Health Canada Santé Canada

# Guidance document on submission information for biologic drugs (Division 4, Schedule D)

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Canada

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Également disponible en français sous le titre :
Ligne directrice sur les informations à soumettre pour les médicaments biologiques (titre 4, annexe D)

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# 1. OVERVIEW

## 1.1. INTRODUCTION

Division 4 in Part C of the Food and Drug Regulations (FDR) is for regulations that are specific to biologic drugs. This guidance document outlines the regulatory requirements and expectations, including submission data, to support Division 4.

Health Canada published the Regulations Amending Certain Regulations made under the Food and Drugs Act (Agile Licensing) (Agile Regulations) on December 18, 2024, in Canada Gazette, Part II (CGII). The regulatory amendments for biologic drugs, a component of the Agile Regulations, consist of 12 regulations. A new Division 4 (10 regulations) replaces the former Division 4. The other regulations are in Divisions 2 and 8 (2 regulations), instead of in the new Division 4, because expectations about storage and pre-market review of biologic drugs are based in those parts of the FDR, respectively. Key points about the changes:

- The coming into force date is July 1, 2025 for the new Division 4. The coming into force date is December 18, 2024 for the new and revised regulations in Divisions 2 and 8, respectively. Requirements – Division 4 (section 2) and Requirements – Other (section 3) explain the regulations under both coming into force dates.
- The former Division 4 dates from the 1950s and 1960s, so is about 75 years old when the new Division 4 comes into force in 2025. Most of the regulations in the former Division 4 were outdated, overly prescriptive or unnecessarily product-specific. They did not reflect advances in science and technology.
- The new regulations maintain and support the flexible and outcome-based practices that currently and appropriately address biologic drugs. The outcome-based approach better addresses advancements in science and technology. The new Division 4 maintains the original intent behind the former regulations. Modernizing requirements for biologic drugs allows the FDR to align more closely with modern science and current practice.
- This document explains **how** there is no change to current practice.

### 1.1.1. Objective

This guidance document explains the new regulations for biologic drugs in comparison to current practice and to the former Division 4 regulations. This is to help stakeholders transition from the former Division 4 to the new Division 4.

Most of the content in Division 4 relates to requirements that extend throughout the product lifecycle for biologic drugs. As part of the renewal of Division 4:

- the regulation about storage is included in Division 2 instead of in the new Division 4 because it relates to good manufacturing practices **and**

- the regulation about on-site evaluations is included in Division 8 instead of in the new Division 4 because it relates to pre-market review

For currently authorized biologic drugs, there is no expected need for additional filing of information to support the measures outlined in the new regulations. Current practices in Health Canada's regulation of biologic drugs already reflect the expectations set out in the new regulations.

### 1.1.2. Scope

This guidance document applies to drugs listed on Schedule D to the Food and Drugs Act (FDA) (biologic drugs):

- Division 4 in Part C of the FDR sets out regulations that are specific to biologic drugs **and**
- Schedule D in the FDA sets out the biologic drugs to which Division 4 applies

This document is for those who fabricate, package/label, test, store, import, distribute and wholesale biologic drugs.

The content of this document does not intend to cover every conceivable case. Other approaches for complying with data information can be considered with appropriate scientific justification and as new technologies emerge. International guidance, like that of the European Medicines Agency (EMA) or the International Council for Harmonisation (ICH), may be used to provide a rationale if Health Canada does not provide specific guidance.

## 1.2. HOW TO USE THIS DOCUMENT

This guidance document is designed to:

- guide stakeholders through the transition from the former Division 4 to the new Division 4 **and**
- be a reference tool

Like other guidance documents, Health Canada will periodically review and update this document as needed. Sections that are no longer relevant, such as references to the former Division 4, may be removed.

A notice, which explained the proposed regulatory amendments for biologic drugs, was published at the same time the draft Agile Regulations were published in *Canada Gazette*, Part 1 (CGI) on December 17, 2022. The comments and questions received about the draft CGI regulations were used to:

- further revise the regulatory amendments for publication in CGII **and**

- expand the CGI Notice into this guidance document

### 1.3. ACRONYMS AND ABBREVIATIONS

**BRDD:** Biologic and Radiopharmaceutical Drugs Directorate
**CGI:** Canada Gazette, Part I
**CGII:** Canada Gazette, Part II
**DIN:** drug identification number
**Div 4:** Division 4
**FDA:** Food and Drugs Act
**FDR:** Food and Drug Regulations
**GMP:** good manufacturing practices
**NOC:** notice of compliance
**OSE:** on-site evaluation
**ROEB:** Regulatory Operations and Enforcement Branch
**WHO:** World Health Organization
**YBPR:** yearly biologic product report

### 1.4. DEFINITIONS

At the time of writing, the following are the original definitions from the original sources. These definitions apply in this guidance document.

