

GUI-0036: Annex 13 to the Good Manufacturing Practices Guide – Drugs used in Clinical Trials

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Table of contents

| | |
|---|----|
| 1. Purpose | 4 |
| 2. Scope | 4 |
| 3. Introduction..... | 5 |
| 4. Pharmaceutical quality management..... | 6 |
| 4.1 Production specification file..... | 7 |
| 5. Personnel..... | 8 |
| 6. Premises and equipment..... | 8 |
| 7. Documentation..... | 9 |
| 7.1 Specifications and instructions..... | 9 |
| 7.2 Order | 10 |
| 7.3 Manufacturing formulas and processing instructions..... | 10 |
| 7.4 Packaging instructions..... | 10 |
| 7.5 Batch records | 11 |
| 8. Production..... | 11 |
| 8.1 Packaging materials..... | 11 |
| 8.2 Manufacturing operations | 11 |
| 8.3 Modifying comparator products | 12 |
| 8.4 Blinding operations | 13 |
| 8.5 Packaging..... | 13 |
| 8.6 Labelling | 14 |
| 9. Quality control..... | 15 |
| 10. Release of batches..... | 16 |
| 11. Outsourced operations..... | 18 |
| 12. Complaints..... | 18 |
| 13. Recalls and returns | 18 |
| 13.1 Recalls | 18 |
| 13.2 Returns..... | 19 |
| 14. Destruction..... | 19 |
| Appendix A – Glossary..... | 20 |
| Appendix B – References..... | 23 |
| Appendix C – Regulatory references | 24 |



1. Purpose

This guide is an annex to the Canadian [Good manufacturing practices guidelines \(GUI-0001\)](#). It applies to manufacturing, handling and storing of clinical trial drugs intended for use in clinical trials.

Good manufacturing practices (GMP) are internationally recognized standards that apply to drug manufacturing. They ensure drug quality and safety.

Drugs intended for use in clinical trials in Canada are regulated under Part C, Division 5 of the [Food and Drug Regulations](#) (regulations). Under section C.05.010(j), sponsors must ensure that drugs for use in clinical trials are manufactured, handled and stored in accordance with the applicable good manufacturing practices requirements referred to in Divisions 2 to 4. Exceptions are those requirements referred to in sections C.02.019, C.02.025 and C.02.026. Sponsors of clinical trials must also ensure that imported drugs are fabricated and packaged/labelled in accordance with these requirements.

The relevant sections of the regulations are noted throughout.

Retention Samples of the Drug

Although the Regulations do not specifically state that samples of clinical trial drugs must be kept, in order to be able to fulfill Health Canada's request for a sample, as specified in this section, it is implicit that retention samples should be kept from the start of a clinical trial until the clinical trial report has been prepared.

2. Scope

This guide covers the manufacturing of human clinical trial drugs, placebo products and comparator products, which includes fabrication, packaging and labelling, and testing. It's relevant to anyone who works with such products as a:

- fabricator
- packager
- labeller
- tester
- sponsor

This document also includes guidance on ordering, shipping and returning clinical supplies.



Product categories covered by the guidelines include:

- human pharmaceuticals
- biologicals
- radiopharmaceuticals

Note: This guide is based on the Pharmaceutical Inspection Cooperation Scheme's (PIC/S) *Annex 13 for the manufacture of investigational medicinal products* (including changes necessary to adapt the text to meet Canadian requirements):

- [Guide to good manufacturing practice for medicinal products annexes](#)

For more information on clinical trial drugs, consult the following guidance documents:

- [Part C, Division 5 of the Food and Drug Regulations “Drugs for clinical trials involving human subjects” \(GUI-0100\)](#)
- [Guidance document for clinical trial sponsors: Clinical trial applications](#)

3. Introduction

Participants in clinical drug trials can be at higher risk of negative effects than people taking authorized drugs. The guidelines in this document are designed to minimize that risk.

Drug production for clinical trials is often more complex than for marketed products. Reasons for this include the following:

- no fixed routines / schedule
- clinical trial designs vary
- the need to randomize and blind participants

There may be incomplete knowledge of the potency and toxicity of the product and a lack of full process validation. The product specifications and manufacturing instructions may be changed during development, but full control and traceability of the changes should be documented and maintained.

As a result, producing drugs for clinical trials requires a highly effective quality system. The trial sponsor is responsible for all aspects of that system.



Note about guidance documents in general

Guidance documents like this one are not legally binding. They are administrative tools to help industry and health care professionals understand how to comply with regulations. They also provide guidance to Health Canada staff, ensuring that the rules enforced are fair, consistent and effective across Canada. This document is a guide to assess your compliance with the relevant GMP requirements for drugs used in clinical trials.

