



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

## Guidance Document Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines Drugs Used In Clinical Trials

**GUI-0036**

Supersedes:  
June 1, 2004

Date Issued:  
August 7, 2009

Date of Implementation:  
December 1, 2009

***Disclaimer***

*This document does not constitute part of the Food and Drugs Act (Act) or the Food and Drugs Regulations (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. This document is not intended to provide legal advice regarding the interpretation of the Act or Regulations. If a regulated party has questions about their legal obligations or responsibilities under the Act or Regulations, they should seek the advice of legal counsel.*

Ce document est aussi disponible en français.

## Table of Contents

1.0 Preface .....	<a href="#">Page 4</a>
2.0 Principle .....	<a href="#">Page 5</a>
3.0 Glossary .....	<a href="#">Page 6</a>
4.0 Quality Management (C.02.013, C.02.014, C.02.015) .....	<a href="#">Page 7</a>
5.0 Personnel (C.02.006) .....	<a href="#">Page 7</a>
6.0 Premises And Equipment (C.02.004, C.02.005, C.02.007) .....	<a href="#">Page 8</a>
7.0 Documentation .....	<a href="#">Page 8</a>
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) .....	<a href="#">Page 8</a>
7.2 Order (C.02.011) .....	<a href="#">Page 8</a>
7.3 Product Specification File (C.02.009, C.02.014, C.02.016, C.02.018, C.02.020, C.02.027) .....	<a href="#">Page 8</a>
7.4 Manufacturing Formulae and Processing Instructions (C.02.011, C.02.020) .....	<a href="#">Page 9</a>
7.5 Packaging Instructions (C.02.011) .....	<a href="#">Page 9</a>
7.6 Processing, testing and packaging batch records (C.02.020, C.02.021, C.05.012(4)) .....	<a href="#">Page 9</a>
8.0 Production .....	<a href="#">Page 10</a>
8.1 Packaging materials (C.02.011, C.02.016) .....	<a href="#">Page 10</a>
8.2 Manufacturing operations (C.02.004, C.02.005, C.02.011, C.02.029) .....	<a href="#">Page 10</a>
8.3 Principles applicable to comparator product (C.02.011, C.02.018, C.02.027) .....	<a href="#">Page 10</a>
8.4 Blinding operations (C.02.011, C.02.014) .....	<a href="#">Page 11</a>
8.5 Randomisation code (C.02.011, C.02.014, C.02.020) .....	<a href="#">Page 11</a>
8.6 Packaging (C.02.006, C.02.011, C.02.015) .....	<a href="#">Page 11</a>
8.7 Labelling (C.02.011, C.02.016, C.05.011) .....	<a href="#">Page 11</a>
9.0 Quality Control (C.02.011, C.02.014) .....	<a href="#">Page 12</a>
10.0 Release of Batches (C.02.014) .....	<a href="#">Page 13</a>
11.0 Shipping (C.02.006, C.02.011, C.02.012, C.02.015, C.02.022) .....	<a href="#">Page 14</a>
12.0 Complaints (C.02.015, C.02.023) .....	<a href="#">Page 15</a>
13.0 Recalls and Returns .....	<a href="#">Page 15</a>
13.1 Recalls (C.02.012, C.02.022) .....	<a href="#">Page 15</a>
13.2 Returns (C.02.014) .....	<a href="#">Page 15</a>
14.0 Destruction (C.02.011, C.02.014, C.05.012(3)(e)) .....	<a href="#">Page 15</a>

Appendix 1: Comparison of Terms ..... [Page 17](#)

Appendix 2: Comparison of the Structure of this Annex with the Canadian *Food and Drug Regulations* [Page 18](#)

Appendix 3: Canadian *Food and Drug Regulations* Referenced in this Document ..... [Page 20](#)

## 1.0 Preface

Drugs intended for use in clinical trials in Canada are regulated under Division 5 of Part C of the *Food and Drug Regulations*. Section C.05.010(j) requires the sponsor to 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, except for Sections C.02.019, C.02.025 and C.02.026. Sponsors of clinical trials shall ensure that imported drugs are fabricated and packaged/labelled in accordance with these requirements.

This Annex to the current edition of the Canadian “Good Manufacturing Practices (GMP) Guidelines (GUI-0001)” (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>) is intended to provide guidance relevant to the fabrication and packaging/labelling of drugs intended for use in human clinical trials, including the placebo and comparator product. If further clarification is required, reference should be made to the Canadian “GMP Guidelines (GUI-0001)”.