**Biological auxiliary material** (*Matériel biologique auxiliaire*): Raw material from a biological source which is intended to be used as a processing aid in the fabrication of the drug. It may be absent from the drug or may remain as an impurity in the drug at the end of the manufacturing process (e.g., biological additives used to supplement cell culture medium in production fermenter, human antithrombin III used to complex and remove human thrombin).
(Guidance Document - Post-Notice of Compliance (NOC) Changes: Quality Document, Guidance documents in section 4.1.1)

**Biological source material** (*Matériel d'origine biologique*):

> "(a) biological material sourced or derived from humans;
> (b) animals, including insects, or any biological material sourced or derived from them;
> (c) plants or any biological material sourced or derived from them; or
> (d) micro-organisms, including bacteria, viruses, fungi and bacteriophages, or any biological material sourced or derived from them."

(new C.04.001, Division 4, Part C, Food and Drug Regulations in section 4.1.2.2)

**Biological starting material** (*Matériel biologique de départ*): Raw material from a biological source which is intended to be used in the fabrication of a drug and from which the active

ingredient is derived either directly (e.g., plasma derivatives, ascitic fluid, bovine lung, etc.) or indirectly (e.g., cell substrate, host/vector production cells, eggs, viral strains, etc.).
(Guidance Document - Post-Notice of Compliance (NOC) Changes: Quality Document, Guidance documents in section 4.1.1)

**Raw material** *(Matière première)***:** Any substance other than packaging material or an in-process drug that is intended for use in drug manufacture, including substances that appear in the master formula but not in the drug, such as solvents and processing aids.
(Good Manufacturing Practices Guide for Drug Products (GUI-0001), Guidance documents in section 4.1.1)

### 1.5. NOTES ABOUT THIS GUIDANCE DOCUMENT

In this document:

- "DIN holder" refers to the manufacturer who was issued the drug identification number (DIN)
- "sponsor" refers to the:
  - individual, corporate body, institution or organization that conducts a clinical trial as per Division 5
  - manufacturer (holder of a DIN or notice of compliance (NOC)) of a marketed drug product
- "shall" expresses a requirement (such as a regulation that the user is obliged to satisfy in order to comply with the regulatory requirements)
- "should" expresses a recommendation that is advised but not required
- "may" and “can” express an option that is permissible within the limits of the guidance document
- “former” refers to regulations before their coming into force under the Agile Regulations (as in the “former C.04.015” (lot release) before July 1, 2025)
- “new” or “revised” refer to regulations after their coming into force under the Agile Regulations (as in the “new C.04.007” (lot release) on and after July 1, 2025)

For the regulations referenced in this document:

- “subsection” means numbering with numbers in round brackets (such as (1), (2))
- “paragraph” means numbering with lowercase letters in round brackets (such as (a), (b)) that is preceded by numbering with numbers in round brackets (such as (1), (2))
- “subparagraph” means numbering with lowercase Roman numerals in round brackets (such as (i), (ii)) that is preceded by numbering with lowercase letters in round brackets (such as (a), (b))

In the English guidance document, there is a 1 term for “drug”. In the French guidance document, there are 2 terms for “drug”. In English, the terms “drug” and “New Drug Submission” match terminology in the Food and Drugs Act and Regulations, and are also

the terms commonly used. In French, the terms "*drogue*" and "*présentation de drogue nouvelle*" are used to match terminology in the Food and Drugs Act and Regulations; otherwise, the equivalent and more prevalent term "*médicament*" is used.

### 1.6. NOTES ABOUT GUIDANCE DOCUMENTS IN GENERAL

The following text is standard for all Guidance documents.

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. They also provide guidance to Health Canada staff on how mandates and objectives should be met fairly, consistently and effectively.

Guidance documents are administrative, not legal, instruments. This means that flexibility can be applied. However, to be acceptable, alternate approaches to the principles and practices described in this document **may be** acceptable provided they are supported by adequate justification. They should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As always, Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, to help us adequately assess the safety, efficacy and quality of a drug. We are committed to ensuring that such requests are justifiable and that decisions are clearly documented.

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

# 2. REQUIREMENTS – DIVISION 4

## 2.1. GENERAL INFORMATION

The regulations in Division 4 are specific to biologic drugs. Division 4 applies additional requirements to appropriately address the risks associated with biologic drugs.

All regulations in the following divisions in Part C of the Food and Drug Regulations (FDR) also apply, unless specific regulations exempt biologic drugs:

- Divisions 1 and 8: submission requirements
- Division 1A: establishment licensing requirements
- Division 2: good manufacturing practices requirements
- Division 5: clinical trial requirements

### 2.1.1. Changes to the FDR

Changes to the FDR for biologic drugs as a result of the Agile Regulations are to:

- replace the former Division 4 regulations (C.04.001 to C.04.683) with updated Division 4 regulations (C.04.001 to C.04.010)
- add a new regulation in Division 2 (C.02.012.1)
- amend a regulation in Division 8 (C.08.003.1)

Visually, the new Division 4 looks very different from the former Division 4 (numbering, length, drafting style). Operationally, it reflects current practice.

