

**Our Mandate:**

To promote good nutrition and informed use of drugs, food, medical devices and natural health products, and to maximize the safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the Canadian marketplace and health system.

# **Health Products and Food Branch Inspectorate**

## **Good Manufacturing Practices (GMP) Guidelines for Active Pharmaceutical Ingredients (APIs)**

### **GUI-0104**

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New Document

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#### **Disclaimer**

*This document does not constitute part of the Food and Drugs Act (Act) or its associated Regulations and in the event of any inconsistency or conflict between that 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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## 1. Introduction

Active Pharmaceutical Ingredients (API) and intermediates for pharmaceutical use (i.e. pharmaceutical, radiopharmaceutical, and biological) and those used to manufacture drugs for clinical trials are regulated under the Divisions 1A and 2, Part C of the *Food and Drug Regulations*. Division 1A, Part C of the *Food and Drug Regulations* defines activities for which Good Manufacturing Practices (GMP) compliance is required and must be demonstrated prior to the issuance of an API establishment licence (EL). Division 2, Part C of the *Food and Drug Regulations* defines the requirements for the GMP of APIs and API intermediates, which are interpreted in the present guidance document.

These *Good Manufacturing Practices (GMP) for Active Pharmaceutical Ingredients (API)* guidelines, GUI-0104, are designed to facilitate compliance by the regulated industry and to enhance consistency in the application of the regulatory requirements. It should be noted that these guidelines do not cover safety aspects for the personnel engaged in the fabrication, packaging/labelling, and testing of APIs and intermediates, or aspects of protection of the environment. These controls are inherent responsibilities of the API fabricator, packager/labeller and tester.

In addition to the present guidelines, a list of further guidance in specific areas related to APIs and API intermediates is provided in Appendix C of this document. Although the definition of active ingredients in Division 2, Part C of the *Food and Drug Regulations* includes APIs and bulk process intermediates (BPI), the present GUI-0104 only applies to APIs. Guidance on the fabrication, packaging/labelling, testing, distribution, wholesaling, and importation of drugs in dosage form, and BPIs for radiopharmaceutical and biological drugs is provided in the *Good Manufacturing Practices Guidelines, 2009 Edition, Version 2* (GUI-0001). Guidance regarding the fabrication, packaging/labelling, testing, distribution, and importation of medical gases is provided in the *Good Manufacturing Practices for Medical Gases* (GUI-0031).

The content of this document should not be regarded as the only interpretation of the *GMP Regulations*, nor does it intend to cover every conceivable case. Alternative means of complying with these *Regulations* can be considered with the appropriate scientific justification. Different approaches may be called for as new technologies emerge.

This document has been written with a view to harmonize with GMP standards from other countries and with those of the Pharmaceutical Inspection Cooperation/Scheme (PIC/S), and the International Conference on Harmonisation (ICH).

## 2. Purpose

The purpose of this guide, GUI-0104, is to provide interpretive guidance for Part C, Division 2, of the *Food and Drug Regulations* for the manufacture of APIs (including their intermediates). These guidelines are designed to facilitate compliance by the regulated industry and to enhance consistency in the application of the regulatory requirements. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

## 3. Scope

The focus of these guidelines is on the manufacture of APIs sold in their final labelled container and/or used in the manufacture of finished dosage forms for human use. Any other further processing steps after the APIs are

in their final labelled container are subject to GUI-0001. More specifically, they apply to the fabrication, packaging/labelling, testing, importation, distribution, wholesale, and re-packaging/re-labelling of APIs (including their intermediates). Agents and brokers of APIs will be considered to be wholesalers if they sell APIs as per the definition of "sell" in the *Food and Drugs Act*. Whether an agent or a broker is acting as a wholesaler within the meaning of the regulatory scheme may require further review/examination. Those who are in fact selling APIs shall comply with the requirements defined in Division 2, Part C of the *Food and Drug Regulations*, as applicable to them.

Any regulatory requirements other than Division 2 requirements that applies or applied to a given activity or product still applies.

This guide does not apply to the following:

- vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it does include APIs that are produced using blood or plasma as raw materials.
- cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps (although they may be subject to GMP)
- medical gases,
- bulk-packaged drug (medicinal) products, and
- manufacturing/control aspects specific to radiopharmaceuticals.
- medical devices, including medical devices classified as combination products where the primary mode of action is a medical device.
- veterinary drugs
- natural health products

Although BPI are defined as active ingredients in subsection C.01A.001(1) of Division 1A in the *Food and Drug Regulations*, the present guide does not apply to BPIs. For further guidance on the manufacture of BPIs, please refer to the *Annex 3 to the Current Edition of the Good Manufacturing Practices Guidelines - Schedule C Drugs* (GUI-0026) and *Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs)* (GUI-0027).

Health Canada considers fabrication, packaging/labelling, and testing of sterile APIs not terminally sterilized as being finished dosage form manufacture and therefore, these guidelines only apply to the manufacture of sterile APIs up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but should be performed in accordance with the *Good Manufacturing Practices Guidelines, Edition 2009, Version 2* (GUI-0001).

**Table 1: GMP Regulations (Division 2) Applicable to API Activities<sup>1</sup>**

Section	Regulation	F <sup>2</sup>	P/L	T	I	D	W <sup>3</sup>
Premises	C.02.004	√	√		√	√	√
Equipment	C.02.005	√	√	√			
Personnel	C.02.006	√	√	√	√	√	√
Sanitation	C.02.007	√	√				
	C.02.008	√	√				
Raw Material Testing	C.02.009	√		*			
	C.02.010	√		*			
Manufacturing Control	C.02.011	√	√		√		
	C.02.012	√	√		√	√	√
Quality Control	C.02.013	√	√		√	√	√
	C.02.014	√	√		√	√	√
	C.02.015	√	√	√	√	√	√
Packaging Material Testing	C.02.016	√	√				
	C.02.017	√	√				
Finished Product Testing	C.02.018	√	√	*	√	√	√
	C.02.019		√				
Records	C.02.020	√	√	√	√		
	C.02.021	√	√	√	√	√	√
	C.02.022				√	√	√
	C.02.023	√	√		√	√	√
	C.02.024	√	√		√	√	√
	C.02.024.1	√	√		√	√	√
Samples	C.02.025	√					
	C.02.026	√					
Stability	C.02.027	√		*	√		
	C.02.028	√		*	√		

- The following are licensable activities as per Division 1A, Part C of the *Food and Drug Regulations*: fabrication, packaging/labelling, testing and importation of APIs.
  - F: Fabricator, P/L: Packager/Labeller, T: Tester, I: Importer, D: Distributor, W: Wholesaler
  - It should be noted that as per the new definition of wholesale as stated in Division 1A, Part C of the *Food and Drug Regulations*, agents and brokers are considered wholesalers and thus should comply with Health Canada's GMP regulatory requirements.
- √ Regulatory Section applies to the API activity  
 \* Where applicable depending on the nature of the activities.

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 below Table 2. Whether or not all steps of a type of manufacturing as shown in Table 1 are completed, the present guidelines apply to the steps shown in blue. The stringency of GMPs in API manufacturing should increase as the process proceeds from early API steps to final steps, purification, and packaging.

**Table 2<sup>4</sup>: Application of GUI-0104 to API Manufacturing**

Type of manufacturing	Manufacturing Steps <sup>a</sup>				
	1	2	3	4	5
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process <sup>b</sup>	Production of Intermediate(s) <sup>b</sup>	Isolation and purification <sup>b</sup>	Physical processing, and packaging <sup>b</sup>
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process <sup>b</sup>	Isolation and purification <sup>b</sup>	Physical processing, and packaging <sup>b</sup>
API extracted from plant sources	Collection of plants	Cutting and initial extraction(s)	Introduction of the API Starting Material into process <sup>b</sup>	Isolation and purification <sup>b</sup>	Physical processing, and packaging <sup>b</sup>
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction <sup>b</sup>	Physical processing, and packaging <sup>b</sup>
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/comminuting			Physical processing, and packaging <sup>b</sup>
Biotechnology: fermentation/cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank <sup>b</sup>	Cell culture and/or fermentation <sup>b</sup>	Isolation and purification <sup>b</sup>	Physical processing, and packaging <sup>b</sup>
“Classical” Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation <sup>b</sup>	Isolation and purification <sup>b</sup>	Physical processing, and packaging <sup>b</sup>

4. This table is from the International Conference on Harmonization Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7, November 2000. This table differs from the original table but only in format and not in content in order to meet the requirements of the [Standard on Web Accessibility](http://www.tbs-sct.gc.ca/ws-nw/wa-aw/index-eng.asp) ( <http://www.tbs-sct.gc.ca/ws-nw/wa-aw/index-eng.asp>).

<sup>a</sup> The GMP requirements increase in columns from left to right.

<sup>b</sup> GUI-0104 applies to this step used in this type of manufacturing.

## 4. Quality Management

### 4.1 Guiding Principle

The holder of an establishment licence, or any activity to which the requirements of Division 2 Part C of the *Food and Drug Regulations* are applicable, must ensure that the fabrication, packaging, labelling, testing, importation, distribution, and wholesaling of APIs comply with these requirements and as per approved specifications in the marketing authorization of the drug in dosage form, and do not place consumers at risk due to inadequate safety and quality.

The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of personnel in many different departments and at all levels within the establishment and its suppliers.

To ensure compliance, there must be a comprehensively designed and correctly implemented quality management system that incorporates GMP, quality assurance and control, lifecycle and risk management as appropriate such as the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. The quality management system including all quality related activities should be defined and fully documented, and its effectiveness monitored.

## **4.2 Relationship among Quality Elements**

The basic concepts of quality assurance, GMP, and quality control are inter-related. They are described here in order to emphasize their relationships and their fundamental importance to the production and control of APIs.

### **4.2.1 Quality Assurance**

Quality assurance is a wide-ranging concept that covers all matters that individually or collectively influence the quality of an API. It is the total of the organized arrangements made with the objective of ensuring that APIs are of the quality required for their intended use. Quality assurance therefore incorporates GMP, along with other factors that are outside the scope of these guidelines.

A system of quality assurance appropriate for the fabrication, packaging, labelling, testing, distribution, importation, and wholesale of APIs should ensure that:

1. APIs are designed and developed in a way that takes into account the GMP requirements;
2. Each fabricator should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel. Managerial responsibilities should be clearly specified;
3. Systems, facilities and procedures are adequate and qualified, whether they are new or modified;
4. Production and control operations are clearly specified;
5. Analytical methods and critical processes are validated;
6. Arrangements are made for the supply and use of the correct raw and packaging materials;
7. All necessary control on APIs and any other in-process monitoring is carried out;
8. Outsourced activities are subject to appropriate controls and meet GMP requirements;
9. Fabrication, packaging/labelling, testing, distribution, importation, and wholesaling are performed in accordance with established procedures;
10. APIs are not released for sale or for further fabrication before the authorized person from the quality control department has approved that each lot has been produced and controlled in accordance with the approved specifications;
11. Satisfactory arrangements exist for ensuring that the APIs are stored, distributed, and subsequently handled in such a way that quality is maintained throughout their expiry or retest date;



12. The quality risk management system should ensure that:
  - the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient and
  - the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.
13. The effectiveness, applicability, and continuous improvement of the quality management system is ensured through regular management review and self-inspection;
14. An annual product quality review of all APIs and intermediates should be conducted with the objective of verifying the consistency of the existing process, and to identify product and process improvements.
15. All quality related activities should be recorded at the time they are performed.

#### **4.2.2 Good Manufacturing Practices for APIs**

GMP are the part of quality assurance that ensures that APIs are consistently produced and controlled in such a way to meet the quality standards appropriate to their intended use, as required by the approved specifications in the market authorization of the drug in dosage form.

GMP basic requirements are as follows:

1. Manufacturing processes are clearly defined and controlled to ensure consistency and compliance with approved specifications;
2. Critical steps of manufacturing processes and significant changes to the process are validated;
3. All necessary key elements for GMP are provided, including the following:
  - qualified and trained personnel,
  - adequate premises and facilities,
  - suitable equipment and utilities,
  - correct materials, containers and labels,
  - approved procedures and instructions, and
  - suitable storage and transport.
4. Instructions and procedures are written in clear and unambiguous language;
5. Operators are trained to carry out and document procedures;
6. 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 are investigated and documented;
7. Records of fabrication, packaging, labelling, testing, distribution, importation, and wholesaling that enable the complete history of a lot to be traced are retained in a comprehensible and accessible form;
8. Control of storage, handling, and transportation of the APIs minimizes any risk to their quality;
9. A system is available for recalling of APIs from sale;

10. Complaints about APIs are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective APIs and to prevent recurrence.

### 4.2.3 Quality Control

Quality control is the part of GMP that is concerned with sampling, specifications, testing, documentation, and release procedures. Quality control ensures that the necessary and relevant tests are carried out and that raw materials, packaging materials, and APIs are released for use or sale, only if their quality is satisfactory. Quality control is not confined to laboratory operations but must be incorporated into all activities and decisions concerning the quality of the API.

The basic requirements of quality control are as follows:

1. Adequate facilities, trained personnel, and approved procedures are available for sampling, inspecting and testing of raw materials, packaging materials, APIs, and, where appropriate monitoring environmental conditions for GMP purposes;
  - 1.1 Samples of raw materials, packaging materials, and APIs are taken according to procedures approved by the quality control department;
  - 1.2 Test methods are validated;
  - 1.3 Records demonstrate that all the required sampling, inspecting, and testing procedures were carried out, and any deviations are recorded and critical deviations investigated;
  - 1.4 Records are made of the results of the self-inspection program;
  - 1.5 The procedures for product release include a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;
  - 1.6 No API is released for sale or for further use prior to approval by the quality control department;
  - 1.7 Sufficient samples of raw material and final API forms are retained to permit future examination if necessary.

## 5. Interpretation of Regulations

### Division 2 – Good Manufacturing Practices

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#### Section C.02.002

In this Division,

- "medical gas" means any gas or mixture of gases manufactured, sold, or represented for use as a drug; (*gaz médical*)
- "packaging material" includes a label; (*matériel d'emballage*)
- "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. (*spécifications*)

**Section  
C.02.002.1**

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

**Sale**

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**Section  
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.

**Section  
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.

**Section  
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.

**Use in Fabrication**

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**Section  
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.

## **Rationale**

The requirements described in these sections are intended to assure that APIs offered for sale at all levels of the supply chain or used in the fabrication of drugs in dosage form are compliant to this Division.

## **Interpretation**

1. APIs used in the fabrication of a drug in dosage form should be fabricated, packaged/labelled, tested and stored in accordance with the requirements of this Division.
2. The distributor of a drug for which that distributor holds the drug identification number and importer of a drug in dosage form should ensure that the API contained in the drug in dosage form meets the requirements of this Division prior to selling the drug in dosage form.

## **Premises**

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### **Section**

#### **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**

The design and construction of API establishments is influenced by various factors such as the nature of the API and the location (climatic regions). API establishments should be designed and constructed in a manner that permits cleanliness and orderliness while preventing contamination. The buildings and facilities should be regularly maintained to prevent deterioration of the premises. Ultimately, the objective of all endeavours in the design and construction of an API establishment is product quality.

## **Interpretation**

1. Buildings and facilities used in the production of APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of production. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.
2. Buildings used in the production of APIs should be properly maintained and repaired and kept in a clean condition.

3. Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.
4. There should be defined areas or other control systems for the following activities:
  - Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection;
  - Quarantine before release or rejection of APIs;
  - Sampling of APIs;
  - Holding rejected materials before further disposition (e.g., return, reprocessing or destruction);
  - Storage of released materials;
  - Production operations;
  - Packaging and labelling operations; and
  - Laboratory operations.
5. Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or the APIs.
6. Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.
7. All utilities that could impact on product quality (e.g., water, steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.
8. Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimise risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.
  - 8.1 If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.
9. Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, production areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.
10. The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

11. Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.
12. Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the API.
13. Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of certain classes of highly sensitizing materials, such as penicillins or cephalosporins.
14. Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.
15. Any production activities (including weighing, milling, or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.
16. Where water used in the process is treated by the fabricator to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

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## Equipment

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### Section 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

The purpose of these requirements is to prevent the contamination of APIs by other APIs, by dust, and by foreign materials such as rust, lubricant and particles coming from the equipment. Contamination problems may arise from poor maintenance, the misuse of equipment, exceeding the capacity of the equipment and the use of worn-out equipment. Equipment arranged in an orderly manner permits cleaning of adjacent areas and does not interfere with other processing operations. It also minimizes the circulation of personnel and optimizes the flow of materials. The fabrication of APIs of consistent quality requires that equipment perform in accordance with its intended use.