The Health Products and Food Branch Inspectorate (the Inspectorate) has based this Annex on the current Pharmaceutical Inspection Cooperation Scheme’s (PIC/S) version of their Annex 13 “Manufacture of Investigational Medicinal Products” with changes necessary to adapt the text to meet Canadian requirements.

The changes are as follows:

- The name of the Annex was changed.
- Footnotes were added to clarify areas where there are differences in Canadian requirements. When the difference is repeated, the footnote is not repeated.
- The definitions in this document have been compared to definitions listed in Section C.05.001. When these definitions were different from Regulations, we have included in this Annex definitions that appear in the Canadian *Food and Drugs Regulations* and indicated the reference to the Regulations (i.e., C.05.001).
- The definition of “Clinical Trial” was changed to match the definition in Section C.05.001.
- References to the applicable Canadian regulations were added (in italic) for each section of the Annex.
- Some terms that are used in this guide differ from those found in the Canadian *Food and Drug Regulations* and the “GMP Guidelines (GUI-0001)”. Appendix 1 provides a comparison of these terms.
- Section 26 was modified and sections 27-32 and Table 1 were removed in order to be replaced with C.05.011 of the *Food and Drug Regulations*.
- Section 36 and the part of section 12 relevant to retention samples were removed since they do not apply in Canada.
- Section 39, the notes immediately following section 55, and Table 2 were removed since they apply to European (EU) Member States and European Economic Area (EEA) partners only, and not to Canada.
- Appendix 2 provides a comparison of the structure of this Annex with the Canadian *Food and Drug Regulations*.
- Appendix 3 provides the applicable *Food and Drug Regulations*.

The “GMP Guidelines (GUI-0001)” and a link to the *Food and Drug Regulations* can be found on Health Canada’s Compliance and Enforcement website at

<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/index-eng.php>

## 2.0 Principle

Investigational medicinal products <sup>1</sup> are produced in accordance with the principles and the detailed guidelines of the Good Manufacturing Practice for Medicinal Products <sup>2</sup>. Other guidelines <sup>3</sup> should be taken into account where relevant and as appropriate to the stage of development of the product. Procedures need to be flexible to provide for changes as knowledge of the process increases, and appropriate to the stage of development of the product.

In clinical trials there may be added risk to participating subjects compared to patients treated with marketed products. The application of GMP to the manufacture of investigational medicinal products is intended to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture. Equally, it is intended to ensure that there is consistency between batches of the same investigational medicinal product used in the same or different clinical trials, and that changes during the development of an investigational medicinal product are adequately documented and justified.

The production of investigational medicinal products involves added complexity in comparison to marketed products by virtue of the lack of fixed routines, variety of clinical trial designs, consequent packaging designs, the need, often, for randomisation and blinding and increased risk of product cross-contamination and mix up. Furthermore, there may be incomplete knowledge of the potency and toxicity of the product and a lack of full process validation, or, marketed products may be used which have been re-packaged or modified in some way.

These challenges require personnel with a thorough understanding of, and training in, the application of GMP to investigational medicinal products. Co-operation is required with trial sponsors who undertake the ultimate responsibility for all aspects of the clinical trial including the quality of investigational medicinal products.

The increased complexity in manufacturing operations requires a highly effective quality system.

The Annex also includes guidance on ordering, shipping, and returning clinical supplies, which are at the interface with, and complementary to, guidelines on Good Clinical Practice.

### Note

Products other than the test product, placebo or comparator may be supplied to subjects participating in a trial. Such products may be used as support or escape medication for preventative, diagnostic or therapeutic reasons and/or needed to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the protocol to induce a physiological response. These products do not fall within the definition of investigational medicinal products and may be supplied by the sponsor, or the investigator <sup>4</sup>. The sponsor should ensure that they are in accordance with the notification/request for authorisation to conduct the trial and that they are of appropriate quality for the purposes of the trial taking into account the

---

<sup>1</sup> The Canadian term is “Drug” as defined in Section C.05.001.

<sup>2</sup> Canadian “Good Manufacturing (GMP) Guidelines (GUI-0001)”

<sup>3</sup> Health Canada guidelines

<sup>4</sup> The Canadian term is “Qualified Investigator” as defined in Section C.05.001.

source of the materials, whether or not they are the subject of a marketing authorisation and whether they have been repackaged. The advice and involvement of a Qualified Person<sup>5</sup> is recommended in this task.