- **Purpose:** The new Division 4, like the former Division 4, contains regulations specific to biologic drugs.
- **Numbers:** The new Division 4 has different numbering than the former Division 4.
    - The new Division 4 has 10 regulations (C.04.001 to C.04.010).
    - The former Division 4 had approximately 194 regulations (C.04.001 to C.04.683).
- **Structure:** The new Division 4 is organized differently than the former Division 4.
    - The new Division 4 is organized by subject.
    - The former Division 4 was organized by a few general topics, then mostly by product.
- **Drafting style:**
    - The 10 regulations in the new Division 4, with the 2 regulations in Divisions 2 and 8, are flexible and outcome-based. They support the flexible and outcome-based practices that currently and appropriately

address biologic drugs (in other words, this is a "catch up" of the regulations to current practice).
    - Most of the regulations in the former Division 4 were prescriptive and product-specific.
- **Miscellaneous:** Other changes were made to update other parts of the FDR with the new Division 4 numbering.

For a detailed comparison of the new Division 4 to current practice and to the former Division 4, refer to Comparison of Division 4 – Former and new in section 5.

## 2.2. C.04.001 – DEFINITIONS

### 2.2.1. Regulation

**C.04.001** The following definitions apply in this Division.

***biological source material*** means
**(a)** biological material sourced or derived from humans;
**(b)** animals, including insects, or any biological material sourced or derived from them;
**(c)** plants or any biological material sourced or derived from them; or
**(d)** micro-organisms, including bacteria, viruses, fungi and bacteriophages, or any biological material sourced or derived from them. (*matériel d'origine biologique*)

***drug*** means a drug that is listed in Schedule D to the Act that is in dosage form or an active ingredient that can be used in the preparation of a drug listed in that Schedule. (*drogue*)

***holder***, in respect of a drug identification number assigned for a drug, means the manufacturer to whom a document setting out the number was issued under subsection C.01.014.2(1). (*titulaire*)

(Refer to Food and Drug Regulations in section 4.1.2.2)

The new C.04.001 replaces the former C.04.001.

### 2.2.2. Explanation in comparison to current practice

There is no change to current practice.

- One definition is the same, 2 are added and 1 is repealed.
- The definition of "drug" for Division 4 remains the same.
- A new general definition for "biological source material" is added (applies to all Division 4 drugs).
- A new definition for drug identification number (DIN) "holder" is added (refers to "manufacturer" to align with Divisions 1 and 8, as it is the manufacturer who applies for and receives the DIN, and files drug submissions).

- The definition of "date of manufacturing" in the former C.04.001 is repealed (not needed because the corresponding product-specific regulations in Division 4 that use the definition are replaced).

For guidance on what is and is not included within the scope of the biological source material definition as it relates to C.04.001 and C.04.004, refer to C.04.004 – Biological source material in section 2.4.

For guidance on labelling biological source material as it relates to C.4.001 and C.04.009(1)(e) and (f), refer to C.04.009, C.04.010 – Labelling, Labelling of prescription drugs in section 2.9.

## 2.3. C.04.002, C.04.003 – PROHIBITIONS ON SALE

### 2.3.1. Regulation

**C.04.002** It is prohibited for a distributor or importer of a drug to sell the drug unless it has been fabricated, packaged/labelled and tested in accordance with this Division.

**C.04.003** It is prohibited for a person to sell a drug that they have fabricated, packaged/labelled or tested unless they have fabricated, packaged/labelled or tested it, as the case may be, in accordance with this Division.

(Refer to Food and Drug Regulations in section 4.1.2.2)

The new C.04.002 and C.04.003 replace the former C.04.001.1.

### 2.3.2. Explanation in comparison to current practice

There is no change to current practice.

The prohibitions support the regulations in Division 4:

- C.04.002 prohibits the sale of biologic drugs and their active ingredients by importers or distributors unless they comply with the regulations in Division 4.
- C.04.003 provides a similar sale prohibition for biologic drugs and their active ingredients that are fabricated, packaged/labelled or tested in Canada by any person (includes a party other than the DIN holder), unless they comply with the regulations in Division 4.

## 2.4. C.04.004 – BIOLOGICAL SOURCE MATERIAL

### 2.4.1. Regulation

**C.04.004 (1)** It is prohibited for a person to use biological source material in the fabrication of a drug unless

**(a)** the biological source material is

**(i)** prepared and stored in a manner that ensures its suitability for use in the fabrication of the drug, and

**(ii)** collected, in the case of material of human or animal origin, under medical or veterinary supervision, as the case may be;

**(b)** the person collects the information that is necessary to allow the tracing of the biological source material; and

**(c)** any human from whom, or animal from which, the biological source material is collected — or any animal that is such material — is free from any disease that would make the material unsuitable for use in the fabrication of the drug.

**(2)** A person who uses biological source material in the fabrication of a drug must ensure that the material meets any specifications for the material that have been provided to the Minister in connection with the drug.