### Interpretation

1. Equipment used in the production of APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization, where appropriate, and maintenance.
2. Equipment should be constructed so that surfaces that contact raw materials, intermediates or APIs do not alter the quality of the APIs beyond the official or other established specifications.
3. Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the APIs beyond the official or other established specifications.
4. Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact APIs so as to 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. Wherever possible, food grade lubricants and oils should be used.
5. Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.
  - 5.1 Ovens, autoclaves and similar equipment contain only one API at a time unless precautions are taken to prevent contamination and mix-ups.
6. Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an API should be appropriately identified.
7. Schedules, procedures, and logs, including assignment of responsibility, should be established for the preventative maintenance of equipment.
8. Equipment that is unsuitable for its intended use should be removed from production areas. When removal is not feasible unsuitable equipment should be clearly labelled as such.
9. Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of APIs should be calibrated according to written procedures and an established schedule. Instruments that do not meet calibration criteria should be clearly identified and not used.
  - 9.1 Equipment calibrations should be performed using standards traceable to certified standards, if existing and current calibration status of critical equipment should be known and verifiable.
  - 9.2 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the APIs manufacture using this equipment since the last successful calibration.
10. Weighing and measuring devices should be of suitable accuracy for the intended use.
11. Production equipment should only be used within its qualified operating range.
12. GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.

13. Appropriate installation qualification (IQ) and operational qualification (OQ) should demonstrate the suitability of computer hardware and software to perform assigned tasks.
14. Commercially available software that has been qualified does not require 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.
15. Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g. system turned off and data not captured). There should be a record of any data change made that includes the previous entry, who made the change, and when the change was made.
16. If computerized system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.
17. Written procedures should be available for the operation and maintenance of computerized systems.
18. Qualification is usually carried out by conducting the following activities, individually or combined:
  - Design Qualification (DQ)
  - Installation Qualification (IQ)
  - Operational Qualification (OQ)
  - Performance Qualification (PQ)

## **Personnel**

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### **Section C.02.006**

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

### **Rationale**

It is essential that qualified and competent personnel be employed to supervise the production and control of APIs. Personnel require education appropriate to the task performed. Education should be supplemented by training and/or experience in the particular task performed. The education, training, competency and attitude of all personnel directly impact's the quality of the products.

### **Interpretation**

1. There should be an adequate number of personnel qualified by appropriate education, training and relevant experience to perform and supervise the fabrication, packaging/labeling, testing, importation, distribution and storage of APIs.



2. The individual in charge of the quality control department of a fabricator, packager/labeller, tester, importer, distributor, and wholesaler; and the individual in charge of the manufacturing department of a fabricator and packager/labeller
  - 2.1 should directly control and personally supervise on site, each working shift during which activities under their control are being conducted.
  - 2.2 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 responsibility.
3. The responsibilities of all personnel engaged in the fabrication, packaging/labeling, testing, importation, distribution and storage of APIs should be specified in writing and personnel should have authority to carry out their responsibilities.
4. Training should be regularly conducted by qualified individuals in accordance with a written program.
  - 4.1 The training should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions.
  - 4.2 Records of training should be maintained.
  - 4.3 Training should be periodically assessed and performance of personnel periodically reviewed.
  - 4.4 Training should be provided prior to implementation of new or revised SOPs.
  - 4.5 Personnel working in areas where highly active, toxic, infectious, or sensitizing materials are handled should be given specific training.
5. Consultants and contractors advising on the manufacture and control of APIs should have appropriate education, training, and relevant experience, or any combination thereof, to advise on the subject for which they are retained.
6. The responsibility for production activities should be described in writing, and should include but not necessarily be limited to:
  - 6.1 Preparing, reviewing, approving and distributing the instructions for the production of APIs according to written procedures;
  - 6.2 Producing APIs and, when appropriate, intermediates according to pre-approved instructions;
  - 6.3 Reviewing all production batch records and ensuring that these are completed and signed;
  - 6.4 Ensuring that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;
  - 6.5 Ensuring that production facilities are clean and when appropriate disinfected;
  - 6.6 Ensuring that the necessary calibrations are performed and records kept;

- 6.7 Ensuring that the premises and equipment are maintained and records kept;
  - 6.8 Ensuring that validation protocols and reports are reviewed and approved;
  - 6.9 Evaluating proposed changes in product, process or equipment; and
  - 6.10 Ensuring that new and, when appropriate, modified facilities and equipment are qualified.
7. The main responsibilities of the quality unit(s) in a manufacturing and packaging/labelling establishment should not be delegated. These responsibilities should be described in writing and should include at a minimum where applicable,
- 7.1 Releasing or rejecting all APIs; in some instances, the quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.
  - 7.2 Establishing a system to release or reject raw materials, intermediates, packaging and labelling materials;
  - 7.3 Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution;
  - 7.4 Ensuring that critical deviations are investigated and resolved;
  - 7.5 Approving all specifications and master production documents;
  - 7.6 Approving all procedures impacting the quality of APIs;
  - 7.7 Ensuring that internal audits (self-inspections) are performed;
  - 7.8 Approving API and intermediate contract fabricators;
  - 7.9 Approving changes that potentially impact APIs quality;
  - 7.10 Reviewing and approving validation protocols and reports;
  - 7.11 Ensuring that quality-related complaints are investigated and resolved;
  - 7.12 Ensuring that effective systems are used for maintaining and calibrating critical equipment;
  - 7.13 Ensuring that materials are appropriately tested and the results are reported;
  - 7.14 Ensuring that there is stability data to support retest or expiry dates and storage conditions on APIs, where appropriate;
  - 7.15 Performing annual product quality reviews; and
  - 7.16 Ensuring that quality control equipment is appropriate to testing activities undertaken.

## Sanitation

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### Section

#### 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 plant, as well as employee attitude, influences the quality of drug products. The quality requirement for drug products demand that such products be fabricated and packaged in areas that are free from environmental contamination and free from contamination by another drug.

There is a significant difference between a finished product production environment (physical process) and an API production environment (chemical process), where aggressive and corrosive reagents may be used. The level of cleanliness required for an API production environment may vary depending on whether it is an open or closed production system and the stage of production. Open production systems (e.g., vessel with no lid) or processes closer to the end of production (e.g., purification) would require a higher level of environmental controls to prevent and/or minimise contamination. Overall, the sanitation program implemented at a site should be effective in preventing unsanitary conditions.

### Interpretation

1. Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.
  - 1.1 There should be an environmental monitoring program with alert and action limits in areas where susceptible products are fabricated or packaged, when applicable.
  - 1.2 The description of the responsibilities of any outside contractors should be available in writing.
2. Non-dedicated equipment should be cleaned between productions of different materials to prevent cross-contamination.
3. Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

4. Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.
5. Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to the API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.
6. Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, and verifiable and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component. Further guidance is detailed in Health Canada's document entitled *Cleaning Validation Guidelines* (GUI-0028).
7. Equipment cleaning/sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).
8. When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labelling materials, intermediates, and APIs.
9. Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:
  - Assignment of responsibility for cleaning of equipment;
  - Cleaning schedules, including, where appropriate, sanitizing schedules;
  - A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;
  - When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;
  - Instructions for the removal or obliteration of previous batch identification;
  - Instructions for the protection of clean equipment from contamination prior to use;
  - Inspection of equipment for cleanliness immediately before use, if practical; and
  - Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.
10. Where equipment is assigned to continuous production or campaign production of successive batches of the same API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of micro-organisms).

11. Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time, if appropriate, product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.
12. Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these proceedings are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.
13. Dusty operations should be contained. The use of unit or portable dust collectors should be avoided in fabrication areas especially in dispensing, unless the effectiveness of their exhaust filtration is demonstrated and the units are regularly maintained in accordance with written approved procedures.

## **Section 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**

Employee's health, behaviour, and clothing may contribute to the contamination of the product. Poor personal hygiene will nullify the best sanitation program and greatly increase the risk of product contamination.

## **Interpretation**

1. Personnel and visitors should practice good sanitation and health habits.
  - 1.1 Requirements concerning cosmetics and jewellery worn by employees should be outlined and observed by employees.
2. 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.
  - 2.1 Employees should be instructed to report to their supervisor any health conditions they have that could adversely affect APIs.

- 2.2 A procedure should be in place to describe the actions to be taken in the event that a person with a communicable disease has been identified as having handled exposed materials.
3. Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn when necessary, to protect APIs from contamination.
  - 3.1 Soiled protective garments, if reusable, should be stored in separate containers until properly laundered and, if necessary, disinfected or sterilized, according to a written procedure. Washing garments in a domestic setting is unacceptable.
4. Personnel should avoid direct contact with APIs.
5. Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

## **Raw Material Testing**

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### **Section**

#### **C.02.009**

- (1) Each lot or batch of raw material shall be tested against the specifications for that raw material prior to its use in the fabrication of a drug.
- (2) No lot or batch of raw material shall be used in the fabrication of a drug unless that lot or batch of raw material complies with the specifications for that raw material.
- (3) Notwithstanding subsection (1), water may, prior to the completion of its tests under that subsection, be used in the fabrication of a drug.
- (4) Where any property of a raw material is subject to change on storage, no lot or batch of that raw material shall be used in the fabrication of a drug after its storage unless the raw material is retested after an appropriate interval and complies with its specifications for that property.
- (5) Where the specifications referred to in subsections (1), (2) and (4) are not prescribed, they shall
  - (a) be in writing;
  - (b) be acceptable to the Director who shall take into account the specifications contained in any publication mentioned in Schedule B to the Act; and
  - (c) be approved by the person in charge of the quality control department.

### **Rationale**

The testing of raw materials before their use has three objectives: to confirm the identity of the raw materials, to provide assurance that the quality of APIs will not be altered by raw material defects, and to obtain assurance that the raw materials have the characteristics that will provide the desired quantity or yield in a given manufacturing process.

### **Interpretation**

1. Specifications should be established and documented for raw materials, intermediates and where necessary, APIs. In addition, specifications may be appropriate for certain other materials, such as process aids or other materials used during the production of APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls. Specifications are approved and dated by the person in charge of the quality control department or by a designated alternate who meets the requirements described under Regulation C.02.006, Interpretation 1.
2. Specifications for raw materials should be established based on process design and overall control strategy to ensure final product quality.
3. Raw materials should be purchased against an agreed specification, from suppliers approved by the quality unit(s).
4. Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.
5. Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.
6. If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.
7. Where the fabricator of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.
8. Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognised standard reference. The suitability of all analytical methods used should nonetheless be verified under actual conditions of use and documented.
9. Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.

Note: Guidance for the validation of particular types of methods can be obtained in publications such as the ICH document entitled *ICH Q2 (R1): Validation of Analytical Procedures: Text and Methodology* or in any standard listed in Schedule B to the *Food and Drugs Act*.

10. Raw materials should be re-evaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

## **Section C.02.010**

- (1) The testing referred to in section C.02.009 shall be performed on a sample taken
  - (a) after receipt of each lot or batch of raw material on the premises of the fabricator; or
  - (b) subject to subsection (2), before receipt of each lot or batch of raw material on the premises of the fabricator, if
    - (i) the fabricator
      - (A) has evidence satisfactory to the Director to demonstrate that raw materials sold to him by the vendor of that lot or batch of raw material are consistently manufactured in accordance with and consistently comply with the specifications for those raw materials, and
      - (B) undertakes periodic complete confirmatory testing with a frequency satisfactory to the Director, and
    - (ii) the raw material has not been transported or stored under conditions that may affect its compliance with the specifications for that raw material.
- (2) After a lot or batch of raw material is received on the premises of the fabricator, the lot or batch of raw material shall be tested for identity.

### **Rationale**

Section C.02.010 outlines options as to when the testing prescribed by Section C.02.009 is carried out. The purchase of raw materials is an important operation that requires a particular and thorough knowledge of the raw materials and their suppliers. To maintain consistency in the fabrication of APIs, raw materials should originate from reliable suppliers.

### **Interpretation**

1. Fabricators of APIs should have a written system for evaluating the suppliers of critical materials.
2. Specific identity testing of each batch of material received on the premises of the API fabricator should be conducted, with the exception of the materials described below in 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.
  - 2.1 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.
3. Vendor approval should include a written evaluation that provides adequate evidence (e.g., past quality history) that the fabricator can consistently provide material meeting specifications. Complete



confirmatory testing should be conducted on at least three batches before reducing in-house testing and after significant change to the manufacturing process. However, as a minimum, complete confirmatory testing should be performed at appropriate intervals and compared with the CoA. Reliability of CoAs should be checked at regular intervals.

- 3.1 A document is issued verifying that the supplier meets the criteria for certification. The document is approved by the quality control department and is reviewed periodically.
- 3.2 A written system should be in place to address testing failures and any subsequent re-qualification of the supplier if required.
4. Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the fabricator's CoA is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.
5. Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.
6. There should be written procedures describing the identification, and testing of materials.
7. If the supplier of a critical material is not the fabricator of that material, the name and address of that fabricator should be known by the API fabricator.
8. Changing the source of supply of critical raw materials should be treated according to *Section C.02.015, Change Control*.
9. Where appropriate, a copy of the residual solvent profile should be obtained. Additionally, for APIs, a copy of the impurity profile should be obtained.
10. 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.
11. Conditions of transportation and storage should be such that they prevent alterations to the potency, purity, or physical characteristics of the critical raw materials.
12. If a delivery or shipment of raw material is made up of different batches, each batch should be considered as separate for the purposes of sampling, testing, and release.
13. If the same batch of raw material is subsequently received, this batch should also be considered as separate for the purpose of sampling, testing, and release. However, full testing to specifications may not be necessary on such a batch provided that all the following conditions are met:
  - 13.1 a specifically discriminating identity test is conducted;

- 13.2 the raw material has not been repackaged or re-labelled;
- 13.3 the raw material is within the re-test date assigned by its vendor; and
- 13.4 evidence is available to demonstrate that all pre-established transportation and storage conditions have been maintained when applicable.

## **Manufacturing Control**

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### **Section 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**

This Regulation requires that measures be taken to maintain the integrity of an API from the moment the various raw materials enter the plant to the time the API is released for sale or for further fabrication. These measures ensure that all manufacturing processes are clearly defined, systematically reviewed in light of experience, and demonstrated to be capable of consistently manufacturing APIs of the required quality that comply with their established specifications. Refer to *Table 2* for the point at which production of the API begins and from which compliance to GMPs should be implemented.

### **Interpretation**

- 1. Access to production areas is restricted to designated personnel.
- 2. All handling of raw materials, products, and packaging materials such as receipt, identification, quarantine, storage, sampling, testing, approval or rejection of materials, tracking, labeling, packaging, dispensing, processing, and distribution should be done in accordance with written procedures or instructions and recorded.
- 3. Validation should extend to those operations determined to be critical to the quality and purity of the API.
  - 3.1 The potential impact of the proposed change on the quality of the API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgement should determine what additional testing and validation studies are appropriate to justify a change in a validated process.

Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

4. A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units. For more information on this matter, refer to *Section 12 Validation* of the *ICH Q7 Guidelines*.
  - 4.1 The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective, concurrent) and the number of process runs.
  - 4.2 A validation report that cross-references the validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.
  - 4.3 Any variations from the validation protocol should be documented with appropriate justification.
5. Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed.
6. Any deviation should be documented and explained. Any critical deviation (i.e. one which could affect the quality and/or purity of the API) should be investigated.
7. Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.
8. 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 or microbial contamination that may adversely alter the established API impurity profile.
9. Provided that validated changeover procedures are implemented, non-medicinal products may be fabricated or packaged/labelled in areas or with equipment that is also used for the production of APIs.
10. Facilities where APIs are fabricated, packaged and labelled should be inspected immediately before use to ensure that all materials not needed for the next operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.
11. Production operations should be conducted in a manner that will prevent contamination of APIs by other materials.