### 3.0 Glossary

#### **Blinding [(Insu (Procédure d’)]**

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s). In relation to an investigational medicinal product, blinding shall mean the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor. Unblinding shall mean the disclosure of the identity of blinded products.

#### **Clinical trial<sup>6,7</sup> (Essai clinique)**

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.

#### **Comparator product (Médicament de comparaison)**

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

#### **Investigational medicinal product<sup>6,7</sup> (Médicament expérimental)**

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorized indication, or when used to gain further information about the authorised form.

#### **Investigator<sup>6,7</sup> (Chercheur)**

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.

#### **Lot Number (Numéro de lot)**

Means any combination of letters, figures, or both, by which any food or drug can be traced in manufacture and identified in distribution.

---

<sup>5</sup> The Canadian term is “Person in charge of the Quality Control Department”, as described in Section C.02.006.

<sup>6</sup> These terms, or their comparable terms used in Canada (see Appendix 1), are defined in Section C.05.001. The term “Investigator” is comparable to “Qualified Investigator” in Canada.

<sup>7</sup> This definition is taken from Section C.05.001.

**Manufacturer/importer of Investigational Medicinal Products<sup>8</sup> (*Fabricant/importateur de médicaments expérimentaux*)**

In connection with investigational medicinal products, any holder of the authorisation to manufacture/import.

**Order (*Commande*)**

Instruction to process, package and/or ship a certain number of units of investigational medicinal product(s).

**Product Specification File (*Dossier des spécifications*)**

A reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product.

**Randomisation (*Randomisation*)**

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

**Randomisation Code (*Clé de randomisation*)**

A listing in which the treatment assigned to each subject from the randomisation process is identified.

**Shipping (*Expédition*)**

The operation of packaging for shipment and sending of ordered medicinal products for clinical trials.

**Sponsor<sup>6</sup> (*Promoteur*)**

An individual, corporate body, institution or organization that conducts a clinical trial.

**4.0 Quality Management (C.02.013, C.02.014, C.02.015)**

1. The Quality System, designed, set up and verified by the manufacturer or importer, should be described in written procedures available to the sponsor, taking into account the GMP principles and guidelines applicable to investigational medicinal products.
2. The product specifications and manufacturing instructions may be changed during development but full control and traceability of the changes should be maintained.

**5.0 Personnel (C.02.006)**

3. All personnel involved with investigational medicinal products should be appropriately trained in the requirements specific to these types of product.
4. The Qualified Person should in particular be responsible for ensuring that there are systems in place that meet the requirements of this Annex and should therefore have a broad knowledge of pharmaceutical development and clinical trial processes. Guidance for the Qualified Person in connection with the certification of investigational medicinal products is given in sections 38 to 41.

---

<sup>8</sup> This definition is not applicable in Canada. Refer to Appendix 1.

## **6.0 Premises And Equipment (C.02.004, C.02.005, C.02.007)**

5. The toxicity, potency and sensitising potential may not be fully understood for investigational medicinal products and this reinforces the need to minimise 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. Consideration should be given to campaign working where appropriate. Account should be taken of the solubility of the product in decisions about the choice of cleaning solvent.

## **7.0 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)**

6. Specifications (for starting materials<sup>9</sup>, primary packaging materials, intermediate, bulk products and finished products), manufacturing formulae and processing and packaging instructions should be as comprehensive as possible given the current state of knowledge. They should be periodically re-assessed during development and updated as necessary. Each new version should take into account the latest data, current technology used, regulatory and pharmacopoeial requirements, 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.
7. Rationales for changes should be recorded and the consequences of a change on product quality and on any on-going clinical trials should be investigated and documented.

### **7.2 Order (C.02.011)**

8. The order should request the processing and/or packaging of a certain number of units and/or their shipping and be given by or on behalf of the sponsor to the manufacturer. It should be in writing (though it may be transmitted by electronic means), and precise enough to avoid any ambiguity. It should be formally authorised and refer to the Product Specification File and the relevant clinical trial protocol as appropriate.