There is flexibility in how you meet the applicable laws and regulations. If you choose to follow an alternate approach to the principles and practices described in this document, you must provide adequate justification. Alternate approaches should be discussed in advance with the relevant program area. This helps ensure that your approach still meets all legal and regulatory requirements.

Health Canada may request additional information or material, or define conditions not specifically described in this document. These requests help us adequately assess compliance with the act and regulations. We are committed to making such requests only when necessary and to document our decisions clearly and transparently.

This document should be read along with the relevant sections of the regulations and other applicable guidance documents.

If there is a discrepancy between this guidance document and the regulations, the regulations always take precedence.

4. Pharmaceutical quality management

C.02.013, C.02.014, C.02.015

The pharmaceutical quality system that is designed, set up and verified by the manufacturer should be described in written procedures, taking into account the GMP principles and guidelines applicable to clinical trial drugs.

The product specifications and manufacturing instructions may be changed during development, but full control and traceability of the changes should be documented and maintained. Deviations from any predefined specifications and instructions should be registered, investigated and corrective and preventive action measures initiated as appropriate.

The selection, qualification, approval and maintenance of suppliers of raw materials, together with their purchase and acceptance, should be documented as part of the



pharmaceutical quality system to ensure the integrity of the supply chain and protect against falsified products. The level of oversight should be proportionate to the risks posed by the individual materials, taking into account their source, manufacturing process, supply chain complexity and the final use to which the material is put in the clinical trial drug. The supporting evidence for each supplier approval and material approval should be documented and maintained.

4.1 Production specification file

C.02.009, C.02.014, C.02.016, C.02.018, C.02.020, C.02.027

The product specification file brings together and contains all of the essential reference documents to ensure that clinical trial drugs are manufactured according to good manufacturing practices for clinical trial drugs and the clinical trial authorization. The product specification file is one of the essential elements of the pharmaceutical quality system.

Applicable sections of the product specification file should be available at the start of manufacturing of the first batch of the clinical trial drug for use in a clinical trial.

The product specification file should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions. It should include, or refer to, the following:

- a) the specifications and analytical methods for raw materials, packaging materials, intermediate, bulk and finished products
- b) manufacturing methods
- c) in-process testing and methods
- d) approved label copy
- e) relevant clinical trial protocols and randomization codes, as appropriate
- f) relevant technical agreements with contract givers, as appropriate
- g) stability data
- h) storage and shipment conditions
- i) details of plans and arrangements for reference samples
- j) details of the supply chain including manufacturing, packaging, labelling and testing sites for the clinical trial drug, preferably in the format of a comprehensive diagram

This list of documents is neither exhaustive nor exclusive.

The contents of the product specification file will vary depending on the product and its stage of development.



Where different manufacturing steps are carried out at different locations under the responsibility of different persons in charge of the quality control department, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations. The manufacturing site should have access to the necessary documentation of the product specification file, including changes, to enable the relevant activities to be performed.

5. Personnel

C.02.006

The guidance in the [Good manufacturing practices guide for drug products \(GUI-0001\)](#) should be taken into account, as appropriate, in relation to the manufacture of clinical trial drugs.

All personnel involved with the manufacture, import, storage or handling of clinical trial drugs should be appropriately trained in the requirements specific to these types of products.

The person in charge of the quality control department who certifies the finished batch of clinical trial drugs for use in the clinical trial should ensure that there are systems in place that meet the requirements of good manufacturing practice. The person in charge of the quality control department should have a broad knowledge of pharmaceutical development, clinical trial processes and supply chain of the batch concerned.

Even where the number of staff involved in the manufacturing of clinical trial drugs is small, there should be, for each batch, separate personnel responsible for production and quality control.

6. Premises and equipment

C.02.004, C.02.005, C.02.007

The toxicity, potency or sensitizing potential may not be fully understood for clinical trial drugs and this reinforces the need to minimize all risks of cross-contamination. The design of equipment and premises, inspection/test methods and acceptance limits to be used after cleaning should reflect the nature of these risks. They should also take account



of the quality risk management principles detailed in the GMP principles and guidelines applicable to clinical trial drugs.

Consideration should be given to campaign production, where appropriate. Account should be taken of the solubility of the product in decisions about the choice of cleaning solvent.

A quality risk management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the clinical trial drugs manufactured. Factors that should be taken into account include:

- a) facility/equipment design and use
- b) personnel and material flow
- c) microbiological controls
- d) physio-chemical characteristics of the active substance
- e) process characteristics
- f) cleaning processes
- g) analytical capabilities relative to the relevant limits established from the evaluation of the clinical trial drugs

Premises and equipment are expected to be qualified in accordance with [GUI-0029: Guide to validation – drugs and supporting activities \(GUI-0029\)](#).