12. In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other APIs. Procedures should be established to ensure the integrity of samples after collection.
13. Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.
14. The acceptance criteria and type and extent of testing can depend on the nature of the API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).
15. Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).
16. In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.
17. Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.
18. Precautions to avoid contamination should be taken when APIs are handled after purification.
19. Production operations on different products may be carried out in the same area provided that appropriate measures and controls are in place to prevent mix-up or cross-contamination.
  - 19.1 Appropriate measures should be established and implemented to prevent cross-contamination from personnel, materials, etc. moving from one dedicated area to another.
  - 19.2 Where applicable, checks should be carried out to ensure that removable and interchangeable transfer lines and other pieces of equipment used for the transfer of materials from one area to another are correctly connected.
20. Equipment or segregated process areas should be identified as to its contents, including name of product and batch number, and its cleanliness status by appropriate means.
21. The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.
22. Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.
23. Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

24. Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labelling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. All containers are verified to ensure that the information on the order, the delivery note and the vendor's labels is in agreement.
  - 24.1 Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use.
25. Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.
26. If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:
  - certificate of cleaning,
  - testing for trace impurities, and
  - audit of the supplier.
27. Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.
28. Critical materials should be transported in a manner that does not adversely affect their quality.
29. Special transport or storage conditions for an API should be stated on the label.
30. Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.
31. Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.
32. Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.
33. Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. The identification number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.
34. Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.
35. Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.
36. Materials should be stored under conditions and for a period that have no adverse effect on their quality, and should normally be controlled so that the oldest stock is used first.

37. Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.
38. Raw materials for API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use.
39. Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended API.
40. Other critical activities should be witnessed or subjected to an equivalent control.
41. All quality related activities should be recorded at the time they are performed.
42. When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still readable.
43. All documents related to the manufacture of APIs should be prepared, reviewed, approved and distributed according to written procedures.
  - 43.1 To ensure uniformity from batch to batch, master production instructions for each API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).

## **Manufacturing Operations**

44. Master production documents should include:
  - The name of the API being manufactured, batch size, and an identifying document reference code, if applicable;
  - A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;
  - An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the 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;
  - The production location and major production equipment to be used;
  - The procedures, or reference to the procedures, to be used in production;
  - Detailed production instructions, including the:
    - sequences to be followed,
    - ranges of process parameters to be used,
    - sampling instructions and in-process controls with their acceptance criteria, where appropriate,

- time limits for completion of individual processing steps and/or the total process, where appropriate; and
  - expected yield ranges at appropriate phases of processing or time;
- Where appropriate, special notations and precautions to be followed, or cross-references to these; and
  - The instructions for storage of the intermediate or API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.
45. Batch production records should be prepared for each API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.
46. The batch production records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.
47. Documentation of completion of each significant step in the batch production records (batch production and control records) should include:
- Dates and, when appropriate, times of commencement and completion of significant intermediate stages (blending, heating, etc.) and of production;
  - Identity of major equipment (e.g., reactors, driers, mills, etc.) used;
  - Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing;
  - Actual results recorded for critical process parameters;
  - Any sampling performed;
  - Signatures of the persons performing and directly supervising or checking each critical step in the operation;
  - In-process and laboratory test results
  - Actual yield at appropriate phases or times;
  - Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately; and
  - Results of release testing.
  - Upon completion, the signature of the person responsible for the processing operations.
48. If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

- Material name and/or item code;
- Receiving or control number or distinctive code;
- Weight or measure of material in the new container; and
- Re-evaluation or retest date if appropriate.

## **Blending**

49. For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous API. 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.
50. Out-of-Specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.
51. Acceptable blending operations include but are not limited to:
  - Blending of small batches to increase batch size
  - Blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same API to form a single batch.
52. Blending processes should be adequately controlled and documented and the blended batch should be tested for conformance to established specifications where appropriate.
53. The batch record of the blending process should allow traceability back to the individual batches that make up the blend.
54. Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process.
55. If the blending could adversely affect stability, stability testing of the final blended batches should be performed.
56. The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

## **Recovery**



57. Recovery (e.g., from mother liquor or filtrates) of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.
58. Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or co-mingling with other approved materials.
59. Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.
60. The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

### **Packaging Operations**

61. Packaging operations should be performed according to comprehensive and detailed written operating procedures or specifications, which include identification of equipment and packaging lines used to package the API or intermediate, the dedication of packaging lines, if necessary, and disposal procedures for the unused printed packaging materials. Packaging orders should be individually numbered.
62. Labelling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other APIs.
63. Access to the label storage areas should be limited to authorised personnel.
64. Packaging and labelling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.
65. There should be documented procedures designed to ensure that correct packaging materials and labels are used.
66. 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.
67. Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.
68. Containers should be clean and, where indicated by the nature of the API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the API beyond the specified limits.
69. If containers are re-used, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.
70. Labels used on containers of APIs should indicate the name or identifying code, the batch number of the product, and storage conditions, when such information is critical to assure the quality of APIs.

71. If the API is intended to be transferred outside the control of the fabricator's material management system the name and address of the fabricator, quantity of contents, and special transport conditions and any special legal requirements should also be included on the label. For APIs with an expiry date, the expiry date should be indicated on the label and CoA. For APIs with a retest date, the retest date should be indicated on the label and/or the CoA.
72. API containers that are transported outside of the fabricator's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.
73. Packaged and labelled APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.
74. Procedures should be used to reconcile the quantities of labels issued, used, destroyed and returned. All discrepancies found between the number of containers labelled and the number of labels issued should be investigated, and the investigation should be approved by the quality unit(s).
75. Upon completion of the labelling operation, all excess labels bearing batch numbers or other batch-related printing should be destroyed and their destruction recorded. Returned labels should be stored in a manner that prevents mix-ups and provides proper identification.
76. Obsolete and out-dated labels should be destroyed.
77. All APIs that have been packaged and labelled should be held in quarantine and be so identified until released by the quality controlled department.
78. Packaging orders should include the following information (recorded at the time each action is taken):
  - 78.1 The date(s) and time(s) of the packaging operations;
  - 78.2 The identification of the personnel who are supervising or verifying packaging operations and the withdrawal of bulks;
  - 78.3 The identification of the operators of the different significant steps;
  - 78.4 Whether the correct products and packaging materials are used;
  - 78.5 Whether any on-line printing is correct;
  - 78.6 Whenever possible, samples of the printed packaging materials used, including specimens bearing the batch number, expiry date, and any additional overprinting, are attached to packaging orders.
  - 78.7 The correct functioning of line monitors;
  - 78.8 Handling precautions applied to a partly packaged product; and

- 78.9 Notes on any special problems, including details of any deviation from the packaging instructions with written approval by qualified personnel.

### **Product Quality Review**

79. Regular quality reviews of APIs should be conducted by the fabricator with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:
- 79.1 A review of critical in-process control and critical API test results;
  - 79.2 A review of all batches that failed to meet established specification(s);
  - 79.3 A review of all critical deviations or non-conformances or related investigations;
  - 79.4 A review of any changes carried out to the processes or analytical methods;
  - 79.5 A review of results of the stability monitoring program;
  - 79.6 A review of all quality-related returns, complaints and recalls; and
  - 79.7 A review of adequacy of corrective actions.
80. 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 action should be documented. Agreed corrective actions should be completed in a timely manner.

### **Section 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**

The purpose of a recall is to remove from the market, an API that represents an undue health risk.

APIs that have left the premises of a fabricator, packager/labeller, distributor, and importer of APIs can be found in a variety of locations. Depending on the severity of the health risk, it may be necessary to recall a product to one level or another. Fabricators, packagers/labellers, distributors, importers and wholesalers of APIs are expected to be able to recall from all their direct customers throughout the supply chain. Additional guidance regarding recalls can be found in Health Canada's documents entitled *Recall Policy* (POL-0016) and GUI-0001.

This Regulation also requires fabricators, packagers/labellers, distributors, and importer to maintain a program of self-inspection. The purpose of self-inspection is to evaluate the compliance with GMP in all aspects of production and quality control. The 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 in Canada, regardless of whether they are domestically produced or imported, must meet the requirements of Part C, Division 2 of the *Food and Drug Regulations*. Contract production and analysis must be correctly defined, agreed on, and controlled in order to avoid misunderstandings that could result in a product, work or analysis of unsatisfactory quality. Normally, a written agreement exists between the parties involved, and that document clearly establishes the duties of each party.

## **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. There should be a written procedure that defines the circumstances under which a recall of an API should be considered.
3. The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall and how the recalled material should be treated), specifically:
  - 3.1 Health Canada should be notified of the recall.
  - 3.2 The recall procedure should be capable of being put into operation at any time, during and outside normal working hours.

- 3.3 The progress and efficacy of the recall should be assessed and recorded at intervals, and a final report should be issued (including a final reconciliation).
4. A system should be in place by which the distribution of each batch of API can be readily determined to permit its recall. This should include any products in transit, any samples removed by the quality control department and any professional samples that have been distributed.
  - 4.1 A written agreement should clearly describe respective responsibilities of all parties involved with respect to recalls.
5. 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.
6. All Canadian and foreign establishments involved in the production, distribution and importation, including agents, brokers, re-packagers and re-labellers of the recalled API should be notified and maintain records of all complaints and recalls that come to their attention.
7. In order to verify compliance with Division 2, Part C of the *Food and Drug Regulations*, regular self-inspections appropriate to the type of operations of the company should be performed in accordance with an approved schedule.
  - 7.1 The self-inspection team should include personnel who are suitably trained and qualified in GMP.
8. A comprehensive written procedure that describes the function of the self-inspection program should be available. Self-inspection findings and corrective/preventive actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective/preventive actions should be completed in a timely and effective manner.
9. All Canadian and foreign establishments involved in the production, distribution and importation, including agents, brokers, re-packagers and re-labellers should comply with GMP as defined in this Guide.
10. Contract fabricator s (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites.
11. To ensure compliance of contractors performing fabrication or packaging/labelling:
  - 11.1 All arrangements for contract fabrication or packaging/labelling should be in accordance with the current regulatory filing for the API concerned.
  - 11.2 There should be a written agreement covering the fabrication or packaging/labelling arranged among the parties involved. The agreement should specify their respective GMP responsibilities relating to the fabrication or packaging/labelling and quality control of the API.
    - 11.2.1 Technical aspects of the agreement should be drawn up by qualified personnel suitably knowledgeable in pharmaceutical technology, and GMP.

- 11.2.2 The agreement should permit the contract giver to audit the facilities of the contractor for compliance with GMP.
- 11.2.3 The agreement should clearly describe as a minimum who is responsible for:
  - 11.2.3.1 purchasing, sampling, testing and releasing materials;
  - 11.2.3.2 undertaking production, quality, and in-process controls; and
  - 11.2.3.3 process validation.
- 11.2.4 No subcontracting of any work should occur without written authorization by the contract giver and approval of the arrangements.
- 11.2.5 The agreement should specify the way in which the quality control department of the distributor or importer releasing the lot or batch for sale, ensures that each lot or batch has been fabricated and packaged/labelled in compliance with the current regulatory filing for the API concerned, if applicable.
- 11.2.6 The agreement should describe the handling of raw materials, packaging materials, intermediates, and APIs if they are rejected.
- 11.3 The contractor's complaint/recall procedures should specify that any records relevant to assessing the quality of a drug product in the event of complaints or a suspected defect are accessible to the distributor or importer.
- 11.4 The fabricator, packager/labeller, distributor, or importer should provide the contractor with all the information necessary to carry out the contracted operations correctly in accordance with the current regulatory filing associated to the API concerned, if applicable, and any other legal requirements. The fabricator, packager/labeller, distributor, or importer should ensure that the contractor is fully aware of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products.
  - 11.4.1 Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.
- 11.5 The fabricator, packager/labeller, distributor, or importer should be responsible for assessing the contractor's continuing competence to carry out the work or tests required in accordance with the principles of GMP described in these guidelines.
  - 11.5.1 Distributors of APIs fabricated, packaged/labelled and tested at Canadian sites should be required only to have a copy of the relevant valid Canadian establishment licence held by the Canadian fabricator or packager/labeller or tester.
  - 11.5.2 Importers of APIs fabricated, packaged/labelled, or tested at a foreign site should meet the requirements described in Health Canada's general [Notice to Stakeholders – Amended Food and Drugs Regulations for Active Ingredients](#).

## Quality Control Department

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### Section 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

Quality control is the part of GMP concerned with sampling, specifications, and testing and with the organization, documentation, and release procedures. This Regulation ensures that the necessary and relevant tests are actually carried out and that raw materials and packaging materials are not released for use and APIs are not released for sale or further used in fabrication, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be incorporated into all activities and decisions concerning the quality of the API.

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

### Interpretation

1. The quality unit(s) should be involved in all quality-related matters.
2. The quality unit should review and approve all quality-related documents. Approved written procedures should be available for the receipt, identification, quarantine, storage, handling, sampling, label, dispensing, processing, distribution, inspecting, testing, and approval or rejection of raw materials, packaging materials, in-process APIs, APIs, and for the recording and storage of laboratory data.
3. The quality unit of the fabricator and packager/labeller should be independent of production and fulfill both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.
4. The quality unit should have access to facilities, including a laboratory, trained personnel, and equipment in order to fulfill its duties and responsibilities.

### Section 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**

The responsibility for the approval of all raw materials, packaging materials and APIs is vested in the quality control department. It is very important that adequate controls be exercised by this department in order to guarantee the quality of the end product.

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

### **Interpretation**

1. All decisions made by the quality control department pursuant to Regulation C.02.014 should be signed and dated by the person in charge of the quality control department or by a designated alternate meeting the requirements described under Section C.02.006. The names of such persons should be specified.
2. 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).
3. The assessment for the release of APIs should embrace all relevant factors, including the production conditions, the results of in-process testing, the fabrication and packaging documentation, compliance with the APIs specifications, an examination of the finished package, and if applicable, a review of the storage and transportation conditions.
4. APIs should only be released for distribution to third parties after they have been released by the quality unit(s). APIs can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.
5. The quality control department should ensure that raw materials and packaging materials are quarantined, sampled, tested, and released prior to their use in the fabrication or packaging/labelling of a drug.
6. Any deviations, non-conformances, and malfunctions or errors including those pertaining to premises, equipment, sanitation, and testing, such as deviations from written procedures, that may have an impact



on the quality and safety of batches pending release or released, should be assessed. Critical deviations should be investigated, and the investigation and its conclusion should be documented.

7. Rejected materials, such as APIs, failing to meet established specifications, should be identified as such and quarantined. These materials should be returned to the vendors, reprocessed, reworked, or destroyed. Actions taken should be recorded.
8. APIs returned from the market should be destroyed unless it has been ascertained that their quality is satisfactory. Returned goods may be considered for resale only after they have been assessed in accordance with a written procedure. The reason for the return, the nature of the product, the storage and transportation conditions, the API's condition and history, and the time elapsed since it was originally sold should be taken into consideration in this assessment. If the conditions under which returned APIs 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. Records of any action taken should be maintained.
  - 8.1 Documentation should be available to support the rationale to place returned goods into inventory for further resale.

## **Reworking**

9. Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for non-conformance should be performed.
10. Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows 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.
11. Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

## **Reprocessing**

12. Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by 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 is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.
13. 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. This is not considered to be reprocessing.
14. Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful

evaluation to ensure that the quality of the intermediate or API is not adversely impacted due to the potential formation of by-products and over-reacted materials.

15. Documents should be available and approved by the QC Department.

## **Section 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 are independently examined by the quality control department. Proper storage, transportation, and distribution of materials and products minimize any risk to their quality. Complaints may indicate problems related to quality. By tracing their causes, one can determine which corrective measures should be taken to prevent recurrence. Having tests carried out by a competent laboratory provides assurance that test results are genuine and accurate.

Written agreements for consultants should describe the education, training, and experience of their personnel and the type of services provided, and should be available for examination and inspection. Written agreements for contract laboratories should describe the type of services provided and their compliance with GMPs and should be available for examination and inspection. Records of the activities contracted should be maintained.

## **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. A formal change control system should be established to evaluate all changes that may affect the production and control of the API.

3. Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials, and computer software.
4. Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organisational units, and reviewed and approved by the quality unit(s).
5. The potential impact of the proposed change on the quality of the API should be evaluated. A risk assessment may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgement should determine what additional testing and validation studies are appropriate to justify a change in a validated process.
  - 5.1 The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.
  - 5.2 After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.
  - 5.3 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.
6. Current dosage form fabricator s should be notified of changes from established production and process control procedures that can impact the quality of the API.
7. All establishments involved in the production, distribution and importation, including agents, brokers, re-packagers and re-labellers should have a system in place to record and investigate all quality related complaint, whether received orally or in writing, in accordance with written procedures.
  - 7.1 If the situation warrants, the agents, brokers, traders, distributors, re-packagers, or re-labellers should review the complaint with the original API fabricator in order to determine whether any further action, either with other customers who may have received this API or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.
  - 7.2 Where a complaint is referred to the original API fabricator, the record maintained by the agents, brokers, traders, distributors, re-packagers, or re-labellers should include any response received from the original API fabricator (including date and information provided).
8. Records of complaints should be retained in order to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective actions. All decisions and measures taken as a result of a complaint are recorded.
9. All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the

registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).