### **7.3 Product Specification File (C.02.009, C.02.014, C.02.016, C.02.018, C.02.020, C.02.027)**

9. The Product Specification File (see glossary) 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 documents:
  - Specifications and analytical methods for starting materials, packaging materials, intermediate, bulk and finished product
  - Manufacturing methods
  - In-process testing and methods
  - Approved label copy
  - Relevant clinical trial protocols and randomisation codes, as appropriate

---

<sup>9</sup> The Canadian term is “Raw materials” as defined in the “GMP Guidelines (GUI-0001)”.



- Relevant technical agreements with contract givers, as appropriate
- Stability data
- Storage and shipment conditions

The above listing is not intended to be exclusive or exhaustive. The contents will vary depending on the product and stage of development. The information should form the basis for assessment of the suitability for certification and release of a particular batch by the Qualified Person and should therefore be accessible to him/her. Where different manufacturing steps are carried out at different locations under the responsibility of different Qualified Persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.

#### **7.4 Manufacturing Formulae and Processing Instructions (C.02.011, C.02.020)**

10. For every manufacturing operation or supply there should be clear and adequate written instructions and written records. Where an operation is not repetitive it may not be necessary to produce Master Formulae and Processing Instructions. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture once the marketing authorisation is granted.
11. The information in the Product Specification File should be used to produce the detailed written instructions on processing, packaging, quality control testing, storage conditions and shipping.

#### **7.5 Packaging Instructions (C.02.011)**

12. Investigational medicinal products are normally packed 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<sup>10</sup>. Sufficient reconciliations should take place to ensure the correct quantity of each product required has been accounted for at each stage of processing.

#### **7.6 Processing, testing and packaging batch records (C.02.020, C.02.021, C.05.012(4))**

13. Batch records should be kept in sufficient detail for the sequence of operations to be accurately determined. These records should contain any relevant remarks which justify the procedures used and any changes made, enhance knowledge of the product and develop the manufacturing operations.
14. Batch manufacturing records should be retained for at least twenty-five years<sup>11</sup> after the completion or formal discontinuation of the last clinical trial in which the batch was used.

### **8.0 Production**

#### **8.1 Packaging materials (C.02.011, C.02.016)**

---

<sup>10</sup> As per Regulation C.05.010(j), the requirement to maintain samples does not apply in Canada.

<sup>11</sup> The applicable regulation is Section C.05.012 (4).

15. 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)**

16. During development critical parameters should be identified and in-process controls primarily used to control the process. Provisional production parameters and in-process controls may be deduced from prior experience, including that gained from earlier development work. Careful 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.
17. Production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production but premises and equipment are expected to be validated. For sterile products, the validation of sterilising processes should be of the same standard as for products authorised for marketing. Likewise, when required, virus inactivation/removal and that of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived products, by following the scientific principles and techniques defined in the available guidance in this area.
18. Validation of aseptic processes presents special problems when the batch size is small; in these cases the number of units filled may be the maximum number filled in production. If practicable, and otherwise 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 is 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 Principles applicable to comparator product (C.02.011, C.02.018, C.02.027)**

19. If the product is modified, data should be available (e.g., stability, comparative dissolution, bioavailability) to demonstrate that these changes do not significantly alter the original quality characteristics of the product.
20. 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 use-by date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the article 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.

## **8.4 Blinding operations (C.02.011, C.02.014)**

21. 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 the batch numbers of the products before the blinding operation. Rapid identification of product should also be possible in an emergency.

### **8.5 Randomisation code (C.02.011, C.02.014, C.02.020)**

22. Procedures should describe the generation, security, distribution, handling and retention of any randomisation code used for packaging investigational products, and code-break mechanisms. Appropriate records should be maintained.

### **8.6 Packaging (C.02.006, C.02.011, C.02.015)**

23. During packaging of investigational medicinal products, it may be necessary to handle different products on the same packaging line at the same time. The risk of product mix up must be minimised by using appropriate procedures and/or, specialised equipment as appropriate and relevant staff training.
24. Packaging and labelling of investigational medicinal products 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 mis-labelling such as label reconciliation, line clearance, in-process control checks by appropriately trained staff should accordingly be intensified.
25. The packaging must ensure that the investigational medicinal product remains in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.

### **8.7 Labelling<sup>12</sup> (C.02.011, C.02.016, C.05.011)**

26. The requirements for drug product labelling should comply with the Regulations of the country where the clinical trial will be conducted and in Canada, the labels on drug products to be used in clinical trials should comply with Section C.05.011 of the *Food and Drug Regulations*. The following information shall be included on labels in both official languages:

- (a) a statement indicating that the drug is an investigational drug to be used only by a qualified investigator; (Similar wording may be used, such as “for clinical trial use only”.)
- (b) the name, number or identifying mark of the drug;
- (c) the expiration date of the drug; (See below section.)
- (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).