7. Documentation

7.1 Specifications and instructions

C.02.009, C.02.010, C.02.011, C.02.015, C.02.016, C.02.018, C.02.020

Specifications for raw materials, primary packaging materials, intermediate products, bulk products and finished products, manufacturing formulae and processing and packaging instructions should be as comprehensive as possible. They should be reassessed during development and updated as necessary.

Each new version should take into account the latest data, current technology used, regulatory and pharmacopoeial developments and should allow traceability to the previous document.

Any changes should be carried out according to a written procedure, which should address any implications for product quality such as stability and bioequivalence. The



approval process for instructions and changes shall involve responsible personnel at the manufacturing site.

Rationales for changes should be recorded and the consequences of a change on product quality and on any ongoing clinical trials should be investigated and fully documented.

7.2 Order

C.02.011

The manufacturer should retain the order for the clinical trial drugs as part of the batch documentation.

The order should request the processing and/or packaging of a certain number of units and/or their distribution and be given by or on behalf of the sponsor to the manufacturer. The order should be in writing, and may be transmitted by electronic means, and be precise enough to avoid any ambiguity. It should be formally authorized by the sponsor or their representative and refer to the product specification file and the relevant clinical trial protocol as appropriate.

7.3 Manufacturing formulas and processing instructions

C.02.011, C.02.020

For every manufacturing operation or supply there should be clear and adequate written instructions and written records, which are prepared using the specific clinical study information detailed in the product specification file. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture once the marketing authorization is granted.

The relevant information in the product specification file should be used to draft the detailed written instructions on processing, packaging, quality control testing and storage, including storage conditions.

7.4 Packaging instructions

C.02.011

Clinical trial drugs are normally packaged in an individual way for each subject included in the clinical trial. The number of units to be packaged should be specified prior to the start of the packaging operations, including units necessary for carrying out quality control.



Reconciliations should take place to ensure that the correct quantity of each product required has been accounted for at each stage of processing.

Procedures should describe the specification, generation, testing, security, distribution, handling and retention of any randomization code used for packaging clinical trial drugs, as well as the code-break mechanism. Relevant records should be maintained for 15 years as per Part C, Division 5 of the *Food and Drug Regulations*.

7.5 Batch records

C.02.020, C.02.021, C.05.012(4)

Batch records should be kept in sufficient detail for the sequence of operations to be accurately determined. These records should contain any relevant remarks that justify procedures used and any changes made, enhance knowledge of the product, develop the manufacturing operations and document deviations from predefined requirements.

Batch manufacturing records should be retained by the manufacturer for at least 15 years after the completion or termination of the last clinical trial in which the given batch was used.

8. Production

8.1 Packaging materials

C.02.011, C.02.016

Specifications and quality control checks should include measures to guard against unintentional unblinding due to changes in appearance between different batches of packaging materials.

8.2 Manufacturing operations

C.02.004, C.02.005, C.02.011, C.02.029

During development, critical parameters and in-process controls should be identified. Provisional production parameters and in-process controls may be deduced from prior experience, including that gained from earlier development work. Consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them



continually to the experience gained in production. Parameters identified and controlled should be justifiable based on knowledge available at the time.

The manufacturing process is not required to be validated to the extent necessary for routine production but premises and equipment are expected to be validated. The validation should be documented in accordance with the required GMP principles and guidelines available. The manufacturer shall identify the process steps that ensures the safety of the subject and the reliability and robustness of the clinical trial data generated in the clinical study.

To avoid cross-contamination, written cleaning procedures and analytical methods to verify the cleaning process should be available.

For sterile products, the validation of controls and processes related to assurance of sterility should be of the same standards as for products authorised for marketing. They should also take account of the principles for the manufacture of sterile clinical drugs. These are detailed in the [Good manufacturing practices guide for drug products \(GUI-0001\)](#).

Likewise, when required, virus inactivation/removal and removal of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived and biological products. The scientific principles and techniques are defined in the [Annex to good manufacturing practices guide: Manufacturing of sterile drugs \(GUI-0119\)](#) and [Process validation: Terminal sterilization processes for drugs \(GUI-0074\)](#)

The validation of aseptic processes can be challenging when batch sizes are small. In such cases, the number of units filled may be the total number filled in production. If practicable, and consistent with simulating the process, a larger number of units should be filled with media to provide greater confidence in the results obtained.