10. Laboratory controls should be followed and documented at the time of performance. Any departures from the above described procedures should be documented and explained.
11. Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:
  - 11.1 A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing;
  - 11.2 A statement of or reference to each test method used;
  - 11.3 A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions;
  - 11.4 A complete 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;
  - 11.5 A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors;
  - 11.6 A statement of the test results and how they compare with established acceptance criteria;
  - 11.7 The signature of the person who performed each test and the date(s) the tests were performed; and
  - 11.8 The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.
12. Reagents and standard solutions should be prepared and labelled following written procedures. “Use by” dates should be applied as appropriate for analytical reagents or standard solutions and data should be available to support these expiry or retest dates.
13. The tests should be performed by a laboratory that meets all relevant GMP requirements.
  - 13.1 Laboratory facilities are designed, equipped, and maintained to conduct the required testing.
    - 13.1.1 In the microbiology laboratory, environmental monitoring should be performed periodically. Microbiological cultures and sample testing are handled in an environment that minimizes contamination.

- 13.1.2 The facility used to perform the sterility testing should comply with the microbial limits of an aseptic production facility which should conform to Grade A within a Grade B background or in an isolator of a Grade A within and appropriate background and limited access to non-essential personnel.
- 13.2 The individual in charge of the laboratory should meet personnel requirements as set forth in C.02.006 and report to a person who has these qualifications.
- 13.3 Laboratory personnel should be sufficient in number and be qualified to carry out the work they undertake.
- 13.4 Laboratory control equipment and instruments should be suited to the testing procedures undertaken. Equipment and records should be maintained as per the interpretations under C.02.005.
- 13.5 Computerized systems are validated, and spreadsheets are qualified.
- 13.6 Water used for microbial and analytical tests meets the requirements of the test or assay in which it is used.
- 13.7 All reagents and culture media are recorded upon receipt or preparation. Reagents made up in the laboratory are prepared according to written procedures and are properly labelled.
  - 13.7.1 Prepared media are sterilized using validated procedures and stored under controlled temperatures.
  - 13.7.2 Prepared media are properly labelled with the lot numbers, expiration date and media identification. The expiration date of media is supported by growth-promotion testing results that show the performance of the media still meets acceptance criteria up to the expiration date.
  - 13.7.3 Sterility and growth-promotion testing are performed to verify the suitability of culture media.
  - 13.7.4 All purchased ready to use media received are accompanied by a certificate of analysis with expiry date and recommended storage conditions as well as the quality control organisms used in growth-promotion and selectivity testing of that media.
    - 13.7.4.1 Procedures are in place to ensure that media are transported under conditions that minimize the loss of moisture and control the temperature.
    - 13.7.4.2 Media are stored according to the vendor's instructions.
    - 13.7.4.3 Sterility and growth-promotion testing are performed on lots received, unless the vendor is certified. Periodic confirmatory testing is performed for ready to use media received from each certified vendor.
    - 13.7.4.4 Records are maintained.

- 13.8 Reference standards are available in the form of the current reference standards listed in Schedule B to the *Food and Drugs Act*. When such standards have not been established or are unavailable, primary standards can be used. Secondary standards are verified against a Schedule B reference standard or against the primary standard and are subject to complete confirmatory testing at predetermined intervals. All reference standards are stored and used in a manner that will not adversely affect their quality. Records relating to their testing, storage, and use are maintained.
- 13.9 Out of Specification (OOS) test results are investigated to determine the cause of the OOS.
- 13.9.1 Procedures are in place to describe the steps to be taken as part of the investigation.
- 13.9.2 In the case of a clearly identified laboratory or statistical error, the original results may be invalidated, and the test repeated. The original results should be retained and an explanation recorded.
- 13.9.3 When there is no clearly identified laboratory or statistical error and retesting is performed, the number of retests to be performed on the original sample and/or a new sample, and the statistical treatment of the resultant data, are specified in advance in the procedure.
- 13.9.4 All valid test results, both passing and suspect, should be reported and considered in batch release decisions.
- 13.9.5 If the original OOS result is found to be valid, a complete investigation, including the batch affected, is conducted and recorded. The investigation should be performed in accordance to written procedures and should include an assessment of root cause, description of corrective actions and preventive actions carried out and conclusions.
- 13.9.6 Out-of-specification investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.
14. 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.
15. Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.
16. Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically re-qualified in accordance with a written protocol.

17. Complete records should also be maintained for:
  - 17.1 Any modifications to an established analytical method;
  - 17.2 Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices;
  - 17.3 All stability testing performed on APIs; and
  - 17.4 Out-of-specification investigations.
18. Where critical data are entered into a computerized system manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.
19. Incidents related to computerized systems that could affect the quality of APIs or the reliability of records or test results should be recorded and investigated.
20. Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.
21. All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.
22. To ensure compliance of contractors conducting testing required under Part C, Division 2 of the *Food and Drug Regulations*:
  - 22.1 A Canadian contract laboratory must have a relevant valid current establishment licence. A foreign testing site must be listed on a Canadian establishment licence, as described in Health Canada's policy document entitled *Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites* (GUI-0080),
  - 22.2 All arrangements for external testing are in accordance with the current regulatory filing for the API concerned if applicable, including the testing of intermediates, raw materials, packaging materials and all other necessary testing required by Part C, Division 2 of the *Food and Drug Regulations*, and
  - 22.3 There is a written agreement covering all activities of testing between the contract laboratory and the parties involved. The agreement specifies their respective responsibilities relating to all aspects of testing.
    - 22.3.1 Technical aspects of the agreement are drawn up by qualified personnel suitably knowledgeable in analysis and GMP,
    - 22.3.2 The agreement permits audit of the facilities and operations of the external laboratory,
    - 22.3.3 The agreement clearly describes, as a minimum, who is responsible for:
      - 22.3.3.1 collection, transportation and storage conditions of samples before testing,

22.3.3.2 keeping stability samples at predetermined temperatures and humidity, if applicable,

22.3.3.3 testing methods to be used, limits and test method validation, and

22.3.3.4 retention of analytical results and supporting documentation (additional guidance under interpretations of C.02.021).

22.3.4 No subcontracting of any work should occur without written authorization.

23. The fabricator should ensure that the contract acceptor (contractor) for transportation of the API knows and follows the appropriate transport and storage conditions.

## **Packaging Material Testing**

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### **Section C.02.016**

- (1) Each lot or batch of packaging material shall, prior to its use in the packaging of a drug, be examined or tested against the specifications for that packaging material.
- (2) No lot or batch of packaging material shall be used in the packaging of a drug unless the lot or batch of packaging material complies with the specifications for that packaging material.
- (3) The specifications referred to in subsections (1) and (2) shall
  - (a) be in writing;
  - (b) be acceptable to the Director who shall take into account the specifications contained in any publication mentioned in *Schedule B* to the *Act*; and
  - (c) be approved by the person in charge of the quality control department.

### **Section C.02.017**

- (1) The examination or testing referred to in section C.02.016 shall be performed on a sample taken
  - (a) after receipt of each lot or batch of packaging material on the premises of the person who packages a drug; or
  - (b) subject to subsection (2), before receipt of each lot or batch of packaging material on the premises of the person who packages a drug, if
    - (i) that person



- (A) has evidence satisfactory to the Director to demonstrate that packaging materials sold to him by the vendor of that lot or batch of packaging material are consistently manufactured in accordance with and consistently comply with the specifications for those packaging materials; and
  - (B) undertakes periodic complete confirmatory examination or testing with a frequency satisfactory to the Director,
- (ii) the packaging material has not been transported or stored under conditions that may affect its compliance with the specifications for that packaging material.
- (2) After a lot or batch of packaging material is received on the premises of the person who packages a drug,
- (a) the lot or batch of the packaging material shall be examined or tested for identity; and
  - (b) the labels shall be examined or tested in order to ensure that they comply with the specifications for those labels.

## Rationale

The suitability of APIs for their subsequent use depends not only on the production process but also on the protection of the API from contamination or degradation before use. Care should be taken in the choice of container, and, as the filling of solid APIs is often a dusty operation, how this is filled and closed will affect the quality. Packaging materials are required to be tested or examined prior to their use in a packaging operation to ensure that materials of acceptable quality are used in the packaging of APIs.

The inner packaging should be controlled by the establishment with respect to identity and traceability. Labelling, storage, and distribution contribute materially to final suitability for use in the manufacture of medicinal products.

Regulation C.02.017 outlines options as to when the testing or examination prescribed by *Regulation C.02.016* is carried out. As with raw materials, the purchase of packaging materials is an important operation that involves personnel who have thorough knowledge of the packaging materials and supplier.

Packaging materials originate only from supplier named in the relevant specifications. It is of benefit that all aspects of the production and control of packaging materials be discussed between the fabricator and the supplier. Particular attention is paid to printed packaging materials; labels are examined or tested after receipt on the premises of the person who packages an API.

## Interpretation

1. There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labelling materials.
2. Each packaging material used in the packaging/labelling of an API should be covered by specifications (as defined under C.02.002) that are approved and dated by the person in charge of the quality control department or by a designated alternate who meets the requirements described under *Regulation C.02.006*, interpretation 1.4.

- 2.1 Where applicable, specifications should be of pharmacopeial or equivalent status, and should be in compliance with the approved specifications in the marketing authorization for the drug in dosage form.
- 2.2 The adequacy of test or examination methods that are not of pharmacopeial or equivalent status should be established and documented.
- 2.3 The use of recycled or reprocessed primary packaging components should be permitted only after a full evaluation of the risks involved, including any possible deleterious effects on product integrity. Specific provision should be made for such a situation in the specifications.
- 2.4 These containers should not be reactive, additive, or absorptive so as to alter the quality of the API beyond the specified limits.
- 2.5 Any packaging material in direct contact with the API should be at minimum of food grade quality.
3. Sampling should take place in an appropriate environment and with precautions to prevent contamination, where necessary.
4. Positive identification of all packaging materials, along with examination of all labels and other printed packaging materials should be conducted following their receipt on the premises of the person who packages the API.
  - 4.1 Master labels should be maintained for comparison to issued labels.
5. Packaging and labelling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.
6. Only packaging materials released by the quality control department should be used in packaging/labelling.
7. Containers should provide adequate protection against deterioration or contamination of the API that may occur during transportation and recommended storage.
8. Containers should be clean and, where indicated by the nature of the API, sanitized to ensure that they are suitable for their intended use.
9. Outdated or obsolete packaging material should be adequately identified and segregated until its disposition.
10. 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.
  - 10.1 Vendor approval should include a written evaluation that provides adequate evidence (e.g., past quality history or evidence of a quality system) that the fabricator can consistently provide

material meeting specifications. Confirmatory testing should be conducted on at least three batches before reducing in-house testing. However, 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**

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### **Section**

#### **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**

Tests on the API complement the controls employed during the manufacturing process. It is the responsibility of each fabricator, packager/labeller, distributor and importer to have adequate specifications, test methods and/or evidence that will help ensure that each drug sold is safe and meets the standard under which it is represented.

### **Interpretation**

1. For each batch of API, appropriate laboratory tests should be conducted to determine conformance to specifications.
2. All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that APIs conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be documented and approved by the appropriate organizational unit and reviewed and approved by the quality unit(s).
  - 2.1 Specifications should be equal to or exceed a recognized standard as listed in *Schedule B* to the *Food and Drugs Act* and should be in compliance with the specifications.

- 2.2 Where a recognized pharmacopoeia (Schedule B to the *Food and Drugs Act*) contains a specification for microbial content, that requirement is included.
3. Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.
  4. Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.
  5. Methods should be validated to include consideration of characteristics included within publications such as the ICH document entitled *ICH Q3(R1): Validation of Analytical Procedures: Text and Methodology*. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.
  6. All tests are performed according to the approved specifications. These tests may be carried out by the fabricator or by their contracted testing laboratory when a written contract specifies the responsibilities of each party.
  7. An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed, and classification of each identified impurity (e.g. inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in *ICH Guideline Q6B*.
  8. The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.
  9. Information on the name of the API including where appropriate its grade, the batch number, and the date of release should be provided on the Certificate of Analysis (CoA). For APIs with an expiry date, the expiry date should be provided on the label and CoA. For APIs with a retest date, the retest date should be indicated on the label and/or CoA.
  10. Authentic CoAs should be issued for each batch of API.
  11. The CoA should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).
  12. Certificates of Analysis should be dated and signed by authorised personnel of the quality unit(s) and should show the name, address and telephone number of the original fabricator. Where the analysis has been carried out by a repackager or reprocessor, the CoA should show the name, address and telephone number of the repackager/reprocessor and a reference to the name of the original fabricator.

13. If new Certificates are issued by or on behalf of repackagers/reprocessors, agents or brokers, these Certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original fabricator and to the original batch Certificate, a copy of which should be attached.
14. Any lot or batch of an API that does not comply with specifications should be quarantined pending final disposition, investigated and documented according to a procedure, and is not made available for sale.

**Section  
C.02.019**

- (1) A packager/labeller of a drug, a distributor referred to in paragraph C.01A.003(b) and an importer of a drug other than an active ingredient shall perform the finished product testing on a sample of the drug that is taken either
  - (a) after receipt of each lot or batch of the drug on their premises in Canada; or
  - (b) before receipt of each lot or batch of the drug on their premises in Canada if the following conditions are met:
    - (i) the packager/labeller, distributor or importer
      - (A) has evidence satisfactory to the Director to demonstrate that drugs sold to them by the vendor of that lot or batch are consistently manufactured in accordance with and consistently comply with the specifications for those drugs, and
      - (B) undertakes periodic complete confirmatory testing, with a frequency satisfactory to the Director, and
    - (ii) the drug has not been transported or stored under conditions that may affect its compliance with the specifications for that drug.
- (2) If the packager/labeller, distributor or importer receives a lot or batch of a drug on their premises in Canada the useful life of which is more than 30 days, the lot or batch shall be tested for identity and the packager/labeller shall confirm the identity after the lot or batch is packaged/labelled.
- (3) Subsections (1) and (2) do not apply to a distributor if the drug is fabricated, packaged/labelled and tested in Canada by a person who holds an establishment licence that authorizes that activity.
- (4) Subsections (1) and (2) do not apply to a distributor or importer if the drug is fabricated, packaged/labelled and tested in an MRA country at a recognized building and both of the following requirements are met:
  - (a) the address of the building is set out in their establishment licence; and
  - (b) they retain a copy of the batch certificate for each lot or batch of the drug that they receive.

## Rationale

C.02.019 outlines conditions and exemptions as to when the finished product (API) testing is to be performed. Paragraph C.02.019(1)(b) outlines requirements that are to be met if the finished product testing is done before receipt on the premises of the packager/labeller of the drug.

## Interpretation

1. Positive identification of each lot or batch in a shipment of that API should be carried out on a sample taken after packaging.
2. Each lot should be accompanied by an authentic CoA or by a copy thereof (an electronic copy with an electronic signature is acceptable). The CoA should exhibit actual numerical results and make reference to the product specifications and test methods used;
3. Evidence should be available to demonstrate that each lot or batch received has been transported and stored in a manner that maintains the quality of the API. Further requirements are described in GUI-0069.

## Records

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### Section

### C.02.020

- (1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) and importer shall maintain all of the following records on their premises in Canada for each drug that they fabricate, package/label, distribute or import:
  - (a) Except in the case of an importer of an active pharmaceutical ingredient, master production documents for the drug;
  - (b) evidence that each lot or batch of the drug has been fabricated, packaged/labelled, tested and stored in accordance with the procedures described in the master production documents;
  - (c) evidence that the conditions under which the drug was fabricated, packaged/labelled, tested and stored are in compliance with the requirements of this Division;
  - (d) evidence that establishes the period during which the drug in the container in which it is sold or made available for further use in fabrication will meet the specifications for that drug; and
  - (e) evidence that the finished product testing referred to in section C.02.018 was carried out, and the results of that testing.
- (2) Every distributor referred to in paragraph C.01A.003(b) and importer shall make available to the Director, on request, the results of testing performed on raw materials and packaging/labelling materials for each lot or batch of drug that it distributes or imports.