**(3)** A person who uses biological source material in the fabrication of a drug must retain any documents containing the information referred to in paragraph (1)(b) for a period that they determine after taking into account the following factors, but the period must end no earlier than five years after the day on which the biological source material was last used in the fabrication of the drug:

**(a)** the nature of the biological source material;

**(b)** the risks associated with the biological source material;

**(c)** the manner in which the biological source material is used in the fabrication of the drug; and

**(d)** if the fabricated drug is in dosage form, the intended use of the drug.

(Refer to Food and Drug Regulations in section 4.1.2.2)

C.04.004:

- incorporates concepts from the former C.04.016 to C.04.018
- replaces the former C.04.050 to C.04.683 because they are overly prescriptive, product-specific or outdated
- maintains the original intent behind approximately 31 regulations about biological source materials from the former C.04.050 to C.04.683

### 2.4.2. Explanation in comparison to current practice

There is no change to current practice.

C.04.004 is to ensure that biological source materials are suitable for use in fabricating the drug, are collected under medical or veterinary supervision, with recordkeeping to allow for the material to be traced.

For currently authorized biologic drugs, there would be no need to file additional information to support the suitable control of biological source materials. The

regulation of biologic drugs in Canada has always included considerations for the suitability of materials from biologic sources used to fabricate a drug.

The former Division 4 stated that records are to be kept. It did not specify the period of time during which these records must be kept, thus implying that records must be kept indefinitely. C.04.004 clarifies the record retention expectations for biologic drugs.

C.04.004 puts a time limit on an activity that is already performed, which is to retain records for biological source material to support the safety, quality and efficacy of the biologic drug. It applies record retention to tracing biological source material (C.04.004(1)(b)), where a retention period must be determined that cannot be less than 5 years (C.04.004(3)).

### 2.4.3. Details

The following is interpretation on in scope materials as they relate to each of the different regulations for biological source materials.

#### *2.4.3.1. Scope of biological source material in C.04.001, C.04.004 and C.04.009*

The scope of the definition of biological source material in C.04.001 is source materials, starting materials, raw materials and auxiliary materials (refer to Definitions in section 1.4). The definition in regulation is broad on purpose to encompass different and specific contexts for the oversight of biological source materials. The scope of biological source material required for the label in C.04.009 is different from the scope of biological source material for record retention in C.04.004. Record retention requirements for biological source materials apply to source materials, starting materials, raw materials and auxiliary materials used to fabricate a drug. However, the requirement to indicate the species name (animal or human) of a biological source material on the label applies only to the medicinal ingredient that is derived from a human or animal source material.

#### *2.4.3.2. Record retention in C.04.004(3)*

Together, C.04.004(1)(b) and C.04.004(3) support the current practice of traceability through recordkeeping.

- Traceability is a key pillar to the oversight of the quality and safety of biologic drugs. The expectation is that a person who uses biological source material to fabricate a drug shall be able to trace that material to ensure the quality and safety of the drug.
- C.04.004(3) meets Health Canada's outcome-based, flexible, risk-based and future-proofing needs for traceability. This is for traceability of 5 years, and for traceability over 5 years based on criteria. Regulations with an indefinite time limit for traceability, like the former C.04.237 in

the former Division 4, are removed. The expectation for recordkeeping time limits is thus lowered from indefinite to finite by C.04.004(3).
- C.04.004(3) covers traceability for the wide spectrum of biologic drugs now and in the future.

In general, for biological source materials that fall under C.04.001(a) and (b) (human and animals), records of the source material and the starting material are expected. For example, records of the human donor (source) and the human-derived material used as the starting material for manufacture are both expected.

In general, for biological source materials that fall under C.04.001(c) and (d) (plants and microorganisms), it is the biological starting material used to fabricate the drug that is subject to record retention, not the original source of that material. For example, records are expected for the cell bank used to manufacture purified protein product, but not for the original source from which the cell bank was obtained (for example, soil).

The 5-year minimum time limit in C.04.009(3) is chosen on purpose to be consistent with Division 2 and the Good Manufacturing Practices Guide for Drug Products (GUI-0001) (refer to References in section 4.1). There is overlap between materials captured under the new Division 4 regulation and those captured under the record retention regulation in Division 2 for raw materials.

The definition of biological source material in C.04.001 is meant to capture current practices for recordkeeping of biological source materials. For a tree pollen allergenic extract product as an example, record retention is expected for the tree pollen material, but not for the trees themselves. That said, the tree pollen material record should include information necessary to trace the material (for example, date and location of the trees from which the pollen was collected).

A retention period for information would have already been determined for existing biological source materials. There is no requirement to do a new risk assessment to determine the retention period.

#### *2.4.3.3. Medical or veterinary supervision in C.04.004(1)(a)(ii)*

The wording in C.04.004(1)(a)(ii) is broad on purpose to not be prescriptively defined nor restricted. It maintains the wording from the former Division 4, which has been sufficient.

The requirement for medical or veterinary supervision only applies to biological source materials of human or animal origin. If an entomologist, or other profession like a beekeeper, may be more appropriate for insects, this is considered equivalent to veterinary supervision.