Filling and sealing are often a manual or semi-automated operation presenting great challenges to sterility, so enhanced attention should be given to operator training and validating the aseptic technique of individual operators.

8.3 Modifying comparator products

C.02.011, C.02.018, C.02.027

If a drug is modified, data should be available (for example, stability, comparative dissolution or bioavailability) to demonstrate that the changes do not significantly alter the original quality characteristics of the drug.



The expiry date stated for the comparator product in its original packaging might not be applicable to the product where it has been repackaged in a different container that may not offer equivalent protection, or be compatible with the product. A suitable retest date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the product may be subjected, should be determined by or on behalf of the sponsor. Such a date should be justified and must not be later than the expiry date of the original package. There should be compatibility of expiry dating and clinical trial duration.

A reference sample of comparator product, which has been repackaged or over encapsulated for blinding purposes, should be taken at the end of processing. This sample should be retained. The additional processing step could have an impact on the stability or be needed for identification purposes in the event of a quality defect investigation, which would not be covered by the commercial retained sample.

8.4 Blinding operations

C.02.011, C.02.014

Where products are blinded, systems should be in place to ensure that the blind is achieved and maintained while allowing for identification of "blinded" products, when necessary, including batch numbers of the products before the blinding operation. Rapid identification of product should also be possible in an emergency that might affect the safety of the patient.

Where the manufacturer has been delegated the responsibility for generation of randomization codes, the manufacturer should ensure that unblinding information is available to the person in charge of the quality control department before clinical trial drugs are supplied.

Where products are blinded, the expiry date assigned to all products should be stated at the expiry of the shortest dated product so that the blinding is maintained.

8.5 Packaging

C.02.006, C.02.011, C.02.015

During packaging of clinical trial drugs, it may be necessary to handle different drugs on the same packaging line at the same time. The risk of product unintentional mixing (mix-ups) must be minimized by using the appropriate procedures and/or specialized equipment as appropriate and relevant staff training. Documentation must be sufficient



to demonstrate that appropriate segregation has been maintained during any packaging operations.

Packaging and labelling of clinical trial drugs are likely to be more complex and more liable to errors, which are also harder to detect than for marketed products, particularly when blinded products with similar appearance are used. Precautions against mislabelling such as reconciliation, line clearance and in-process control checks by appropriately trained staff, should accordingly be intensified.

The packaging must ensure that clinical trial drugs remain in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.

Re-packaging operations may be performed by authorized personnel at a hospital, health centre or clinic that meet the requirements of relevant national laws or requirements (for example, in healthcare establishments that are not otherwise subject to good manufacturing practices).

8.6 Labelling

C.02.011, C.02.016, C.05.011

The labelling of clinical trial drugs shall comply with Section C.05.011 of the *Food and Drug Regulations*. The following must be included on labels in both official languages, unless their absence can be justified (for example, use of a centralized electronic randomization system):

- a) a statement indicating that the drug is an investigational drug to be used only by a qualified investigator
- b) the name, number or identifying mark of the drug
- c) the expiration date of the drug
- d) the recommended storage conditions for the drug
- e) the lot number of the drug
- f) the name and address of the sponsor
- g) the protocol code or identification
- h) the information required by subparagraph C.03.202(1)(b)(vi) if the drug is a radiopharmaceutical as defined in Section C.03.201

If stability studies to support expiry dating for a clinical trial drug are still ongoing at the time of labelling, alternate approaches to providing information regarding expiry dating can be considered. Regardless of the approach taken, data should be in place at all times to support the ongoing suitability of the clinical trial drug at the time of use.



The information that shall appear on the labelling should comply with any relevant national laws or requirements. The labelling operation should be performed at an authorized manufacturing site in accordance with relevant GMP requirements.

If it becomes necessary to change the expiry date, an additional label should be affixed to the clinical trial drug. This additional label should state the new expiry date and repeat the batch number and protocol code / identification number. It may be superimposed on the old expiry date, but for quality control reasons, not on the original batch number.

The re-labelling operation should be performed by appropriately trained staff in accordance with good manufacturing practices principles and specific standard operating procedures and should be checked by a second person. This additional labelling should be properly documented in the batch records. To avoid mistakes, the additional labelling activity should be carried out in an area that is partitioned or separated from other activities. A line clearance at the start and end of activity should be carried out and label reconciliation performed. Any discrepancies observed during reconciliation should be investigated and accounted for before release.

The re-labelling operation may be performed by the person in charge of the quality control department at a hospital, health centre or clinic that meet the relevant national laws or requirements (such as healthcare establishments that are not subject to good manufacturing practices).