- (3) Every fabricator shall maintain on their premises written specifications for all raw materials and adequate evidence of the testing of those raw materials referred to in section C.02.009 and of the test results.
- (4) Every person who packages a drug shall maintain on their premises written specifications for all packaging materials and adequate evidence of the examination or testing of those materials referred to in section C.02.016 and of any test results.
- (5) Every fabricator, packager/labeller and tester shall maintain on their premises in Canada detailed plans and specifications of each building in Canada where they fabricate package/label or test drugs and a description of the design and construction of those buildings.
- (6) Every fabricator, packager/labeller and tester shall maintain on their premises in Canada personnel records in respect of each person who is employed to supervise the fabrication, packaging/labelling and testing of drugs, including the person's title, responsibilities, qualifications, experience and training.

**Section  
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.

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

### **Section 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.

### **Section 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.

## **Section 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 an essential part of the quality assurance system and should therefore be applied to all aspects of GMP. Its aims are to define the specifications for all materials and methods of fabrication, packaging/labelling, and control; to ensure that the quality control department has all the information necessary to make a decision as to whether or not a batch of an API should be released for sale; and to provide an audit trail that will allow for thorough investigation of the history of any batch that is suspected to be defective.

Evidence that APIs have been fabricated, packaged/labelled, tested, and stored under prescribed conditions can be maintained only after developing adequate record systems. This evidence and related information should provide assurance that imported APIs are fabricated and packaged/labelled in a like manner to those produced in Canada.

## **Interpretation**

1. Any documentation requested for evaluation by Health Canada should be provided in one of the official languages.
2. Fabricator, packagers/labellers, testers, importers, distributors, and wholesalers are responsible for obtaining all quality or regulatory information, as applicable, related to the production of APIs from any party that provides services such as, but not limited to, agents, brokers, distributors, repackagers, or relabellers.

3. For all sections of these Good Manufacturing Practices guidelines for APIs, standard operating procedures (SOPs) should be established and retained for reference and inspection. These SOPs should be regularly reviewed and kept up to date by qualified personnel. The reasons for any revisions should be documented and a system should be in place to ensure that only current SOPs are in use.
  - 3.1 The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.
  - 3.2 SOPs should be reviewed, approved, signed, and dated by the quality control department.
  - 3.3 SOPs should not be altered without the approval of the quality control department.
  - 3.4 The retention period of documents should be specified in applicable SOPs. For example, the type of documents that need to be retained are development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records.
4. Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. The above may also be maintained in electronic format provided that backup copies are also maintained and that the electronic records are readily retrievable in a printed format. During the retention period, such records should be secured and readily available by the fabricator, packager/labeller, or importer within 48 hours of the Inspector's request. Records that can be promptly retrieved from another location by electronic or other means are acceptable.
  - 4.1 Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.
5. Where an electronic system is used to create, modify or store records required to be maintained 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.
  - 5.1 An electronic signature is an acceptable alternative to a handwritten signature as long as it is authenticated and secure. The validation of electronic signature identification systems should be documented.
6. An alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the change should be recorded.
7. Fabricators and packagers/labellers of APIs should maintain evidence that the conditions under which the API was fabricated, packaged/labelled, tested, and stored should be in compliance with the requirements of Part C, Division 2 of the *Food and Drug Regulations*. All of these records should be retained for (a) in the case of an API 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.
  - 7.1 Detailed plans and specifications of each building in Canada where fabrication, packaging/labelling or testing occurred, including a description of the design and construction of those buildings, should be maintained in the premises of the establishment where the API

- activity occurred. These records should be retained for a period of at least one year past the expiration date of the API to which the records apply.
- 7.2 This evidence includes records generated under subsection C.02.012(2) and evidence that manufacturing and packaging processes and analytical methods are validated.
- 7.3 In cases where equipment is employed, the records of cleaning, calibration, maintenance, and use can be part of the batch record or maintained separately.
- 7.4 Records of equipment calibrations should be maintained on the premises.
- 7.5 Records in respect of each person who is employed to supervise the fabrication, packaging/labelling, and testing of APIs, including organization charts; each person's title, job description, responsibilities, qualifications, experience, and training; and the name(s) of each person's designated alternate(s).
- 7.6 Records should be maintained detailing the name, address, qualifications/experience of any consultant employed for GMP purposes, along with the services that each consultant provides.
- 7.7 Records on the operation of the sanitation program.
- 7.8 Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).
- 7.9 Records of the self-inspection program including the evaluation, conclusions, and corrective measures implemented.
- 7.10 Evidence establishing the period of time during which the API in the container in which it is sold or made available for further use in fabrication should meet the specifications for that API.
- 7.10.1 The documentation to be maintained should include the written stability program, the data generated in accordance with that program, and the conclusions leading to the establishment of the period of time during which each API in the package in which it is sold complies with the specifications for that API.
- 7.11 Records of storage conditions for materials (e.g. controlled temperature and humidity when necessary).
8. Evidence that each lot or batch of the API has been fabricated, packaged/ labelled, tested, and stored in accordance with the procedures described in the master production documents. This evidence should include the following:
- 8.1 Written procedures followed for the review and approval of batch production and laboratory control records, including packaging and labelling, to determine compliance of the API with established specifications before a batch is released or distributed.

- 8.2 Manufacturing records, packaging records, test methods, and test results for raw materials, packaging materials, and APIs.
- 8.3 When the API is fabricated or packaged outside Canada/premises of the importer, records should be readily available by the importer within 48 hours, upon Health Canada's request.
9. The following documents should be maintained by the fabricator, packager/labeller, wholesaler (agents, brokers, traders and any other party providing services), distributor referred to in paragraph C.01A.003(a) and importer of an API as they relate to all operations in Canada. These records should be retained for a period, in the case of an API that has a retest date, three years after the lot or batch has been completely distributed or in any other case, one year after the expiration date of the lot or batch.
- 9.1 Distribution records of all sales of an API.
- 9.1.1 Records of all sales of each lot or batch of the API should be retained or kept readily accessible in a manner that will permit a complete and rapid recall of any lot or batch of the API.
- 9.1.2 Records to indicate that all customers who have received a recalled API have been notified.
- 9.1.3 Records of returned APIs should be maintained. For each return, documentation should include:
- the name and address of the consignee;
  - the API, lot or batch number, and quantity returned;
  - the reason for return; and
  - the use or disposal of the returned API.
- 9.2 Records of complaints or any information received orally or in writing respecting the quality of an API or its deficiencies or hazards, and of subsequent investigations of complaints, including corrective actions taken.
- 9.2.1 Complaint records should include the following information:
- the name and address of the complainant (if available);
  - the name and phone number of the person submitting the complaint (if available);
  - the nature of the complaint (including the name and batch number of the API);
  - the date on which the complaint was received;
  - the action initially taken (including the dates and identity of the person taking the action);
  - the actions taken, if any;

- the response provided to the complainant, where possible (including the date on which the response was sent); and
- the final decision on the API batch or lot.

10. The following documents should be maintained by the fabricator and the packager/labeller on their premises and retained for a period of at least five years after the materials were last used in the fabrication or packaging/labelling of the API, unless the person's establishment licence specifies some other period.

10.1 The written specifications for the materials.

10.2 Adequate evidence of the receipt and sources of each shipment of materials for the manufacture of APIs. The following information should be included:

- the name of the fabricator,
- the date of receipt and the number allocated on receipt;
- the identity and quantity of each shipment of each batch;
- the name of the supplier; and
- the supplier's control number(s), if known, or other identification number.

10.3 Adequate evidence of the testing, or examination of those materials as per section C.02.009 and C.02.016 and of the results of this testing. The following information should be included:

- documentation of the examination and/or tests of materials for conformity with established specifications and conclusions derived from this;
- the final decision as to whether the batches were accepted or rejected; and
- records tracing the use of the materials.

10.3.1 Laboratory records should be maintained.

11. The following documents should be maintained by the fabricator, and/or packager/labeller, of an API. All of these records should be retained for (a) in the case of an API 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.

11.1 Master production documents for each API.

The master production documents should be signed and dated by a qualified person and then independently checked, dated, and signed by a person in the quality unit. These documents should include the following information:

- The name of the API manufactured and an identifying document reference code, if applicable;
- The list of raw materials used and designated by names or codes sufficiently specific to identify any special quality characteristics;
- The accurate quantity with a unit of measure or ratio of each raw material used. 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;
- The location of production and major production equipment used;
- The detailed production instructions, including the sequences to follow, ranges of process parameters to use, sampling instructions and in-process controls with their acceptance criteria, where appropriate, time limits for completion of individual processing steps and/or the total process, where appropriate, and expected yield ranges at appropriate phases of processing or time;
- Where appropriate, any special notations and precautions to follow, or cross-references to these, and
- The instructions for storage of the API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

12. Packagers/labellers, importers, agents, brokers, traders, distributors, wholesalers should maintain complete traceability of APIs that they distribute. Documents that should be retained and available include:

12.1 name identity of original fabricator and packager/labeller;

12.2 address of original fabricator and packager/labeller;

12.3 purchase orders;

12.4 bills of lading (transportation documentation);

12.5 receipt documents;

12.6 name or designation of the API or intermediate;

12.7 fabricator's or packager/labeller's batch number;

12.8 transportation and distribution records;

12.9 all authentic Certificates of Analysis, including those of the original fabricator;

12.10 retest or expiry date.

13. The fabricator, packager/labeller, wholesaler, distributor referred to in paragraph C.01A.003(a), importer of an API, including any party other than the original fabricator who may trade and/or take

possession, repackaging, re-label, manipulate, or store an API, should add the following information to the documentation that accompanies the API:

- 13.1 the establishment licence number; if the establishment does not have an establishment licence, they should add their name, address, telephone number, fax number and email address;
- 13.2 the activity including fabrication, packaging/labelling, wholesale, distribution or importation and the date on which the activity was conducted;
- 13.3 the expiration date and/or retest date; and
- 13.4 the lot number of the API.

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## Samples

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### Section 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.

### Section 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 responsible officials at fabricating, establishments and at Health Canada have ready access to those samples that are essential for re-examination should a product quality concern arise.

## Interpretation

1. A representative sample should be taken for the purpose of performing a retest.
2. The packaging and holding of retained samples is for the purpose of potential future evaluation of the quality of batches of APIs and not for future stability testing purposes.
3. Appropriately identified retained samples of each API batch should be retained by the fabricator of an API for one year after the expiry date of the batch, or for three years after distribution of the batch, whichever is the longer. For APIs with retest dates, similar retained samples should be retained for three years after the batch is completely distributed by the fabricator.
  - 3.1 Retention samples may be stored at another site pursuant to a written agreement clearly describing the respective responsibilities of each party.
4. The retained sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.
5. The sample should be stored under the conditions indicated on the label.
6. Retention samples should be maintained in accordance with a written procedure.

Retention samples may be stored at another site pursuant to a written agreement clearly describing the respective responsibilities of each party.

## Stability

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### Section

#### 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

The purpose of the written stability program is to ascertain the expiry or retest date of an API, therefore to determine how long the APIs can be expected to remain within specifications under recommended storage conditions. The expiry or retest date for an API should be based on well-designed stability studies. The requirements for the stability studies are outlined in the various Health Canada, and ICH Guidelines.

## Interpretation



1. When an intermediate is intended to be transferred outside the control of the fabricator's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data, test results).
2. An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.
3. Preliminary API expiry or retest dates can be based on pilot scale batches if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale; and (2) the quality of the API represents the material to be made on a commercial scale.
  - 3.1 Accelerated stability data are considered to be preliminary information only. The accelerated data are supported by long term testing. When the shelf-life is assigned based on accelerated data and extrapolated long-term data, it should be verified by additional long term stability data as these data become available.
4. Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.
  - 4.1 Stability studies to justify assigned expiration or retest dates should be conducted if the API is repackaged in a different type of container than that used by the API fabricator.
5. Normally the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least two years, fewer than three batches can be used.
6. For imported products, stability studies originating from foreign sites are acceptable provided that the data meet the requirements of the various Health Canada and ICH guidelines regarding stability and that the site can demonstrate GMP compliance.
7. Where appropriate, the stability storage conditions should be consistent with the ICH guidelines on stability.
8. Analytical test procedures used in stability evaluation are validated in accordance with the ICH document entitled, *ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology*. Assays are to be stability-indicating, (e.g., sufficiently specific to detect and quantify degradation products and to distinguish between degraded and non-degraded materials). Limits for individual specified, unspecified, and total degradation products are included.

**Section**  
**C.02.028**

- (1) Every distributor referred to in paragraph C.01A.003(b) and importer of a drug in dosage form shall monitor, by means of a continuing program, the stability of the drug in the package in which it is sold.

- (2) Every fabricator and importer of an active ingredient shall monitor, by means of a continuing program, the stability of the drug in the package in which it is sold.

## **Rationale**

The purpose of the written continuing stability program is to monitor the validity of the API expiry or retest date on an on-going basis.

## **Interpretation**

1. Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.
2. 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.
3. At least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.
4. For APIs with short shelf-lives, testing should be done more frequently. For example, for those APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first three months and at three month intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g. 9 month testing) can be considered.)
5. Where appropriate, the stability storage conditions should be consistent with the ICH guidelines on stability.
6. Any differences in the protocol for the continuing stability program and the protocol for the formal stability studies should be scientifically justified.
7. Worst case situations should be addressed by the continuing stability program (e.g., inclusion of reworked or reprocessed lots).
8. Any confirmed out of specification result or significant negative trend that may have an impact on the quality of the API should be assessed and may require further stability studies.
9. For imported APIs, stability studies originating from foreign sites are acceptable, provided that the data meet the requirements of the various Health Canada and ICH guidelines regarding stability and that the site can demonstrate GMP compliance. It should be the importer's responsibility to obtain and maintain up to date records associated with the ongoing stability program.

## **Sterile Products**

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### **Section**

## **C.02.029**

In addition to the other requirements of this Division, a drug that is intended to be sterile shall be fabricated and packaged/labelled

- (a) in separate and enclosed areas;
- (b) under the supervision of personnel trained in microbiology; and
- (c) by a method scientifically proven to ensure sterility.

This guideline applies to the manufacture of sterile APIs only up to the point immediately prior to the API being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but should be performed in accordance with the *Good Manufacturing Practices Guidelines, Edition 2009, Version 2* (GUI-0001).

## **Medical Gases**

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### **Section**

#### **C.02.030**

This guideline does not apply to medical gases. The guidance regarding the fabrication, packaging, labelling, testing, distribution, and importation of medical gases is described in the guideline *Good Manufacturing Practices for Medical Gases* (GUI-0031).

## Appendix A

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### Acronyms

AI:	Active Ingredient
API:	Active Pharmaceutical Ingredient
DIN:	Drug Identification Number
GMP:	Good Manufacturing Practices
HPFB:	Health Products and Food Branch
ICH:	International Conference on Harmonisation
ICH Q7:	<i>Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7</i>
MPD:	Master Production Documents
NOC:	Notice of Compliance
OOS:	Out of specification
PIC/S:	Pharmaceutical Inspection Cooperation/Scheme
WHO:	World Health Organization

## Appendix B

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### Glossary of Terms

The following definitions apply to the terms used in these guidelines; they also apply to the terms used in the annexes unless otherwise specified therein. Definitions quoted from other documents are identified in brackets at the end of the definition.

**Acceptance Criteria** (*critère d'acceptation*) - Numerical limits, ranges, or other suitable measures for acceptance of test results. (ICH Q7)

**Active Ingredient** (*ingrédient actif*) - Means a drug that, when used as a raw material in the fabrication of a drug in dosage form, provides its intended effect. (Division 1A, Part C, *Food and Drug Regulations*)

**Active Pharmaceutical Ingredient** (*ingrédient pharmaceutique actif*) - Means an active ingredient that is used in the fabrication of a pharmaceutical. (Division 1A, Part C, *Food and Drug Regulations*)

**Alternate Sample Retention (ASR) Site** (*site alternatif pour la rétention des échantillons*) - An alternate site specified on a Drug Establishment Licence for the storage of samples pursuant to section C.02.025 (1) of the *Food and Drug Regulations*. (GUI-0001)

**API Establishment Licence** (*licence d'établissement pour les IPA*) – A licence issued to a person in Canada to conduct licensable activities in a building which has been inspected and assessed as being in compliance with the requirement of Division 2 of the *Food and Drug Regulations*.