#### *2.4.3.4. Specifications in C.04.004(2)*

C.04.004(2) is designed to capture only those biological source materials with specifications. There are several biological source materials for which specifications are established and provided to the Minister by the sponsor. In those cases, the materials must meet those specifications for use in fabricating the drug. For example, viral seed banks used in the manufacture of a vaccine have specifications provided to the Minister in connection with the drug. That said, if a biological source material does not have specifications, then this regulation would not apply.

## 2.5. C.04.005 – PREVENTION OF CONTAMINATION

### 2.5.1. Regulation

**C.04.005 (1)** Every person who fabricates a drug and every person who packages a drug in an immediate container must

**(a)** segregate all work involving infectious agents that require special handling, including spore-bearing pathogenic micro-organisms; and

**(b)** minimize the possibility of contamination of biological source material and drugs at the premises where the person fabricates or packages the drug, including by taking measures to protect against infection any individual who has access to the area where the person fabricates or packages the drug.

**(2)** It is prohibited for a person to conduct laboratory procedures of a diagnostic nature in their premises unless the conduct of those procedures is segregated from the fabrication, packaging/labelling and testing of drugs.

(Refer to Food and Drug Regulations in section 4.1.2.2)

C.04.005(1) and (2):

- are based on the former C.04.013 and C.04.014, respectively
- replace the former C.04.050 to C.04.683 because they are overly prescriptive, product-specific or outdated
- maintain the original intent behind approximately 10 regulations about the prevention of contamination from the former C.04.050 to C.04.683

### 2.5.2. Explanation in comparison to current practice

There is no change to current practice.

The outcome-based regulation is a general framework to minimize the potential for contamination of drugs, active ingredients and biological source material between processes.

- C.04.005(1) adds to the former C.04.013 the explicit oversight for biological source materials and the concept of protecting the drug by minimizing the risk of contamination in transmission chains involving personnel. It is implicit in the former C.04.013.
- C.04.005(2) maintains the same objective as the former C.04.014.

For currently authorized biologic drugs, there is no expected need for additional filing of information to support measures in place to prevent cross-contamination. Current practice in the regulation of biologic drugs in Canada already includes expectations for appropriate segregation between manufacturing steps in cases where cross-contamination with an infectious agent could be of concern.

Infectious agents or the impacts of their propagation during the manufacturing process for a biologic drug (for example, unintended contamination of a cell culture for a recombinant product) may have negative consequences for the quality and safety of the finished product. This is the case even if infectious agents are not directly communicable to humans. All materials of biologic origin should be sourced and controlled appropriately, and appropriate controls should be in place where cross-contamination could reasonably be foreseen.

### 2.5.3. Details

#### *2.5.3.1. Examples for how C.04.005(1) applies to biologic drugs*

C.04.005(1) is a general regulation that replaces specific requirements for specific products. For example, C.04.005(1) addresses a problem posed by the former C.04.071(b). The former C.04.071(b) requires that everyone employed in the manufacture of the Bacille Calmette-Guérin (BCG) vaccine have a chest X-ray for tuberculosis every 6 months. This requirement applies even if they do not have symptoms of, or have not been exposed to, persons infected with tuberculosis.

- Health Canada has used enforcement discretion of C.04.071(b) for years. This is based on the known human health risks of X-ray exposure and the availability of diagnostic blood tests that are suitably sensitive to detect active and latent disease.

C.04.005(1)(b) is designed to minimize the possibility of contaminating biological source material. This regulation supports current practice and:

- applies to new products coming to market
- addresses post-market authorization situations where contamination of biological source material is detected
- requires that appropriate measures be taken to reduce or eliminate that contamination

#### *2.5.3.2. Note for C.04.005(2)*

Segregation is to be from any and all listed activities: fabrication, packaging/labelling and testing of drugs.

## 2.6. C.04.006 – REFERENCE PREPARATIONS

### 2.6.1. Regulation

**C.04.006** Reference preparations that are used to test the purity or potency of a drug must allow for the control of the quality of the drug.

(Refer to Food and Drug Regulations in section 4.1.2.2)

C.04.006:

- replaces the former C.04.050 to C.04.683 because they are overly prescriptive, product-specific or outdated
- maintains the original intent behind approximately 70 regulations about reference preparations from the former C.04.050 to C.04.683

### 2.6.2. Explanation in comparison to current practice

There is no change to current practice.

The regulation clearly outlines the expectation that reference preparations be appropriate for their intended function. Unless there are extenuating circumstances (such as product efficacy failure, observed potency drift), there is no need to file information for existing products other than for reportable changes.

For more information on reportable changes, consult the Guidance Document - Post-Notice of Compliance (NOC) Changes: Quality Document (refer to References in section 4.1).

Sponsors are not expected to see a change from current practice for information or materials to support reference preparations of clinical trial materials as a consequence of C.04.006.

## 2.7. C.04.007 – LOT RELEASE

### 2.7.1. Regulation

**C.04.007 (1)** In this section, ***suitable for sale***, in respect of a lot of a drug, means that the lot has been fabricated, packaged/labelled and tested in accordance with these Regulations and in a manner that is consistent with information provided to the Minister regarding the quality and safety of the drug.