9. Quality control

C.02.011, C.02.013, C.02.014

The manufacturer should establish and maintain a quality control system placed under the authority of a person who has the requisite qualifications and is independent of production.

As processes may not be standardized or fully validated, testing takes on more importance in ensuring that each batch meets the approved specification at the time of testing.

Quality control of the clinical trial drug, including that of the comparator product or placebo, should be performed in accordance with the information submitted in the application for the clinical trial, as authorized by the relevant country.

Verification of the effectiveness of blinding should be performed and recorded.



10. Release of batches

C.02.006, C.02.011, C.02.012, C.02.014, C.02.015, C.02.022

Release of clinical trial drugs should not occur until after the person in charge of the quality control department has certified that the relevant requirements have been met (two step release procedure: certification and release). The person in charge of the quality control department should take into account the elements listed below, as appropriate.

The scope of the certification can be limited to assuring that the products are in accordance with the authorization of the clinical trial and any subsequent processing carried out by the manufacturer for the purpose of blinding, trial-specific packaging and labelling.

The information in the product specification file should form the basis for assessment of the suitability for certification and release of a particular batch by the person in charge of the quality control department and should therefore be accessible to him or her.

Assessment by the person in charge of the quality control department of each batch for certification prior to release should take account of the required GMP principles and guidelines detailed in the [Good manufacturing practices guide for drug products \(GUI-0001\)](#) and may include as appropriate:

- a) batch records, including control reports, in-process test reports and release reports demonstrating compliance with the product specification file, the order, protocol and randomization code
 - o These records should include all deviations or planned changes, and any consequent additional checks and tests, and should be completed and endorsed by the staff authorized to do so according to the quality system.
- b) production conditions
- c) cleaning records
- d) the qualification status of facilities, validation status of processes and methods
- e) examination of finished packs
- f) the results of any analyses or tests performed after importation, where relevant
- g) stability plan and reports
- h) the source and verification of conditions of storage and shipment
- i) audit reports concerning the quality system of the manufacturer
- j) documents certifying that the manufacturer is authorized to manufacture clinical trial drugs for export (as applicable under national law), by the appropriate authorities in the relevant country



- k) where relevant, regulatory requirements for marketing authorization, good manufacturing practices standards applicable and any official verification of compliance with good manufacturing practice
- l) verification of the supply chain including manufacturing, packaging, labelling and testing sites for the clinical trial drugs
- m) all factors of which the person in charge of the quality control department is aware that are relevant to the quality of the batch

Clinical trial drugs can be manufactured and packaged at different sites under the supervision of a different person in charge of the quality control department. Sharing of responsibilities among the persons in charge of the quality control department in relation to compliance of a batch must be defined, for consistency, in a document formally agreed by all parties.

Where required to support certification, the person in charge of the quality control department has to ensure that the clinical trial drug has been stored and transported under conditions that maintain product quality and supply chain security. Relevant situations may include short expiry date products released prior to final certification from the person in charge of the quality control department or where return of clinical trial drugs to an authorized manufacturer for re-labelling and re-packaging remains a possibility.

Where the manufacturer is delegated by the sponsor to perform the regulatory release in addition to certification by the person in charge of the quality control department, the arrangements should be defined in an agreement between the sponsor and the manufacturer. Relevant clinical trial authorization and amendment information should be available for reference in the product specification file. The manufacturer should ensure the necessary clinical trial authorizations are in place prior to shipping product for use in the trial.

After certification by the person in charge of the quality control department, the clinical trial drugs should be stored and transported under conditions that maintain product quality and supply chain security.

The person in charge of the quality control department is not required to certify re-packaging or re-labelling performed by authorized personnel at a hospital, health centre or clinic that meet the relevant national laws or requirements.

For more guidance on storage and transportation, consult:

- [Guidelines for environmental control of drugs during storage and transportation \(GUI-0069\)](#)



11. Outsourced operations

Activities that are outsourced should be defined, agreed and controlled by written contracts between the contract giver and the party to whom the operations are outsourced. This should be done in accordance with the principles detailed in the [Good manufacturing practices guide for drug products \(GUI-0001\)](#).

12. Complaints

C.02.015, C.02.023

There should be written procedures describing the actions to be taken upon receipt of a complaint at the manufacturing, storage or importation site. All complaints should be documented and assessed to establish if they represent a potential quality defect or other issue. The procedures should ensure that the sponsor is able to assess the complaints to determine if they justify the reporting of a serious breach to the relevant competent authority.

The investigation of quality defect should be performed in accordance with the principles detailed in the [Good manufacturing practices guide for drug products \(GUI-0001\)](#).