**API Starting Material** (*Produit de départ de l'IPA*) – 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)

**Batch (or Lot)** (*lot de fabrication ou lot*) - A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. (ICH Q7)

**Batch Number** (*numéro de lot de fabrication*) - 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)

**Bioburden** (*Charge microbienne*) - The level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected. (ICH Q7)

**Biological Drug** (*drogue biologique*) - A drug that is listed in Schedule D to the *Food and Drugs Act*.

**Bulk APIs** (*IPAs en vrac*) – An API that is not in its final shipping package configuration.

**Bulk Process Intermediate** (*produit intermédiaire en vrac*) - Means an active ingredient that is used in the fabrication of either a drug of biological origin that is listed in Schedule C or a drug that is listed in Schedule D to the Act. (Division 1A, Part C, *Food and Drug Regulations*)

**Calibration** (*étalonnage*) - 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** (*production consécutive*) – Sequential processing of material, either more than one product in a multi-product facility or more than one lot of the same product in a dedicated facility, over a defined period of time. Campaign production could occur at any point in a production process where common rooms/suites and/or equipment are reused for multiple products/lots. (GUI-0001)

**Certificate of Analysis (CoA)** (*certificat d'analyse*) - 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. (GUI-0001)

**Certificate of Manufacture** (*certificat de fabrication*) - A document issued by a vendor to a distributor or importer that attests that a specific lot or batch of drug has been produced in accordance with its master production documents. Such certificates include a detailed summary of current batch documentation, with reference to respective dates of revision, manufacture, and packaging, and are signed and dated by the vendor's quality control department.

**Change control** (*contrôle des changements*) - A written procedure that describes the action to be taken if a change is proposed (a) to facilities, materials, equipment, and/or processes used in the fabrication, packaging, and testing of drugs, or (b) that may affect the operation of the quality or support system. (GUI-0001)

**Changeover Procedure** (*procédure de conversion*) - A logical series of validated steps that ensures the proper cleaning of suites and equipment before the processing of a different product begins. (GUI-0001)

**Computerized System** (*système informatisé*) - Consists of all components, including but not limited to hardware, software, personnel, and documentation, necessary to capture, process, transfer, store, display, and manage information. (GUI-0001)

**Concurrent validation** (*validation concomitante*): 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. (GUI-0029)

**Containment** (*confinement*) - Total isolation of one or more steps of a manufacturing process to prevent cross-contamination of the product, or staff, from all other steps of the process. (GUI-0001)

**Contamination** (*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** (*entrepreneur*) - Legal entity carrying out activities on behalf of a company pursuant to a written agreement. This includes other sites within the same corporate structure. (GUI-0001)

**Critical** (*critique*) - 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)

**Cross-Contamination** (*contamination croisée*) - Contamination of a material or product with another material or product. (ICH Q7)

**Design Qualification (DQ)** (*qualification de conception*) - Documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose. (ICH Q7)

**Deviation** (*déviation*) - Departure from an approved instruction or established standard. (ICH Q7)

**Director** (*directeur*) - “The Assistant Deputy Minister, Health Products and Food Branch, of the Department of Health.” (A.01.010)

**Distributor** (*distributeur*) or **Manufacturer** (*fabricant*) - “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 (C.01A.003):

(a) a distributor of an active ingredient or of a drug in dosage form that is listed in *Schedule C* to the *Act*; and

(b) a distributor of a drug for which the distributor holds the drug identification number.

**Dosage Form** (*forme posologique*) - 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. (GUI-0001)

**Drug** (*drogue*) - means a drug in dosage form, or a drug that is a bulk process intermediate that can be used in the preparation of a drug listed in *Schedule C* to the *Act* or in *Schedule D* to the *Act* that is of biological origin.

It does not include a dilute drug premix, a medicated feed as defined in Section 2 of the *Feeds Regulations, 1983*, a drug that is used only for the purposes of an experimental study in accordance with a certificate issued under Section C.08.015 or a drug listed in Schedule H to the *Act*. (C.01A.001(2))

**Drug Establishment Licence** (*licence d'établissement pour les produits pharmaceutiques*): A licence issued to a person in Canada to conduct licensable activities in a building which has been inspected and assessed as being in compliance with the requirements of Divisions 2 to 4 of the *Food and Drug Regulations*.

**Drug Identification Number** (*numéro d'identification d'une drogue*): A Drug Identification Number (DIN) is a computer-generated eight digit number assigned by Health Canada to a drug product prior to being marketed in Canada. It uniquely identifies all drug products sold in a dosage form in Canada and is located on the label of prescription and over-the-counter drug products that have been evaluated and authorized for sale in Canada. A DIN uniquely identifies the following product characteristics: manufacturer; product name; active ingredient(s); strength(s) of active ingredient(s); pharmaceutical form; route of administration. (GUI-0001)

**Expiry Date (or Expiration Date)** – (*date limite d'utilisation*) Means

- (a) in the case of a drug in dosage form, the earlier of the following dates, expressed at minimum as a year and month:
  - (i) the date up to and including which the drug maintains its labelled potency, purity and physical characteristics, and
  - (ii) the date after which the manufacturer recommends that the drug not be used; and
- (b) in the case of an active ingredient, whichever of the following dates is applicable, expressed at minimum as a year and month:
  - (i) the retest date, or
  - (ii) the date after which the manufacturer recommends that the active ingredient not be used. (date limite d'utilisation) (C.01.001 (1))

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

**Filling** (*remplissage*) – Transferring a bulk drug into its final container and enclosing it in the container. (GUI-0001)

**Import** (*importer*) - “Means to import into Canada a drug for the purpose of sale” (C.01A.001)

**Impurity** (*impureté*) - Any component present in the intermediate or API that is not the desired entity. (ICH Q7)

**Impurity Profile** (*profil d'impureté*) - A description of the identified and unidentified impurities present in an API. (ICH Q7)

**In-process Control** (*contrôle en cours de fabrication*): 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** (*analyse en cours de fabrication*) - The examination or testing of any material or mixture of materials during the manufacturing process. (GUI-0001)

**Installation Qualification (IQ)** (*qualification de l'installation*) - 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** (*produit intermédiaire*) - 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)

**Label** (*étiquette*) - "Includes any legend, word, or mark attached to, included in, belonging to, or accompanying any food, drug, cosmetic, device, or package (Section 2 of the *Act*). As described in package/label, the action of labelling refers to affixing the inner or outer label to the drug." (C.01A.001)

**Lot** (*lot*) – Refer to the definition of Batch. (ICH Q7)

**Lot Number** (*numéro de lot*) – "Any combination of letters, figures, or both, by which any food or drug can be traced in manufacture and identified in distribution." (A.01.010)

**Manufacture** (*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** (*fabricant*) or **Distributor** (*distributeur*) – Refer to definition of distributor.

**Marketing Authorization** (*autorisation de mise en marché*) - A legal document issued by Health Canada, authorizing the sale of a drug in dosage form or a device based on the health and safety requirements of the *Food and Drug 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). (GUI-0001)

**Master Formula** (*formule-type*) - A document or set of documents specifying the raw materials with their quantities and the packaging materials, together with detailed processing instructions, including in-process controls and precautions required to produce a specified quantity of an API.

**Master Production Documents (MPD)** (*document-type de production*) - Documents that include specifications for raw material, and for packaging material; master formula (including composition and instructions as described in the definition above), sampling procedures, and other critical processing related standard operating procedures (SOPs), whether or not these SOPs are specifically referenced in the master formula.

**Material** (*matière*) - 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** (*ingrédient médicinal*) - Refer to the definition of active pharmaceutical ingredient.

**Mother Liquor** (*liquide-mère*) - 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** (*pays participant à un ARM*) - "A country that is a participant to a mutual recognition agreement with Canada." (C.01A.001)



**Mutual Recognition Agreement (MRA)** (*accord de reconnaissance mutuelle (ARM)*) – “An international agreement that provides for the mutual recognition of compliance certification for Good Manufacturing Practices for drugs.” (C.01A.001)

**Operational Qualification (OQ)** (*qualification opérationnelle*) - Documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges. (ICH Q7)

**Package** (*emballer*) - “As described in package/label, the action of packaging refers to putting a drug in its immediate container.” (C.01A.001)

**Package/Label** (*emballer/étiqueter*) - “To put a drug in its immediate container or to affix the inner or outer label to the drug.” (C.01A.001). This includes the repackaging and relabelling of previously packaged and labelled drugs.

**Packaging Batch Record** (*registre d'emballage de lot de fabrication*) - Records demonstrating that the batch of a drug was packaged in accordance with the approved master production documents. (GUI-0001)

**Packaging Material** (*matériel d'emballage*) – 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 during storage and transport and those components in direct contact with the-final API.

**Performance Qualification (PQ)** (*qualification de rendement*) - 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** (*produit pharmaceutique*) - “A drug other than a drug listed in Schedule C or D to the *Act*.” (C.01A.001).

**Potency** (*teneur*) - The activity or amount of active moiety, or any form thereof, indicated by label claim to be present. (GUI-0001)

**Procedure** (*procédure*) – 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** (*adjuvant de procédé*) - 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 (PV)** (*validation du procédé*) - Documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes. (ICH Q7)

**Production** (*production*) - All operations involved in the preparation of an API, from receipt of materials, through processing and packaging, to completion of the final API, including storage.

**Production Batch Record** (*fiche de lot de fabrication*) - Records demonstrating that the batch of a final API was fabricated in accordance with the approved master production documents.

**Purified Water** (*eau purifiée*) - As defined in any standard listed in Schedule B to the *Food and Drugs Act*. (GUI-0001)

**Purity** (*pureté*) - 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** (*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 (QA)** (*assurance qualité*) - 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 (QC)** (*contrôle de qualité*) - Checking or testing that specifications are met. (ICH Q7)

**Quality Risk Management** (*gestion des risques à la qualité*) - 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** (*unité de qualité*) - An organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization. (ICH Q7)

**Quarantine** (*quarantaine*) - The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection. (ICH Q7)

**Raw Material** (*matière première*) - A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs. (ICH Q7)

**Reconciliation** (*bilan comparatif*) - A comparison, making due allowance for normal variation, between the amount of product or materials theoretically produced or used and the amount actually produced or used. (GUI-0001)

**Recovery** (*récupération*) - The introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture. (GUI-0001)

**Reference Standard, Primary** (*étalon de référence primaire*) - 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** (*étalon de référence secondaire*) - 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)

**Repackaging/Relabelling** (*réemballer/réétiqueter*) - Replacement of packaging or labelling of previously packaged and labelled products. (GUI-0001)

**Reprocessing** (*retraitement*) - 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** (*date de réanalyse*) - “The date when a material should be re-examined to ensure that it is still suitable for use.” (ICH Q7)

**Reworking** (*reprise*) - 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** (*vendre*) - “Offer for sale, expose for sale, have in possession for sale, and distribute, regardless of whether the distribution is made for consideration.” (Section 2 of the *Food and Drugs Act*)

**Shelf Life** (*durée de conservation*) - The time interval during which a drug 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. (GUI-0001)

**Signed** (*signature*) - 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** (*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** (*spécifications*) - “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)** - (*procédure opératoire normalisée (PON)*) - 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. (GUI-0001)

**System** (*système*) - A regulated pattern of interacting activities and techniques that are united to form an organized whole. (GUI-0001)

**Test** (*analyser*) - To perform the tests, including any examinations, evaluations, and assessments, as specified in the Division 2 of the *Food and Drug Regulations*. (GUI-0001)

**Validation** (*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/Supplier** (*fournisseur*) - Any person or company that sells or supplies goods or services to another company. Also called supplier.

**Veterinary Drugs** (*médicaments vétérinaires*) - Drugs that are administered to food-producing and companion animals. (GUI-0001)

**Wholesaler** (*grossiste*) - “Means 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* or in Schedule F to these *Regulations* or a controlled drug as defined in subsection G.01.001(1); or
- (b) an active ingredient; or
- (c) a narcotic as defined in the *Narcotic Control Regulations*.” (C.01A.001(1))

As per the new definition of wholesaler in Division 1A, Part C of the *Food and Drug Regulations*, agents, brokers, traders are considered wholesalers.

**Yield, Expected** (*rendement prévu*) - 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** (*rendement théorique*) - 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)

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## Appendix C

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### ICH Q7 Guideline: Section 18 - Specific Guidance for APIs Manufactured by Cell Culture/Fermentation

#### 18.1 General

- 18.10 Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone Section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for “classical” processes for production of small molecules and for processes using recombinant and non-recombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.
- 18.11 The term “biotechnological process” (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.
- 18.12 The term “classical fermentation” refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g. irradiation or chemical mutagenesis) to produce APIs. APIs produced by “classical fermentation” are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.
- 18.13 Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.
- 18.14 Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or API quality. While this Guide starts at the cell culture/fermentation step, prior steps (e.g. cell banking) should be performed under appropriate process controls. This Guide covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.
- 18.15 Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).
- 18.16 In general, process controls should take into account:
- Maintenance of the Working Cell Bank (where appropriate);
  - Proper inoculation and expansion of the culture;

- Control of the critical operating parameters during fermentation/cell culture;
  - Monitoring of the process for cell growth, viability (for most cell culture processes) and productivity where appropriate;
  - Harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality;
  - Monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production; and
  - Viral safety concerns as described in ICH Guideline Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*.
- 18.17 Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

## **18.2 Cell Bank Maintenance and Record Keeping**

- 18.20 Access to cell banks should be limited to authorized personnel.
- 18.21 Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.
- 18.22 Records of the use of the vials from the cell banks and storage conditions should be maintained.
- 18.23 Where appropriate, cell banks should be periodically monitored to determine suitability for use.
- 18.24 See ICH Guideline Q5D *Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products* for a more complete discussion of cell banking.

## **18.3 Cell Culture/Fermentation**

- 18.30 Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.
- 18.31 Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.
- 18.32 Personnel should be appropriately gowned and take special precautions handling the cultures.
- 18.33 Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.
- 18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilized.
- 18.35 Culture media should be sterilized before use when appropriate to protect the quality of the API.
- 18.36 There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the

product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

- 18.37 Records of contamination events should be maintained.
- 18.38 Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

#### **18.4 Harvesting, Isolation and Purification**

- 18.40 Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment and areas designed to minimize the risk of contamination.
- 18.41 Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.
- 18.42 All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.
- 18.43 If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.
- 18.44 Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

#### **18.5 Viral Removal/Inactivation steps**

- 18.50 See the ICH Guideline Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* for more specific information.
- 18.51 Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.
- 18.52 Appropriate precautions should be taken to prevent potential viral contamination from pre-viral to post-viral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.
- 18.53 The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carry-over (e.g. through equipment or environment) from previous steps.

## Appendix D

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### ICH Q7 Guideline: Section 19 – APIs for Use in Clinical Trials

#### 19.1 General

- 19.10 Not all the controls in the previous sections of this Guide are appropriate for the manufacture of a new API for investigational use during its development. Section 19 provides specific guidance unique to these circumstances.
- 19.11 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. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

#### 19.2 Quality

- 19.20 Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism of approval of each batch.
- 19.21 A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.
- 19.22 Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.
- 19.23 Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.
- 19.24 Process and quality problems should be evaluated.
- 19.25 Labelling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

#### 19.3 Equipment and Facilities

- 19.30 During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use.
- 19.31 Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

#### 19.4 Control of Raw Materials

- 19.40 Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.



19.41 In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

### **19.5 Production**

19.50 The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.

19.51 Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

### **19.6 Validation**

19.60 Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration, and, where appropriate, equipment qualification assures API quality during this development phase.

19.61 Process validation should be conducted in accordance with Section 12 when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.

### **19.7 Changes**

19.70 Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.

### **19.8 Laboratory Controls**

19.80 While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.

19.81 A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.

19.82 Expiry and retest dating as defined in Section 11.6 applies to existing APIs used in clinical trials. For new APIs, Section 11.6 does not normally apply in early stages of clinical trials.

### **19.9 Documentation**

19.90 A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

19.91 The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.

19.92 A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

## Appendix E

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### Annexes to the Current Edition of these API GMP Guidelines

Annexes are available on [Health Canada's website](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/index-eng.php): (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/index-eng.php>).