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.

---

<sup>12</sup> The “Labelling” section (sections 26 to 32) is replaced by the Canadian labelling requirements specified in Section C.05.011. Additional guidance is provided.

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.

33. If it becomes necessary to change the expiration date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new expiration date and repeat the batch number. It may be superimposed on the previous expiration date, but, for quality control reasons, not on the original batch number. This operation should be performed at an appropriately authorised manufacturing site. However, when justified, it may be performed at the investigational site by or under the supervision of the clinical trial site pharmacist, or other health care professional in accordance with national regulations and with the sponsor's requirements. Where this is not possible, it may be performed by the clinical trial monitor(s) who should be appropriately trained. The operation should be performed in accordance with GMP principles, specific and standard operating procedures and under contract, if applicable, and should be checked by a second person. This additional labelling should be properly documented in both the trial documentation and in the packaging records.

#### **9.0 Quality Control (C.02.011, C.02.014)**

34. As processes may not be standardised or fully validated, testing takes on more importance in ensuring that each batch meets its specification.
35. Quality control should be performed in accordance with the Product Specification File and in accordance with required information. Verification of the effectiveness of blinding should be performed and recorded.
36. <sup>13</sup>
37. Consideration should be given to retaining samples from each packaging run/trial period until the clinical report has been prepared to enable confirmation of product identity in the event of, and as part of an investigation into inconsistent trial results.

#### **10.0 Release of Batches (C.02.014)**

38. Release of investigational medicinal products (see section 43) should not occur until after the Qualified Person has certified that the relevant requirements <sup>14</sup> have been met. The Qualified Person should take into account the elements listed in section 40 as appropriate.
39. <sup>15</sup>
40. Assessment of each batch for certification prior to release may include as appropriate:

---

<sup>13</sup> As per Section C.05.010(j), the requirement to maintain samples does not apply in Canada.

<sup>14</sup> The applicable regulation is Section C.02.014.

<sup>15</sup> This section was removed since it is only applicable in EU and EEA countries.

- a. batch records, including control reports, in-process test reports and release reports demonstrating compliance with the product specification file, the order, protocol and randomisation code. These records should include all deviations or planned changes, and any consequent additional checks or tests, and should be completed and endorsed by the staff authorised to do so according to the quality system;
- b. production conditions;
- c. the validation status of facilities, processes and methods;
- d. examination of finished packs;
- e. where relevant, the results of any analyses or tests performed after importation;
- f. stability reports;
- g. the source and verification of conditions of storage and shipment;
- h. audit reports concerning the quality system of the manufacturer;
- i. documents certifying that the manufacturer is authorised to manufacture investigational medicinal products or comparators for export by the appropriate authorities in the country of export;
- j. where relevant, regulatory requirements for marketing authorisation, GMP standards applicable and any official verification of GMP compliance;
- k. all other factors of which the Qualified Person is aware that are relevant to the quality of the batch.

The relevance of the above elements is affected by the country of origin of the product, the manufacturer, and the marketed status of the product (with or without a marketing authorisation, in the EU or in a third country) and its phase of development.

The sponsor should ensure that the elements taken into account by the Qualified Person when certifying the batch are consistent with the required information . See also section 44.

41. Where investigational medicinal products are manufactured and packaged at different sites under the supervision of different Qualified Persons, other recommendations should be followed as applicable<sup>16</sup>.
42. Where, permitted in accordance with local regulations, packaging or labelling is carried out at the investigator site by, or under the supervision of a clinical trial pharmacist, or other health care professional as allowed in those regulations, the Qualified Person is not required to certify the activity in question. The sponsor is nevertheless responsible for ensuring that the activity is adequately

---

<sup>16</sup> The applicable regulation is Section C.02.014.

documented and carried out in accordance with the principles of GMP and should seek the advice of the Qualified Person in this regard.

### **11.0 Shipping (C.02.006, C.02.011, C.02.012, C.02.015, C.02.022)**

43. Shipping of investigational products should be conducted according to instructions given by or on behalf of the sponsor in the shipping order.