When the conclusions of the investigation differ between the manufacturer and the sponsor, results should be discussed, in a timely manner. This should involve the person in charge of the quality control department and those responsible for the relevant clinical trial in order to assess any potential impact on the trial, product development and on subjects.

13. Recalls and returns

13.1 Recalls

C.02.012, C.02.022

Procedures for the recall of clinical trial drugs and documenting such recalls should be in line with applicable GMP principles and guidelines. They should be agreed upon by the sponsor in cooperation with the manufacturer, if they are different. The manufacturer, qualified investigator and the sponsor's representative need to understand their obligations under the retrieval procedure. The procedures for retrieval of clinical trial



drugs should be in accordance with the principles detailed in the [Good manufacturing practices guide for drug products \(GUI-0001\)](#).

To facilitate recall, a detailed inventory of the shipments made by the manufacturer should be maintained.

For additional information on product recall see the [Drug, natural health product and biocide recall guide \(GUI-0039\)](#).

13.2 Returns

C.02.014

Returned clinical trial drugs should be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of returned products should be kept. Relevant records should be maintained for 15 years as per Part C, Division 5 of the *Food and Drug Regulations*.

14. Destruction

C.02.011, C.02.014, C.05.012(3)(e)

The manufacturer or sponsor's representative should destroy clinical trial drugs only with prior written authorization by the sponsor. The arrangement for destruction of clinical trial drugs has to be described in the protocol. Any arrangement between sponsor and manufacturer in this regard should be defined in their technical agreement.

Destruction of unused clinical trial drugs should be carried out only after reconciliation of delivered, used and recovered products and after investigation and satisfactory explanation of any discrepancies upon which the reconciliation has been accepted.

Records of destruction operations should be retained, including a dated certificate of destruction or a receipt for destruction to the sponsor. These documents should clearly identify or allow traceability to the batches and/or patient numbers involved and the actual quantities destroyed.



Appendix A – Glossary

Acronyms and abbreviations

EU: European Union

GMP: Good manufacturing practices

ICH: International Council for Harmonisation

PIC/S: Pharmaceutical Inspection Cooperation/Scheme

Terms

These definitions explain how terms are used in this document. Definitions cited directly from other documents are noted in brackets at the end of the definition. If there is a conflict with a definition in the [Food and Drugs Act \(the Act\)](#) or [Food and Drug Regulations](#) (regulations), the definition in the act or regulations prevails.

Blinding: When 1 or more of the trial parties are kept unaware of the treatment assignment(s). Single-blinding refers to the subject(s) being unaware of the assignment(s). Double-blinding refers to the subject(s), qualified investigator(s), monitor and possibly data analyst(s) being unaware of the assignment(s). In terms of a trial drug, blinding means deliberately disguising the identity of the product as per the instructions of the sponsor. Unblinding is the disclosure of the identity of the blinded products. (*insu (procédure)*)

Campaign production: Manufacturing a series of batches of the same product in sequence in a given period of time and/or maximum number of batches followed by an appropriate (validated) cleaning procedure. (*production consecutive*)

Clinical trial: An investigation of a drug for use in humans that involves human subjects and is intended to:

- discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug
- identify any adverse events in respect of the drug
- study the absorption, distribution, metabolism and excretion of the drug or
- ascertain the safety or efficacy of the drug

(C.05.001, regulations) (*essai clinique*)

Clinical trial drug: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial. This includes a product with a marketing authorization when:



- used or assembled (formulated or packaged) in a way different from the authorized form or
- used for an unauthorized indication or
- used to gain further information about the authorized form

(Médicaments destinés aux essais cliniques)

Comparator product: An investigational or marketed product (for example, active control) or placebo used as a reference in a clinical trial. *(médicament de comparaison)*

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

Investigational product: Refer to the definition for clinical trial drug. *(Médicament expérimental)*

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

Order: An instruction to process, package and/or ship a certain number of units of drug(s). *(commande)*

Person in charge of the quality control department: A person responsible for securing that each batch of bulk process intermediate or drug in dosage form has been manufactured and checked in compliance with the laws in force and in accordance with the specifications and/or requirements of the marketing authorization. This term is equivalent to the EU term “qualified person” and PIC/S term “responsible person”. *(Personne responsable du service du contrôle de la qualité)*

Product specification file: A reference file containing all the information needed to draft the written instructions for processing, packaging, quality control testing, batch release and shipping a trial drug. *(dossier des spécifications)*

Qualified investigator (QI): The person responsible to the sponsor for conducting the clinical trial at a clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located and is:

- a) in the case of a clinical trial respecting a drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional medical or dental association and
- b) in any other case, a physician and a member in good standing of a professional medical association