**(2)** The Minister may, for the purpose of assessing whether a lot of a drug in dosage form is suitable for sale, request that the following persons provide the Minister with any information, samples of the drug or its active ingredients, or material to be used to test the samples:

**(a)** a fabricator of the drug;
**(b)** a packager/labeller of the drug;
**(c)** an importer of the drug; or
**(d)** the holder of the drug identification number.

**(3)** It is prohibited for a person who is requested to provide information, samples or material under subsection (2), and any other person whom the Minister notifies of the request, to sell drugs from the lot to which the request relates unless the Minister notifies the person that the lot is suitable for sale.

(Refer to Food and Drug Regulations in section 4.1.2.2)

C.04.007(1) to (3):

- are the equivalent of the former C.04.015
- replace the former C.04.050 to C.04.683 because they are overly prescriptive, product-specific or outdated
- maintain the original intent behind approximately 20 regulations about lot release from the former C.04.050 to C.04.683

### 2.7.2. Explanation in comparison to current practice

There is no change to current practice or to the existing lot release program.

C.04.007(2) provides authority to the Minister to ask for information, samples of the drug or its active ingredients, or material to be used to test the samples. When C.04.007(2) indicates if a request is made for information or samples of a drug lot, C.04.007(3) sets out that the lot cannot be sold until the request is met and the Minister indicates the lot is suitable for sale. This currently takes the form of a lot release decision letter.

Health Canada uses a risk-based, tiered approach to administer the lot release program set out in Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs (refer to References in section 4.1).

C.04.007(1) to (3) support the guidance on lot release. The regulations and guidance continue to provide flexibility by allowing for biologic drugs to be moved between evaluation groups on a case-by-case basis, with each group having different levels of regulatory oversight based on the degree of risk associated with the drug.

For DIN holders of biologic drugs currently on the Canadian market, there is no expected change from current practice for information or materials to support lot release as a consequence of C.04.007. As a risk-based oversight program, lot release activities and the materials required are evaluated periodically to assess if they are still appropriate. Changes in sample requirements or in materials needed to carry out testing would be communicated directly to the DIN holder as an outcome of a periodic review.

For sponsors, there is no expected change from current practice for information or materials to support lot release of clinical trial materials as a consequence of C.04.007.

### 2.7.3. Details

#### *2.7.3.1. Flexibility in C.04.007*

C.04.007 is flexible by design and allows Health Canada to determine the lot release requirements, if any. The regulation does not prevent a risk-based approach and offering additional risk-based flexibilities where appropriate.

Requesting information, samples or materials for testing is at the discretion of the Minister. As such, Health Canada may decide to not solicit information, samples or materials for any given product regulated under Division 4. The discretion also allows flexibilities to accommodate unique challenges posed by some new types of products (for example, products with unique sampling or testing requirements can be addressed through guidance, policy or specified on a per product basis). The regulation does not prevent the alignment of international testing if or when deemed appropriate.

C.04.007 reflects current practice with respect to “fabricator, packager/labeller or importer of the drug, or the holder of the drug identification number”. While the request is most often directed to the DIN holder, this is not always the case.

Health Canada’s guidance on lot release reflects the flexibility of C.04.007.

## 2.8. C.04.008 – PERIODIC QUALITY REPORTING

### 2.8.1. Regulation

**C.04.008** The holder of the drug identification number for a drug in dosage form must, at the request of the Minister, provide the Minister, on an annual basis or at any longer interval specified by the Minister, with information regarding the quality of the drug and its active ingredients, including information regarding the consistency of the fabrication and packaging processes for the drug and the ingredients.

(Refer to Food and Drug Regulations in section 4.1.2.2)

### 2.8.2. Explanation in comparison to current practice

There is a change to current practice, which is increased flexibility.

C.04.008 formalizes Health Canada's current discretionary practice of periodic quality reporting to monitor the state of control and consistency of the manufacturing process for biologic drugs (for example, yearly biologic product reports, or YBPRs). C.04.008 aligns with current practice, which is that the use of periodic quality reporting is discretionary and risk-based (in other words, YBPRs are not mandatory for all biologic drugs at all times). The regulation thus maintains current flexibility, with periodic quality reporting reserved for when the Minister makes such a request.

C.04.008 also introduces the flexibility for the Minister to extend the interval between periodic reports from an annual basis to a longer interval if circumstances warrant.

The regulation aligns with current practice, which is that the use of this type of reporting supports the lot release program with periodic information as necessary. The purpose of C.04.008 is to ask for information when needed, which supports current practice. In principle, the lot release program is a risk-based oversight strategy, for which Health Canada has a responsibility to revisit the current context over time. Periodic quality reporting provides that context to enable a streamlined and less resource-intensive lot release grouping for many products.

Finally, periodic quality reporting supports the life cycle approach to biologic drugs to:

- assess the ongoing safety and quality of products
- verify the consistency of manufacturing processes **and**
- highlight any trends

### 2.8.3. Details

C.04.008 is discretionary and flexible by design. It allows Health Canada to continue the current practice of taking a risk-based approach to requesting information now and in the future.

