9.44
66	9.40
67	9.34
68	9.35
69	9.36
70	9.21
71	9.22
72	9.42
73	9.43
74	9.45
75	9.31
76	9.32
77	9.33
78	7.20 (partial)
79	Not applicable
80	2.50
81	2.51
C.02.012 - Manufacturing Control	
1	10.11

2	15.10
3	15.15 (partial)
4	Not applicable
5	15.13 (partial)
6	15.14
7	Not applicable
8	Not applicable
9	10.24 (partial)
10	Not applicable
11	Not applicable
12	10.11 (partial)
13	Not applicable
14	Not applicable
15	2.41
16	2.40
17	16.1
18	16.11 (partial), 16.12 (partial), 16.13 (partial), 16.14 (partial), 16.16 (partial)
<b>C.02.013 - Quality Control Department</b>	
1	2.20
2	Not applicable
3	2.13
4	Not applicable
5	2.11 (partial)
<b>C.02.014 - Quality Control Department</b>	
1	Not applicable
2	Not applicable
3	10.20
4	7.20 (partial)
5	Not applicable
6	14.10, 14.51
7	14.52
8	Not applicable
9	14.52 (partial)
10	14.30
11	14.31
12	14.32
13	14.20
<b>C.02.015 - Quality Control Department</b>	

1	2.18
2	2.21, 7.10 (partial)
3	13.10
4	13.11
5	13.12
6	13.13
7	13.13
8	13.14
9	13.16
10	13.15
11	13.17
12	17.71, 17.72, 15.12
13	11.12
14	11.11 (partial)
15	5.40 (partial), 5.43, 5.44, 5.48, 6.16 (partial)
16	5.47
17	5.45
18	5.46
19	2.16 (partial)
20	6.60
21	6.61
22	11.16 (partial)
23	Not applicable
24	11.17
25	11.19
26	11.18
27	Not applicable
28	10.23
<b>C.02.016 and C.02.017 - Packaging Material Testing</b>	
1	9.10
2	9.11, 9.21 (partial)
3	7.34
4	7.30 (partial)
5	2.17 (partial)
6	9.20
7	9.21 (partial)
8	9.33 (partial)
9	7.31
<b>C.02.018 - Finished Product Testing</b>	

1	11.20
2	11.12, 11.13
3	12.80
4	12.81 (partial)
5	16.12 (partial)
6	11.21
7	11.22
8	11.40, 11.41
9	11.42
10	11.43
11	11.44
12	14.10 (partial)
<b>C.02.019 - Finished Product Testing</b>	
1	Not applicable
2	Not applicable
3	11.42 (partial)
4	10.21 (partial)
<b>C.02.020 to C.02.024 - Records</b>	
1	Not applicable
2	17.60
3	Not applicable
4	5.43 (partial)
5	6.18 (partial)
6	6.11, 16.12
7	6.16
8	6.14
9	6.40, 6.41
10	Not applicable
11	6.30 (partial)
12	6.30 (partial)
13	3.31 (partial)
14	Not applicable
15	15.11
16	Not applicable
17	17.20
18	12.10 (partial)
19	Not applicable
20	Not applicable
<b>C.02.025 and C.02.026 - Samples</b>	

1	11.63
2	11.70
3	11.71
4	Not applicable
5	11.72
6	Not applicable
C.02.027 - Stability	
1	11.60
2	11.61
3	11.62
4	13.16
5	11.52
6	11.53
7	Not applicable
8	Not applicable
C.02.028 - Stability	
1	11.50
2	11.52
3	11.54
4	11.55
5	11.56
6	Not applicable
7	11.15 (partial)
8	Not applicable