(C.05.001, regulations) (chercheur qualifié (CQ))



Randomization: The process of assigning trial subjects to treatment or control groups by using the element of chance to reduce bias. (*randomisation*)

Randomization code: A number that identifies the treatment assigned to each subject from the randomization process (*code de randomisation*)

Shipping: The act of packaging and shipping drugs for clinical trials. (Expédition)

Sponsor: An individual, corporate body, institution or organization that conducts a clinical trial. (C.05.001, regulations) (*promoteur*)



Appendix B – References

Legislation – Canada

[Food and Drugs Act](#)

[Food and Drug Regulations](#)

Quality documents

[Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs \(GUI-0119\)](#)

[Drug, natural health product and biocide recall guide \(GUI-0039\)](#)

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

[Guidance document for clinical trial sponsors: Clinical trial applications](#)

[Guidance document: Part C, Division 5 of the Food and Drug Regulations “Drugs for clinical trials involving human subjects” \(GUI-0100\)](#)

[Guidelines for environmental control of drugs during storage and transportation \(GUI-0069\)](#)

[Terminal sterilization processes for pharmaceutical products \(GUI-0074\)](#)

[Validation guidelines for pharmaceutical dosage forms \(GUI-0029\)](#)

International guidance documents

[Guide to good manufacturing practice for medicinal products: Annexes \(PIC/S\)](#)



Appendix C – Regulatory references

Annex 13 to the Good manufacturing practices guide for drugs used in clinical trials: Regulations referenced in this document

Premises

C.02.004

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

- a) permits the operations therein to be performed under clean, sanitary and orderly conditions
- b) permits the effective cleaning of all surfaces therein and
- c) prevents the contamination of the drug and the addition of extraneous material to the drug

Equipment

C.02.005

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

- a) permits the effective cleaning of its surfaces
- b) prevents the contamination of the drug and the addition of extraneous material to the drug and
- c) permits it to function in accordance with its intended use

Personnel

C.02.006

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

Sanitation

C.02.007



- 1) Every person who fabricates or packages/labels a drug shall have a written sanitation program that shall be implemented under the supervision of qualified personnel.
- 2) The sanitation program referred to in subsection (1) shall include:
 - a) cleaning procedures for the premises where the drug is fabricated or packaged/labelled and for the equipment used in the fabrication or packaging/labelling of the drug and
 - b) instructions on the sanitary fabrication and packaging/labelling of drugs and the handling of materials used in the fabrication and packaging/labelling of drugs

Raw material testing

C.02.009

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

C.02.010

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



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

Manufacturing control

C.02.011

- 1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) and importer of a drug shall have written procedures prepared by qualified personnel in respect of the drug to ensure that the drug meets the specifications for that drug.
- 2) Every person required to have written procedures referred to in subsection (1) shall ensure that each lot or batch of the drug is fabricated, packaged/labelled and tested in compliance with those procedures.

C.02.012

- 1) Every fabricator, packager/labeller or 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) The distributor referred to in C.01A.003(b) of a drug that is fabricated, packaged/labelled and tested in Canada by a person who holds an establishment licence that authorizes those activities is not required to comply with the requirements of subsection (2) in respect of that drug.
- 4) If a drug is fabricated or packaged/labelled in an MRA country at a recognized building, the distributor referred to in paragraph C.01A.003(b) or importer of the drug is not required to comply with the requirements of subsection (2) in respect of that activity for that drug if:
 - a) the address of the building is set out in their establishment licence and
 - b) that person retains a copy of the batch certificate for each lot or batch of the drug that they receive

Quality control department

C.02.013

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



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

C.02.014

- 1) No lot or batch of drug shall be made available for sale unless the sale of that lot or batch is approved by the person in charge of the quality control department.
- 2) A drug that is returned to the fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) or importer thereof shall not be made available for further sale unless the sale of that drug is approved by the person in charge of the quality control department.
- 3) No lot or batch of a raw material or of packaging/labelling material shall be used in the fabrication or packaging/labelling of a drug, unless the material is approved for that use by the person in charge of the quality control department.
- 4) No lot or batch of a drug shall be reprocessed without the approval of the person in charge of the quality control department.

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.
- 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.