The default is that periodic quality reporting is not mandatory: it is only when solicited. The reporting, when needed, supports the lot release program with periodic information. The regulation addresses the differences in approach to different biologic drugs (in other words, some have periodic quality reporting and some do not).

The regulation does not prescriptively state specific formats of periodic quality reporting. It is outcome-based for quality information regarding the fabrication, testing and packaging processes for the drug and its ingredients. For example, Health Canada currently accepts information presented in the format of an annual product quality report with additional information included.

While it is recommended to use the template specified in the Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs (refer to References in section 4.1), alternate formats are accepted. The sponsor may submit a report prepared for another competent regulatory authority that has similar information as the periodic quality report. If an alternative is chosen, it is recommended that the sponsor update it with Canadian-specific information.

Note: The term "*rapports périodiques sur la qualité*" (the noun) is in the heading of the French version of C.04.008, while the term "periodic quality reporting" (the act) is in the heading of the English version.

- This is to satisfy legal rules on how to draft bilingually in the Food and Drug Regulations (FDR). Both terms in French and English refer to the act of providing information on a given subject. C.04.008 is drafted consistently with other instances in the FDR of the term "reporting" in English and "*rapports*" in French.
- This does not legally mean that Health Canada is restricted to a single, specific report named "*rapport périodique sur la qualité*" and "periodic quality report" under C.04.008 now or in the future. The flexibility for annual product reports, reports prepared for another competent regulatory authority and YBPRs continues.

## 2.9. C.04.009, C.04.010 – LABELLING, LABELLING OF PRESCRIPTION DRUGS

### 2.9.1. Regulation

**C.04.009 (1)** The principal display panel of both the inner and outer labels of a drug in dosage form must show

**(a)** the drug's brand name, if any;

**(b)** the drug's proper name, if any, which, if there is a brand name, must immediately precede or follow the brand name in type not less than one-half the size of that of the brand name;

**(c)** if there is no proper name, the drug's common name, which, if there is a brand name, must immediately precede or follow the brand name in type not less than one-half the size of that of the brand name;

**(d)** the net quantity of the drug in the immediate container for the purpose of the inner label and the net quantity of the drug in the outer package for the purpose of the outer label;

**(e)** if the drug is sterile, an indication to that effect;

**(f)** if any of the drug's medicinal ingredients are sourced or derived from human biological source material, an indication to that effect; and

**(g)** if any of the drug's medicinal ingredients are sourced or derived from animal biological source material, the animal species from which each of those ingredients is sourced or derived.

**(2)** The inner and outer labels of a drug in dosage form must show on any panel

**(a)** the name of the holder of the drug identification number assigned for the drug;

**(b)** the potency of the drug, if applicable;

**(c)** the recommended dose of the drug;

**(d)** the lot number of the drug;

**(e)** the expiration date of the drug;

**(f)** adequate directions for use of the drug; and
**(g)** any other information that is necessary to prevent injury to human health.

**(3)** Paragraph (2)(f) does not apply if adequate directions for use of the drug must be displayed on the label in accordance with section C.01.004.02 or C.01.004.03.

**(4)** Despite paragraph (2)(g), if another provision of these Regulations requires that information referred to in that paragraph be shown on a particular panel of a label, the information must be shown on that panel.

**(5)** The outer label of a drug in dosage form must show on any panel
**(a)** the address of the holder of the drug identification number assigned for the drug;
**(b)** a quantitative list of any preservatives contained in the drug, by their proper names, or if a preservative has no proper name, by its common name;
**(c)** the approved storage conditions for the drug;
**(d)** any other information that is necessary for the proper storage and handling of the drug, accompanied, as the case may be, by any designated space for the addition of supplementary information in this regard by the person who stores or handles the drug; and
**(e)** in the case of a new drug for extraordinary use in respect of which a notice of compliance has been issued under section C.08.004.01, the following statement, displayed in capital letters and in a legible manner:

"HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR [naming purpose] BASED ON LIMITED CLINICAL TESTING IN HUMANS.

SANTÉ CANADA A AUTORISÉ LA VENTE DE CETTE DROGUE NOUVELLE POUR USAGE EXCEPTIONNEL AUX FINS DE [indication de la fin] EN SE FONDANT SUR DES ESSAIS CLINIQUES RESTREINTS CHEZ L'ÊTRE HUMAIN."

**(6)** The inner label requirements of these Regulations do not apply in respect of a drug in dosage form whose immediate container is too small to accommodate an inner label that meets those requirements if
**(a)** the inner label shows
**(i)** the drug's brand name, if any,
**(ii)** the drug's proper name, if any,
**(iii)** the drug's common name, if there is no proper name,
**(iv)** the drug identification number assigned for that drug, preceded by the expression "Drug Identification Number" or "Drogue : identification numérique", or both, or the abbreviation "DIN",
**(v)** the name of the holder of the drug identification number assigned for the drug,
**(vi)** the net quantity of the drug in the container,
**(vii)** the drug's potency, if applicable, unless the drug contains more than one medicinal ingredient and the drug's brand name is unique for a particular potency of the drug,
**(viii)** the drug's lot number,
**(ix)** the drug's expiration date,
**(x)** the drug's route of administration, and
**(xi)** any other information that is necessary to prevent injury to human health; and
**(b)** the outer label meets the applicable requirements of these Regulations.