1. Annex 1 to the Current Edition of the Good Manufacturing Practices Guidelines - Selected Category IV Monograph Drugs (GUI-0066)
2. Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines - Schedule D Drugs, Biological Drugs (GUI-0027)
3. Annex 3 to the Current Edition of the Good Manufacturing Practices Guidelines - Schedule C Drugs (GUI-0026)
4. Annex 4 to the Current Edition of the Good Manufacturing Practices Guidelines - Veterinary Drugs (GUI-0012)
5. Annex 5 to the Current Edition of the Good Manufacturing Practices Guidelines - Positron Emitting Radiopharmaceuticals (PERs) (GUI-0071)
6. PIC/S Annex 11: Computerised Systems
7. Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines - Drugs Used in Clinical Trials (GUI-0036)
8. Annex 14 to the Current Edition of the Good Manufacturing Practices Guidelines - Schedule D Drugs, Human Blood and Blood Components (GUI-0032)
9. Annex 17 to the Current Edition of the Good Manufacturing Practices Guidelines - Guidance on Parametric Release (GUI-0046)

## References

### Justice Canada

Acts and regulations of Canada are available on Justice Laws website.

1. *Food and Drugs Act*
2. *Food and Drug Regulations*

### Health Canada

**Guidance documents and Questions and Answers that relate to GMPs are available on Health Canada's website**

3. Good Manufacturing Practices (GMP) Guidelines, Edition 2009, Version 2 (GUI-0001)
4. Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites (GUI-0080)
5. Annex 3 to the Current Edition of the Good Manufacturing Practices Guidelines - Schedule C Drugs (GUI-0026)
6. Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)
7. Good Manufacturing Practices Questions and Answers
8. Active Pharmaceutical Ingredients Questions and Answers
9. Risk Classification of GMP Observations (GUI-0023)
10. Guidelines for Temperature Control of Drug Products during Storage and Transportation (GUI-0069)
11. Product Recall Procedures
12. Cleaning Validation Guidelines (GUI-0028)
13. Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers/Labellers, Distributors and Importers (GUI-0042)
14. Process Validation Guidelines:
  - Moist Heat Sterilization for Pharmaceuticals (GUI-0010)
  - Irradiation Sterilization for Pharmaceuticals (GUI-0009)

Gaseous Sterilization for Pharmaceuticals (GUI-0007)

Aseptic Processes for Pharmaceuticals (GUI-0006)

15. Importation and Exportation Questions and Answers
16. Alternate Sample Retention Site Guidelines (GUI-0014)

**Documents that relate to stability are available on Health Canada's website in the Drug Products section under Application and Submissions.**

17. Stability Testing of Existing Drug Substances and Products (TPD)

**Guidance documents developed by the International Conference on Harmonisation (ICH) and adopted by Health Canada are available on the web in the Drug Products section under ICH (International Conference on Harmonisation).**

18. ICH Q1A(R2): Stability Testing of New Drug Substances and Products
19. ICH Q1B: Stability Testing: Photostability Testing of New Drug Substances and Products
20. ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology
21. ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
22. ICH Q8: Pharmaceutical Development
23. ICH Q9: Quality Risk Management
24. ICH Q10: Pharmaceutical Quality System

## Appendix F

### Cross-walk between ICH Q7 and GUI-0001 documents

Interpretations of the API Guide	Section of ICH Q7	Section of GUI-0001
<b>Quality Management</b>		
4.1	2.10, 2.12	4.1
4.2	not applicable	4.2
4.2.1	not applicable	4.2.1
4.2.1.1	not applicable	4.2.1.1
4.2.1.2	2.11	4.2.1.2
4.2.1.3	2.3.10	4.2.1.3
4.2.1.4	not applicable	4.2.1.4
4.2.1.5	not applicable	4.2.1.5
4.2.1.6	2.17	4.2.1.6
4.2.1.7	not applicable	4.2.1.7
4.2.1.8	not applicable	4.2.1.8
4.2.1.9	not applicable	4.2.1.9
4.2.1.10	2.17, partial 2.14	4.2.1.10
4.2.1.11	not applicable	4.2.1.11
4.2.1.12	not applicable	4.2.1.12
4.2.1.13	not applicable	4.2.1.13
4.2.1.14	not applicable	4.2.1.14
4.2.1.15	2.15	not applicable
4.2.2	not applicable	4.2.2
4.2.2.1	not applicable	4.2.2.1
4.2.2.2	not applicable	4.2.2.2
4.2.2.3	not applicable	4.2.2.3
4.2.2.4	not applicable	4.2.2.4
4.2.2.5	not applicable	4.2.2.5
4.2.2.6	2.16	4.2.2.6
4.2.2.7	not applicable	4.2.2.7
4.2.2.8	not applicable	4.2.2.8
4.2.2.9	not applicable	4.2.2.9
4.2.2.10	not applicable	4.2.2.10
4.2.3	not applicable	4.2.3
4.2.3.1	not applicable	4.2.3.1
4.2.3.1.1	not applicable	4.2.3.1.1
4.2.3.1.2	not applicable	4.2.3.1.2
4.2.3.1.3	not applicable	4.2.3.1.3
4.2.3.1.4	2.41	4.2.3.1.4
4.2.3.1.5	not applicable	4.2.3.1.5
4.2.3.1.6	not applicable	4.2.3.1.6
4.2.3.1.7	not applicable	4.2.3.1.7
<b>C.02.003 – Sale and Use in Fabrication</b>		
1.	not applicable	not applicable
2.	not applicable	not applicable
<b>C.02.004 – Premises</b>		
1.	4.10	C.02.004: 1, 11, Partial 3, Partial 3.1, C.02.007: 2.9, Records: 5.4
2.	4.70	C.02.004: 1, 2.1-2.4, 9, Partial 3.1, Records: 5.4
3.	4.11	C.02.004: 2, 2.5, 6.1, 6.2, 11, C.02.005: 3.3, 3.4
4.	4.14	C.02.004: Partial 2.2, 2.3, 6.1-6.4, C.02.011: 48, 49

5.	4.16	C.02.004: Partial 2.3, 10, C.02.011: 12
6.	4.24	C.02.004: 3.5
7.	4.20	C.02.004: 3.6, 7, C.02.007: 2.9
8.	4.21	C.02.004: 3.6, 4
8.1	4.22	not applicable
9.	4.15	C.02.004:5
10.	4.13	C.02.004: 6, 11, C.02.005: 3.3
11.	4.50	C.02.004: 6.5
12.	4.23	C.02.004: 8
13.	4.40	C.02.004: 11, 11.2.1, C.02.005: 3.6
14.	4.41	C.02.004: 11, 11.1, 11.2.2, C.02.005: 3.6
15.	4.43	C.02.004: 11.2.2, 11.4, C.02.011: Partial 9
16.	4.33	C.02.005: 3.7

### C.02.005 - Equipment

1.	5.10	C.02.005: 1, 1.1, 1.3, 3.3, 5, Partial 1.2, Partial 1.5, Partial 4.2, Partial 4.3, Partial 4.4
2.	5.11	C.02.005: 1, Partial 1.2, 2, 2.1, 2.3, 4.1, 4.4
3.	5.22	C.02.005: 1.1, 1.2, 1.3, 1.4, 2.4
4.	5.14	C.02.005: 2.2, 3.2
5.	5.15	C.02.005: 2.4, 2.5, 3.2
5.1	not applicable	C.02.005: 3.1
6.	5.13	C.02.005: 3.5
7.	5.16, 5.20	C.02.005: 4, Partial 4.2
8.	not applicable	C.02.005: 5.2
9.	5.30, 5.34	C.02.005: 5.1, 5.3, 5.4, C.02.011: 13
9.1	5.31	not applicable
9.2	5.33, 5.35	not applicable
10.	Partial 8.10	C.02.005: 5.1, C.02.011: 22
11.	5.12	C.02.005: 5.2, 5.3, C.02.011: 35.10
12.	5.40	C.02.005: 5.3, C.02.015: Partial 7.5
13.	5.41	C.02.005: 5.3
14.	5.42	not applicable
15.	5.43	not applicable
16.	5.44, 5.48	not applicable
17.	5.49	not applicable
18.	12.30	C.02.005: 5.3

### C.02.006 - Personnel

1.	3.10	C.02.006: 1, 1.1, 1.2, 1.3, 1.4, 3, 3.1, 3.2, 4, 4.1, 4.2, 5, 5.1, 5.3
2.	not applicable	C.02.006: 1
2.1	not applicable	C.02.006:1.3
2.2	not applicable	C.02.006: 1.4
3.	3.11	C.02.006: 5.2
4.	Partial 3.12	C.02.006: 6, 6.1
4.1	Partial 3.12	C.02.006: 6
4.2	Partial 3.12	C.02.006: 6.4
4.3	Partial 3.12	C.02.006: 6.2, 6.6
4.4	not applicable	C.02.006: 6.3
4.5	not applicable	C.02.006: 6.5
5.	3.30	C.02.006: 7
6.	2.3	C.02.011: Partial 1
6.1	2.3.1	C.02.011: Partial 1
6.2	2.3.2	C.02.011: Partial 23
6.3	2.3.3	C.02.011: 27.10
6.4	2.3.4	C.02.011: 5
6.5	2.3.5	C.02.004: 1, 2, 3, 9, 11

		C.02.005: 1, 3, 4
6.6	2.3.6	C.02.005: 5.1 Records: 2.3
6.7	2.3.7	C.02.004: 2 C.02.005: 4, 5 Records: 2.3, 5.4, 6.4
6.8	2.3.8	C.02.011: Partial 3
6.9	2.3.9	C.02.011: 4
6.10	2.3.10	C.02.004: Partial 7 C.02.005: Partial 5.3
7	2.22	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.1	2.22.1	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.2	2.22.2	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.3	2.22.3	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.4	2.22.4	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.5	2.22.5	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.6	2.22.6	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.7	2.22.7	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.8	2.22.8	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.9	2.22.9	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.10	2.22.10	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.11	2.22.11	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.12	2.22.12	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.13	2.22.13	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.14	2.22.14	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.15	2.22.15	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
7.16	not applicable	C.02.009: Partial 1, 7, C.02.011: 3, 4, 5, 19, C.02.012: 3.2 C.02.014: 2, 2.1, 3, C.02.015: 4, 6, C.02.016: 1, C.02.018: Partial 1
<b>C.02.007 - Sanitation</b>		
Rationale	4.70	C.02.007: 3
1.	4.71	C.02.007: 1, 2, 2.1, 2.4, 2.10
1.1	not applicable	C.02.007: 2.9
1.2	not applicable	C.02.007: 2.5
2.	5.24	C.02.007: 2.3
3.	5.25	C.02.007: 2.4, 3.2
4.	4.60	C.02.007: 2.6
5.	12.70	C.02.007: 3.1
6.	12.74	C.02.007: 3.2, 3.4
7.	12.75	C.02.007: 3.3
8.	4.72	C.02.004: 2

		C.02.007: 2.7, 2.8
9.	5.21	C.02.005: 1, 1.1, 1.3, 1.4, 1.6, C.02.007: 1, 2.2, 2.3, 2.4, 2.10, 3.2, Partial 1.2
10.	5.23	C.02.007: 2.3, 2.8, 3.5, Partial 2.7
11.	6.20	C.02.005: 5.5
12.	12.76	not applicable
13.	not applicable	C.02.007: 5
<b>C.02.008 - Sanitation</b>		
1.	3.20	C.02.008: 2.1, Partial 1, Partial 2, Partial 2.4, Records: Partial 5.4, 6.4
1.1	not applicable	C.02.008: 2.5
2.	3.24	C.02.008: 1.3, 1.4
2.1	not applicable	C.02.008: 1.2
2.2	not applicable	C.02.008: 1.5
3.	3.21	C.02.008: 2.1, 2.7
3.1	not applicable	C.02.008: 2.6
4.	3.22	C.02.008: 2.2
5.	3.23	C.02.008: 2.3
<b>C.02.009 – Raw Materials Testing</b>		
1.	6.17	C.02.009: 1, C.02.018: 1, Records: 5.1
2.	not applicable	not applicable
3.	7.12	C.02.009 : Partial 1
4.	4.30	C.02.005: Partial 3.7
5.	4.31	C.02.009: Partial 4
6.	4.32	C.02.009: Partial 4, Partial 4.1, Partial 4.2
7.	4.34	C.02.005: Partial 3.7
8.	12.80	C.02.009: Partial 5, C.02.018: 2
9.	12.81	C.02.009: Partial 5, C.02.018: 2
10.	7.50	not applicable
<b>C.02.010 – Raw Materials Testing</b>		
1.	7.11	C.02.010: Partial 1
2.	7.30	C.02.010: Partial 1, C.02.017: Partial 1
2.1	not applicable	C.02.010: 3
3.	7.31	C.02.010: Partial 1, Partial 1.3, C.02.017: Partial 1
3.1	not applicable	C.02.010 : 1.7
3.2	not applicable	C.02.010 : 1.4
4.	7.32	not applicable
5.	7.33	C.02.009 : Partial 6, C.02.013 : Partial 3, C.02.015: 4
6.	Partial 7.10	C.02.011: Partial 1, Partial 17
7.	7.13	Records: 5.3, 6.3
8.	7.14	not applicable
9.	not applicable	C.02.010: 1.3
10.	not applicable	C.02.010: 1.8
11.	not applicable	C.02.010: 4
12.	not applicable	C.02.010: 5
13.	not applicable	C.02.010: 6
13.1	not applicable	C.02.010: 6.1
13.2	not applicable	C.02.010: 6.2
13.3	not applicable	C.02.010: 6.3
13.4	not applicable	C.02.010: 6.4
<b>C.02.011 – Manufacturing Control</b>		
1.	not applicable	C.02.011: 8
2.	Partial 7.10	C.02.011: 1, 17
3.	12.12	C.02.011: 2
3.1	12.60, 13.13	C.02.011: 4, C.02.015: 6
4.	12.20	C.02.011: 3



4.1	12.21	C.02.011 : Partial 3
4.2	12.22	not applicable
4.3	12.23	not applicable
5.	Partial 12.30	C.02.005: 5.3
6.	8.15, 8.20	C.02.011: 5, 19, 35.12, Partial 41
7.	8.14	C.02.011: 6, 7
8.	8.50	C.02.005: 2, 3, C.02.011: Partial 9
9.	not applicable	C.02.011: 9
10.	9.44	C.02.011: 10
11.	8.51	C.02.004: 3.2, 3.3, 3.4, C.02.011: 11, 20, Partial 9, Records: 5.4, 6.4
12.	8.35	C.02.011: 12
13.	8.30	not applicable
14.	8.31	not applicable
15.	8.32	not applicable
16.	8.33	not applicable
17.	8.34	not applicable
18.	8.52	C.02.004: 3.2, 3.3, 3.4, C.02.011: Partial 9
19.	4.42	C.02.004: 1, 2
20.	5.26	C.02.005: 3.5, C.02.011: 14
21.	8.16	C.02.005: 3.5, C.02.011: 14, 34
22.	7.44	C.02.011: 15
23.	8.17	C.02.011: 15
24.	7.20	C.02.011: 16, 17, 19
24.1	7.20	C.02.011: 16
25.	7.21	C.02.011: 16, 17, 19
26.	7.22	C.02.011: 16, 17, 19
27.	8.21	C.02.011: 48
28.	10.21	C.02.011: 48 C.02.015: 3
29.	10.22	C.02.015 : 3.2
30.	7.34	C.02.004: 6.4, C.02.011: 20
31.	7.35	C.02.011: 17
32.	7.23	C.02.011: 14
33.	7.24	C.02.010: 5, 6, 6.1, 6.2, 6.3, 6.4 C.02.011: 14, 21.5 C.02.017: 5
34.	7.40	C.02.004: 4 C.02.011: 48 C.02.017: Partial 3, 3.1, 3.2, 3.4, 3.5
35.	7.41	not applicable
36.	7.42	not applicable
37.	7.43	not applicable
38.	Partial 8.10	C.02.005: 5.1, C.02.011: 22
39.	8.12	C.02.011: 22
40.	8.13	not applicable
41.	2.15	C.02.011: 35.4
42.	6.14	C.02.011: 35.4 Records: Interpretation paragraph
43.	6.10	C.02.011: 1
43.1	6.40	C.02.011: 23
44.	6.41, 8.20	C.02.011: 24, 24.1, 24.3, 24.4, 24.5, 24.7, 24.8, 24.9, 25, 25.1, 25.2, 27, 27.1, 27.3, 27.4, 35.7, Partial 24.6
45.	6.50	C.02.011: 26, Records: 2.2
46.	6.51	C.02.011: 26, 27.2, Records: 2.2
47.	6.52	C.02.011: 27.3 to 27.10, 35, 35.1 to 35.4, Records: 2.2
48.	8.11	C.02.011: Partial 21, Partial 21.4