The transportation and storage conditions should be verified and documented upon arrival of the drug used in clinical trials at the investigator site. The storage conditions must be maintained in accordance with the label indications.<sup>17</sup>

44. Investigational medicinal products should remain under the control of the Sponsor until after completion of a two step release procedure: certification by the Qualified Person; and release following fulfilment of the relevant requirements. The sponsor should ensure that these are consistent with the details actually considered by the Qualified Person. Both releases should be recorded and retained in the relevant trial files held by or on behalf of the sponsor.
45. De-coding arrangements should be available to the appropriate responsible personnel before investigational medicinal products are shipped to the investigator site.
46. A detailed inventory of the shipments made by the manufacturer or importer should be maintained. It should particularly mention the addressees' identification.
47. Transfers of investigational medicinal products from one trial site to another should remain the exception. Such transfers should be covered by standard operating procedures. The product history while outside of the control of the manufacturer, through for example, trial monitoring reports and records of storage conditions at the original trial site should be reviewed as part of the assessment of the product's suitability for transfer and the advice of the Qualified Person should be sought. The product should be returned to the manufacturer, or another authorised manufacturer for re-labelling, if necessary, and certification by a Qualified Person. Records should be retained and full traceability ensured.

### **12.0 Complaints (C.02.015, C.02.023)**

48. The conclusions of any investigation carried out in relation to a complaint which could arise from the quality of the product should be discussed between the manufacturer or importer and the sponsor (if different). This should involve the Qualified Person and those responsible for the relevant clinical trial in order to assess any potential impact on the trial, product development and on subjects.

### **13.0 Recalls and Returns**

---

<sup>17</sup> Further guidance relating to the storage and transportation are detailed in Health Canada's document entitled "Guidelines for Temperature Control of Drug Products during Storage and Transportation (GUI-0069)".

### **13.1 Recalls (C.02.012, C.02.022)**

49. Procedures for retrieving investigational medicinal products and documenting this retrieval should be agreed by the sponsor, in collaboration with the manufacturer or importer where different. The investigator and monitor need to understand their obligations under the retrieval procedure.
50. The Sponsor should ensure that the supplier of any comparator or other medication to be used in a clinical trial has a system for communicating to the Sponsor the need to recall any product supplied.

### **13.2 Returns (C.02.014)**

51. Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in approved written procedures.
52. Returned investigational medicinal products should be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of the returned medicinal products should be kept.

### **14.0 Destruction (C.02.011, C.02.014, C.05.012(3)(e))**

53. The Sponsor is responsible for the destruction of unused and/or returned investigational medicinal products. Investigational medicinal products should therefore not be destroyed without prior written authorisation by the Sponsor<sup>18</sup>.
54. The delivered, used and recovered quantities of product should be recorded, reconciled and verified by or on behalf of the sponsor for each trial site and each trial period. Destruction of unused investigational medicinal products should be carried out for a given trial site or a given trial period only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted. Recording of destruction operations should be carried out in such a manner that all operations may be accounted for. The sponsor should ensure that records are kept.
55. When destruction of investigational medicinal products takes place, a dated certificate of, or receipt for destruction, should be provided to the sponsor. These documents should clearly identify, or allow traceability to, the batches and/or patient numbers involved and the actual quantities destroyed.

---

<sup>18</sup> The applicable regulation is Section C.05.012(3)(e).

**Appendix 1:  
Comparison of Terms**

<b>Terms used in this Annex</b>	<b>Comparable terms commonly used in Canada</b>	<b>Where the Canadian terms are defined/ described</b>
Qualified Person	Person in charge of the Quality Control Department	Section C.02.006, GMP Guidelines (GUI-0001)
Investigational medicinal product	Drug	Section C.05.001
Investigator	Qualified investigator	Section C.05.001
Manufacturer	Fabricator, packager/labeller	Glossary, GMP Guidelines (GUI-0001)
Starting Material	Raw material	Glossary, GMP Guidelines (GUI-0001)