Packaging material testing

C.02.016

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



Finished product testing

C.02.018

- 1) Each lot or batch of a drug shall, before it is made available for further use in fabrication or for sale, be tested against the specifications for that drug.
- 2) No lot or batch of a drug shall be made available for further use in fabrication or for sale unless it complies with the specifications for that drug.
- 3) The specifications referred to in subsections (1) and (2) shall:
 - a) be in writing
 - b) be approved by the person in charge of the quality control department and
 - c) comply with the act and these regulations

Records

C.02.020

- 1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) and importer shall maintain on their premises in Canada for each drug that they fabricate, package/label, distribute or import:
 - a) 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) adequate evidence of the testing referred to in section C.02.018
- 2) Every distributor referred to in paragraph C.01A.003(b) and importer shall make available on request the results of testing performed on raw materials and packaging/labelling materials for each lot or batch of a drug sold.
- 3) Every fabricator shall maintain on their premises written specifications for all raw materials and adequate evidence of the testing of those raw materials referred to in section C.02.009 and of the test results.
- 4) Every person who packages a drug shall maintain on their premises written specifications for all packaging materials and adequate evidence of the examination or testing of those materials referred to in section C.02.016 and of any test results.
- 5) Every fabricator, packager/labeller and tester shall maintain on their premises in Canada detailed plans and specifications of each building in Canada where they fabricate, package/label or test drugs and a description of the design and construction of those buildings.
- 6) Every fabricator, packager/labeller and tester shall maintain on their premises in Canada personnel records in respect of each person who is employed to supervise the fabrication,



packaging/labelling and testing of drugs, including the person's title, responsibilities, qualifications, experience and training.

C.02.021

- 1) Subject to subsection (2), all records and evidence on the fabrication, packaging/labelling, testing and storage of a drug that are required to be maintained under this Division shall be retained for a period of at least one year after the expiration date on the label of the drug, unless otherwise specified in the person's establishment licence.
- 2) All records and evidence on the testing of raw materials and packaging/labelling materials that are required to be maintained under this Division shall be retained for a period of at least five years after the materials were last used in the fabrication or packaging/labelling of a drug unless otherwise specified in the person's establishment licence.

C.02.022

Every distributor referred to in section C.01A.003, wholesaler and importer of a drug shall retain records of the sale of each lot or batch of the drug, which enable them to recall the lot or batch from the market for a period of at least one year after the expiration date of the lot or batch unless otherwise specified in their establishment licence.

C.02.023

- 1) On receipt of a complaint respecting the quality of a drug, every distributor referred to in paragraph C.01A.003(b), and importer of the drug shall make a record of the complaint and of its investigation and retain the record for a period of at least one year after the expiration date of the lot or batch of the drug, unless otherwise specified in their establishment licence.
- 2) On receipt of any information respecting the quality or hazards of a drug, every distributor referred to in paragraph C.01A.003(b), and importer of the drug shall make a record of the information and retain it for a period of at least one year after the expiration date of the lot or batch of the drug unless otherwise specified in their establishment licence.

Stability

C.02.027

Every distributor referred to in paragraph C.01A.003(b) and importer shall establish the period of time during which each drug in the package in which it is sold comply with the specifications.

Sterile products

C.02.029



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

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

Drugs for clinical trials involving human subjects

C.05.001

The definitions in this section apply to this Division.

"clinical trial" means an investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug.

"drug" means a drug for human use that is to be tested in a clinical trial.

"qualified investigator" means the person responsible to the sponsor for the conduct of the clinical trial at a clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is:

- a) in the case of a clinical trial respecting a drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional medical or dental association and
- b) in any other case, a physician and a member in good standing of a professional medical association

"sponsor" means an individual, corporate body, institution or organization that conducts a clinical trial.

C.05.010

Every sponsor shall ensure that a clinical trial is conducted in accordance with good clinical practices and, without limiting the generality of the foregoing, shall ensure that ... (j) the drug is manufactured, handled and stored in accordance with the applicable good manufacturing practices referred to in Divisions 2 to 4 except sections C.02.019, C.02.025 and C.02.026.

C.05.011



Despite any other provision of these regulations respecting labelling, the sponsor shall ensure that the drug bears a label that sets out the following information in both official languages:

- a) a statement indicating that the drug is an investigational drug to be used only by a qualified investigator
- b) the name, number or identifying mark of the drug
- c) the expiration date of the drug
- d) the recommended storage conditions for the drug
- e) the lot number of the drug
- f) the name and address of the sponsor
- g) the protocol code or identification and
- h) if the drug is a radiopharmaceutical as defined in section C.03.201, the information required by subparagraph C.03.202(1)(b)(vi)

C.05.012

- 3) The sponsor shall maintain complete and accurate records in respect of the use of a drug in a clinical trial, including information in both official languages:
 - e) records respecting the shipment, receipt, disposition, return and destruction of the drug
- 4) The sponsor shall maintain all records referred to in this division for a period of 15 years