49.	8.40	not applicable
50.	8.41	not applicable
51.	8.42	not applicable
52.	8.43	C.02.011: 28
53.	8.44	not applicable
54.	8.45	not applicable
55.	8.46	not applicable
56.	8.47	C.02.027: Partial 1.5
57.	14.40	C.02.011: 28.1
58.	14.41	not applicable
59.	14.42	not applicable
60.	14.43	not applicable
61.	not applicable	C.02.011: 29
62.	9.41	C.02.011: 29, 38
63.	9.30	C.02.011: Partial 43, 43.1
64.	9.44	C.02.011: 25.4, 31
65.	9.40	C.02.011: 25.1, 25.5, 29, 35.8, 35.13, 38, 45, 46 C.02.017: Partial 3, Partial 3.1, Partial 3.2, Partial 3.4, Partial 3.5
66.	9.34	not applicable
67.	9.35	C.02.011: 43, 47
68.	9.21	C.02.011: 33
69.	9.22	not applicable
70.	9.42	C.02.011: 21, 21.1, 21.2, 21.3, 50
71.	9.43	C.02.011: 21, 21.1 to 21.4, Partial 35.7
72.	9.46	not applicable
73.	9.45	C.02.011: 25.6, 35.5, 35.6, 35.8
74.	9.31	C.02.011: 35.14, 42
75.	9.32	C.02.011: 39
76.	9.33	C.02.011: 40
77.	not applicable	C.02.011: 49
78.	not applicable	C.02.011 : 35
78.1	not applicable	C.02.011 : 35.1
78.2	not applicable	C.02.011 : 35.3
78.3	not applicable	C.02.011 : 35.4
78.4	not applicable	C.02.011 : 35.8
78.5	not applicable	C.02.011 : 35.9
78.6	not applicable	C.02.011 : 35.10
78.7	not applicable	C.02.011 : 35.11
78.8	not applicable	C.02.011 : 35.12
78.9	not applicable	C.02.011 : 37
79.	2.50	C.02.011: 51, 51.1, 51.2, 51.3, 51.4, 51.5, 51.6, 51.7 C.02.015: 4, C.02.028: 1
80.	2.51	C.02.011: 55
81.	not applicable	C.02.011: 53
82.	not applicable	C.02.011: 54

### C.02.012 – Manufacturing Control

Rationale	17.40	C.02.012 : Interpretation paragraph
1.	2.18	C.02.012 :1.4
2.	15.13	C.02.012: Partial 1, Partial 1.10, Partial 1.11, 1.2 Records: 3.2
3.	15.14	C.02.012: 1.3, 1.5, 1.9, Partial 1 Records: 3.2
3.1	not applicable	C.02.012: 1.1
3.2	not applicable	C.02.012: 1.4
3.3	not applicable	C.02.012: 1.10
4.	10.24	C.02.012: 1.6

		Records: 2.1, 2.1.1, 2.1.2
4.1	15.14	C.02.012: 1.8
5.	10.11	C.02.012: 1.9
6.	17.70	C.02.012: 1.11 Records: 3.1
7.	2.40	C.02.012: 2, 2.1, 2.2, 2.4
7.1	not applicable	C.02.012: 2.3
8.	2.41	C.02.012: 2.1, 2.5, Records: 2.2
9.	Partial 16.10, 17.11	C.02.012: 3.2.2
10.	16.11	not applicable
11.	not applicable	C.02.012: 3.
11.1	not applicable	C.02.012: 3.1
11.2	16.12	C.02.012: 3.2
11.2.1	not applicable	C.02.012: 3.2.1
11.2.2	16.13	C.02.012: 3.2.2
11.2.3	not applicable	C.02.012: 3.2.3
11.2.3.1	not applicable	C.02.012: 3.2.3.1
11.2.3.2	not applicable	C.02.012: 3.2.3.2
11.2.3.3	not applicable	C.02.012: 3.2.3.3
11.2.4	16.14	C.02.012: 3.2.4
11.2.5	not applicable	C.02.012: 3.2.5
11.2.6	not applicable	C.02.012: 3.2.6
11.3	not applicable	C.02.012: 3.3
11.4	not applicable	C.02.012: 3.4
11.4.1	16.16	not applicable
11.5	not applicable	C.02.012: 3.5
11.5.1	not applicable	C.02.012: 3.5.1
11.5.2	not applicable	C.02.012: 3.5.2
<b>C.02.013 – Quality Control Department</b>		
1.	2.20	C.02.015: 4
2.	2.21, Partial 7.10, Partial 11.11	C.02.011: 1, 17 C.02.013: 3 C.02.014: 3 C.02.015: 3
3.	2.13	not applicable
4.	11.10	C.02.013: 2 C.02.015: 7, 7.1
<b>C.02.014 – Quality Control Department</b>		
1.	Partial 2.14, Partial 2.22	C.02.014: 1
2.	2.17	not applicable
3.	2.22	C.02.014: 2
4.	10.20	not applicable
5.	not applicable	C.02.014: 3
6.	2.16, 6.53	C.02.014: 2.1, 2.2
7.	14.10, 14.50	C.02.011: 15 C.02.014: 5 C.02.018: 4
8.	14.51	C.02.014: 4
8.1	not applicable	C.02.014: 4.1
9.	14.30	C.02.014: 6
10.	14.31	C.02.014: 6, 6.1 to 6.7
11.	14.32	C.02.014: 6, 6.1 to 6.7
12.	14.20	C.02.014: 7, 7.1-7.5, 7.7
13.	14.21	not applicable
14.	14.22	C.02.014: 7, 7.1 to 7.7

15.	not applicable	not applicable
<b>C.02.015 – Quality Control Department</b>		
1.	2.18	C.02.012 : 1.4
2.	13.10	C.02.015 : 5
3.	13.11	C.02.014 : 4 C.02.015 : 5
4.	13.12	C.02.015 : 5
5.	13.13	C.02.011 : 4 C.02.015 : 5
5.1	13.16	C.02.015 : Partial 6
5.2	13.15	C.02.015 : Partial 6
5.3	13.14	C.02.015 : Partial 6
6.	13.17	not applicable
7.	15.10	C.02.015 : 4 Records : 3.1, 3.2
7.1	17.71	not applicable
7.2	17.72	not applicable
8.	15.12	C.02.015 : 5 Records : 3.2
9.	11.12	C.02.009 : Partial 2, C.02.015 : Partial 3, C.02.016 : Partial 2, 3, C.02.018 : 1.2
10.	11.14	C.02.015 : 6
11.	6.60	C.02.014 : 1, C.02.015 : 1, Records : 4.2
11.1	6.60	C.02.014 : 1, C.02.015 : 1, Records : 4.2
11.2	6.60	C.02.014 : 1, C.02.015 : 1, Records : 4.2
11.3	6.60	C.02.014 : 1, C.02.015 : 1, Records : 4.2
11.4	6.60	C.02.014 : 1, C.02.015 : 1, Records : 4.2
11.5	6.60	C.02.014 : 1, C.02.015 : 1, Records : 4.2
11.6	6.60	C.02.014 : 1, C.02.015 : 1, Records : 4.2
11.7	6.60	C.02.014 : 1, C.02.015 : 1, Records : 4.2
11.8	6.60	C.02.014 : 1, C.02.015 : 1, Records : 4.2
12.	11.16	not applicable
13.	not applicable	C.02.015 : 7
13.1	not applicable	C.02.015 : 7.1
13.1.1	not applicable	C.02.015 : 7.1.1
13.1.2	not applicable	C.02.015 : 7.1.2
13.2	not applicable	C.02.015 : 7.2
13.3	not applicable	C.02.015 : 7.3
13.4	not applicable	C.02.015 : 7.4
13.5	not applicable	C.02.015 : 7.5
13.6	not applicable	C.02.015 : 7.6
13.7	not applicable	C.02.015 : 7.7
13.7.1	not applicable	C.02.015 : 7.7.1
13.7.2	not applicable	C.02.015 : 7.7.2
13.7.3	not applicable	C.02.015 : 7.7.3
13.7.4	not applicable	C.02.015 : 7.7.4
13.7.4.1	not applicable	C.02.015 : 7.7.4.1
13.7.4.2	not applicable	C.02.015 : 7.7.4.2
13.7.4.3	not applicable	C.02.015 : 7.7.4.3
13.7.4.4	not applicable	C.02.015 : 7.7.4.4
13.8	not applicable	C.02.015 : 7.8
13.9	2.16, 11.15	C.02.015 : 7.9
13.9.1	not applicable	C.02.015 : 7.9.1
13.9.2	not applicable	C.02.015 : 7.9.2
13.9.3	not applicable	C.02.015 : 7.9.3
13.9.4	not applicable	C.02.015 : 7.9.4

13.9.5	not applicable	C.02.015 : 7.9.5
13.9.6	8.36	not applicable
14.	11.17	C.02.015 : Partial 7.8
15.	11.18	C.02.015 : Partial 7.8
16.	11.19	C.02.015 : Partial 7.8
17.	6.61	Records : 2.3
17.1	6.61	C.02.015 : 6
17.2	6.61	C.02.005 : 5.1 C.02.015 : Partial 7.4
17.3	6.61	Records : Partial 2.4, 2.4.1
17.4	6.61	C.02.015: Partial 7.9 Records: 2.3
18.	5.45	not applicable
19.	5.46	not applicable
20.	5.47	not applicable
21.	6.72	C.02.015 : 7.9.4
22.	not applicable	C.02.015 : 7.10
22.1	not applicable	C.02.015 : 7.10.1
22.2	not applicable	C.02.015 : 7.10.2
22.3	not applicable	C.02.015 : 7.10.3
22.3.1	not applicable	C.02.015 : 7.10.3.1
22.3.2	not applicable	C.02.015 : 7.10.3.2
22.3.3	not applicable	C.02.015 : 7.10.3.3
22.3.3.1	not applicable	C.02.015 : 7.10.3.3.1
22.3.3.2	not applicable	C.02.015 : 7.10.3.3.2
22.3.3.3	not applicable	C.02.015 : 7.10.3.3.3
22.3.3.4	not applicable	C.02.015 : 7.10.3.3.4
22.3.4	not applicable	C.02.015 : 7.10.3.4
23.	10.23	C.02.015 : Partial 3.6
<b>C.02.016 – Packaging Material Testing and C.02.017 – Packaging Material Testing</b>		
1.	9.10	not applicable
2.	not applicable	C.02.016: Partial 1
2.1	not applicable	C.02.016 : 2
2.2	not applicable	C.02.016 : 3
2.3	not applicable	C.02.016 : Partial 1
2.4	9.21	not applicable
2.5.	not applicable	not applicable
3.	not applicable	C.02.016: 7
4.	not applicable	C.02.017: 4
4.1	6.31, 9.36	C.02.011 : 25.3, Partial 37
5.	9.11	C.02.016 : Partial 4
6.	not applicable	C.02.016 : 4
7.	9.20	not applicable
8.	9.21	not applicable
9.	not applicable	C.02.016: 5
10.	not applicable	C.02.017: 1
10.1	7.31	C.02.010: 1 C.02.017: Partial 1
<b>C.02.018 – Finished Products Testing</b>		
1.	11.20	not applicable
2.	11.12, Partial 6.17	C.02.018: 1
2.1	not applicable	C.02.018: 1.2
3.	11.13, 11.23	C.02.015: 6 C.02.018: 1.1
4.	12.80	C.02.018: 2

5.	Partial 12.81	C.02.018: Partial 2
6.	not applicable	C.02.018: 3
7.	11.21	not applicable
8.	11.22	not applicable
9.	11.41	C.02.011: Partial 21.4
10.	11.40	not applicable
11.	11.42	not applicable
12.	11.43	not applicable
13.	11.44	not applicable
14.	Partial 11.15	C.02.018: 4 C.02.019: Partial 5
<b>C.02.019 – Finished Products Testing</b>		
1.	not applicable	C.02.019: 1
2.	not applicable	not applicable
3.	not applicable	not applicable
<b>C.02.020 to C.02.024 – Records</b>		
1.	not applicable	Partial Records Interpretation Paragraph
2.	17.60	not applicable
3.	not applicable	Partial Records Interpretation Paragraph
3.1	6.11	not applicable
3.2	Partial 6.10	Partial Records Interpretation Paragraph
3.3	not applicable	Partial Records Interpretation Paragraph
3.4	6.12	not applicable
4.	6.15, 6.16	Partial Records Interpretation Paragraph
4.1	16.15	not applicable
5.	not applicable	Records: 1
5.1	6.18	Partial Records Interpretation Paragraph
6.	6.14	Partial Records Interpretation Paragraph
7.	not applicable	Records: Partial 2.3, 8
7.1	6.13	Records: 5.5
7.2	not applicable	Records: 2.3.1
7.3	6.21	not applicable
7.4	5.32	C.02.005: 5.1
7.5	not applicable	Records: 7, 7.1
7.6	3.31	Records: Partial 2.3.2
7.7	not applicable	Records: 5.4
7.8	6.71	not applicable
7.9	not applicable	Records: 3.2
7.10	not applicable	Records: 2.4
7.10.1	not applicable	Records: 2.4.1
7.11	10.10	C.02.004: 4, C.02.015: 2, C.02.025/C.02.026: 2.2
8.	not applicable	Records: 2.2
8.1	6.70	not applicable
8.2	not applicable	Records: 2.2.1
8.3	not applicable	Records: 2.2.2
9.	not applicable	Records: 3, 4, 8
9.1	not applicable	Records: 3.1
9.1.1	not applicable	Records: 3.1.1
9.1.2	not applicable	Records: 3.1.2
9.1.3	14.52	not applicable
9.2	Partial 15.10	Records: 4.1, 4.2
9.2.1	15.11	not applicable
10.	not applicable	Records: 5, 6
10.1	6.17	Records: 5.1, 6.1
10.2	6.30, 9.12	Records: 2.2.1, 5.3, 6.3

10.3	6.30	Records: 6.2
10.3.1	Partial 11.11	Records: 2.2.1, 5.2, 6.2
11.	6.13	Records: 2, 10
11.1	6.40, 6.41	Records: 2.1
12.	17.20	not applicable
12.1	17.20	not applicable
12.2	17.20	not applicable
12.3	17.20	not applicable
12.4	17.20	not applicable
12.5	17.20	not applicable
12.6	17.20	not applicable
12.7	17.20	not applicable
12.8	17.20	not applicable
12.9	17.20	not applicable
12.10	17.20	not applicable
13.	not applicable	not applicable
13.1	not applicable	not applicable
13.2	not applicable	not applicable
13.3	not applicable	not applicable
13.4	not applicable	not applicable
<b>C.02.025 and C.02.026 – Samples</b>		
1.	11.63	not applicable
2.	11.70	not applicable
3.	11.71	not applicable
4.	11.72	C.02.025: 2.1, 3
5.	not applicable	C.02.025: 1.2
6.	not applicable	C.02.025: 1.3
<b>C.02.027 – Stability</b>		
1.	11.60	C.02.027: 1
2.	11.61	Records: 2.4, 2.4.1, C.02.027: Partial 1.1
3.	11.62	C.02.027: Partial 1
3.1	not applicable	C.02.027:1.1
4.	11.52	C.02.027: 1.2
4.1	not applicable	not applicable
5.	11.53	C.02.027: Partial 1.3
6.	not applicable	C.02.027: 1.4
7.	11.56	C.02.027: Partial 1.4
8.	Partial 11.51	C.02.027: 1.7
<b>C.02.028 – Stability</b>		
1.	11.52	C.02.027: 1.2
2.	11.50	Records: 2.4, 2.4.1 C.02.028: 1
3.	11.54	C.02.028: 1.2
4.	11.55	not applicable
5.	11.56	Rationale Paragraph
6.	not applicable	C.02.028: 1.1
7.	not applicable	C.02.028: 1.3
8.	not applicable	C.02.028: 1.4
9.	not applicable	C.02.028: 1.5