**Appendix 2:**  
**Comparison of the Structure of this Annex with the Canadian *Food and Drug Regulations***

<b>Sections of this Annex</b>		<b>Corresponding Canadian GMP Sections/ Regulations</b>
Quality Management		Quality Control Department C.02.013-15
Personnel		Personnel C.02.006
Premises and Equipment		Premises C.02.004 Equipment C.02.005 Sanitation C.02.007
Documentation	Specifications and instructions	Raw Material Testing C.02.009-10 Manufacturing Control C.02.011 Quality Control Department C.02.015 Packaging Material Testing C.02.016 Finished Product Testing C.02.018 Records C.02.020
	Order	Manufacturing Control C.02.011
	Product Specification File	Raw Material Testing C.02.009 Quality Control Department C.02.014 Packaging Material Testing C.02.016 Finished Product Testing C.02.018 Records C.02.020 Stability C.02.027
	Manufacturing Formulae and Processing Instructions	Manufacturing Control C.02.011 Records C.02.020
	Packaging Instructions	Manufacturing Control C.02.011
	Processing, testing and packaging batch records	Records C.02.020-21 Records C.05.012 (4)
Production	Packaging materials	Manufacturing Control C.02.011 Packaging Material Testing C.02.016
	Manufacturing operations	Premises C.02.004 Equipment C.02.005 Manufacturing Control C.02.011 Sterile Products C.02.029
	Principles applicable to comparator product	Manufacturing Control C.02.011 Finished Product Testing C.02.018 Stability C.02.027
	Blinding operations	Manufacturing Control C.02.011 Quality Control Department C.02.014

	Randomisation code	Manufacturing Control C.02.011 Quality Control Department C.02.014 Records C.02.020
	Packaging	Personnel C.02.006 Manufacturing Control C.02.011 Quality Control Department C.02.015
	Labelling	Manufacturing Control C.02.011 Packaging Material Testing C.02.016 Labelling C.05.011
Quality Control		Manufacturing Control C.02.011 Quality Control Department C.02.014
Release of Batches		Quality Control Department C.02.014
Shipping		Personnel C.02.006 Manufacturing Control C.02.011-12 Quality Control Department C.02.015 Records C.02.022
Complaints		Quality Control Department C.02.015 Records C.02.023
Recalls and Returns	Recalls	Manufacturing Control C.02.012 Records C.02.022
	Returns	Quality Control Department C.02.014
Destruction		Manufacturing Control C.02.011 Quality Control Department C.02.014 Records C.05.012 (3) (e)

## **Appendix 3:** **Canadian Food and Drug Regulations Referenced in this Document**

### **Division 2**

### **Good Manufacturing Practices**

#### **Premises**

##### **C.02.004**

The premises in which a lot or batch of a drug is fabricated or packaged/labelled 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 Director 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 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.

#### **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.

### **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 use of 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 section C.01A.003(b) and importer of a drug shall maintain a system designed 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 paragraph 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 that person's establishment licence; and
- b. that person retains a copy of the batch certificate for each lot or batch of the drug received by that person.

## **Quality Control Department**

### **C.02.013**

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

(2) The quality control department referred to in subsection (1) 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 raw material or of packaging/labelling material shall be used in the fabrication or packaging/labelling of a drug, unless that 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 every complaint on quality that is received respecting and cause corrective action to be taken where necessary.

(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 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.

### **Finished Product Testing**

#### **C.02.018**

(1) Each lot or batch of a drug shall, prior to its availability for sale, be tested against the specifications for that drug.

(2) No lot or batch of a drug shall be available 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 sold

(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 establishing the period of time during which the drug in the container in which it is sold 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 his premises

- (a) the written specifications for the raw material; and
- (b) adequate evidence of the raw materials testing referred to in section C.02.009.

(4) Every person who packages a drug shall maintain on his premises

- (a) the written specifications for the packaging materials; and
- (b) adequate evidence of the packaging material examination or testing referred to in section C.02.016.

(5) Every fabricator shall maintain on their premises in Canada:

- (a) detailed plans and specifications of each building in Canada at which they fabricate, package/label or test; and
- (b) a description of the design and construction of those buildings.

(6) Every fabricator, packager/labeller and tester shall maintain on their premises in Canada details of the personnel employed to supervise the fabrication, packaging/labelling and testing, including each 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.

## **Division 3**

### **Schedule C Drugs**

#### **C.03.202**

(1) Every package containing a radiopharmaceutical, other than a radionuclide generator, shall carry,  
(b) on the outer label

- (vi) the radiation warning symbol required by the *Atomic Energy Control Regulations* and the statement "Caution—Radioactive Material" "Attention—Produit radioactif", (vii) the names and a statement of the amounts of any preservatives or stabilizing agents contained in the drug,

## **Division 5**

### **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

- (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 25 years.