**(7)** The expiration date referred to in paragraph (2)(e) and subparagraph (6)(a)(ix) may be omitted from the label of a drug that is to be stockpiled by the following entities for use in emergency situations if the date is communicated by an alternative means to the individuals who administer the drug:

**(a)** the Government of Canada or the government of a province for the use of a department or agency of that government; or
**(b)** a municipal government or an institution of a municipal government.

**C.04.010 (1)** In the case of a drug in dosage form that is a prescription drug, the symbol "Pr" must be shown on
**(a)** the upper left quarter of the principal display panel of both the inner and the outer labels; or
**(b)** if the drug is packaged in a single-dose container, on the upper left quarter of the principal display panel of the outer label.
**(2)** Subsection (1) does not apply to a drug that is
**(a)** sold to a person who holds an establishment licence under Division 1A; or
**(b)** sold by a pharmacist under a prescription or by a practitioner, if its label shows suitable directions for use and meets the requirements set out in section C.01.005.

(Refer to Food and Drug Regulations in section 4.1.2.2)

C.04.009(1) to (7) and C.04.010(1) and (2):

- are the equivalent of the former C.04.019 and C.04.020, respectively
- replace the former C.04.050 to C.04.683 because they are overly prescriptive, product-specific or outdated
- maintain the original intent behind approximately 28 regulations about labelling from the former C.04.050 to C.04.683

### 2.9.2. Explanation in comparison to current practice

There is no change to current practice.

The labelling regulations reflect current practice where the intent is no change for DIN holders. Thus, the labelling regulations come into force at the same time as the rest of the new Division 4.

If there happens to be non-compliance to current practice, then the approach to regulatory compliance is next filing for current products.

### 2.9.3. Details

Most labelling requirements in the new Division 4 have the same wording as in the former Division 4.

The following are explanations for differences in wording between the new Division 4 and the former Division 4. Some differences provide additional transparency on current expectations, as applicable (for example, C.04.009(1)(f) and (g), C.04.009(2)(g)). Other differences are a drafting change in how the regulations are set out in the FDR (for example, C.01.004(5)(c)).

There are no changes to current practice. The order of the following explanations matches the numerical order in C.04.009.

#### *2.9.3.1. The connection between C.01.004(5)(c) and C.04.009 – Exclusion*

The exclusion of biologic drugs from some Division 1 labelling is moved from Division 4 to Division 1, specifically into C.01.004(5)(c).

The former Division 4 had the exclusion:

> **C.04.019** The provisions of section C.01.004 do not apply to a drug as defined in this Division but every package of such drug shall carry

The revised Division 1 has the exclusion.

> **C.01.004 (5)** Subsections (1) to (3) do not apply to a drug that is
> **(c)** listed in Schedule D to the Act.
>
> (Refer to Food and Drug Regulations in section 4.1.2.2)

#### *2.9.3.2. C.04.009(1)(d) – Net quantity*

C.04.009(1)(d) is for the labelling of net quantity:

- For the inner label, the net quantity is for the drug in the immediate container.
- For the outer label, the net quantity is for the drug in the outer package.

The information is important to have on both the inner and outer labels as the net quantity will differ when there are multiple containers within a package.

#### *2.9.3.3. C.04.009(1)(e) – Sterility*

C.04.009(1)(e) is for the labelling of sterility.

The regulation is flexible to allow for the ISO symbol for sterile.

#### *2.9.3.4. C.04.009(1)(f) and (g) – Biological source material*

C.04.009(1)(f) and (g) are for the labelling of biological source material. The labelling is for human or animal biological source material from which the drug's medicinal ingredients are sourced or derived.

The labelling requirement is to indicate human or the species of animal on the principal display panel of the inner and outer labels for drugs containing medicinal ingredients that are:

- a human or animal material **or**
- derived from a human or animal material

The following should be considered when meeting the labelling requirement to indicate the species of animal on the principal display panel of the label:

- The biological or common animal species name is preferred (for example, dog, cat, wasp).
- Scientific adjectives (for example, porcine or bovine) may be acceptable when the animal species is implied and broadly understood.
- A recognized culinary name (for example, pork, beef, egg or milk) may be acceptable when the animal species is implied and broadly understood.
- The scientific species name (for example, *Candida albicans*) may be appropriate when the other names are not available or not appropriate, or when the scientific species name is broadly understood.
- Broad terms (for example, “mammalian” or “animal-derived”) are not acceptable.

In most cases, the term “human” or the animal species is contained in the proper name, common name or medicinal ingredient name. This is sufficient to meet the requirements. Examples are human serum albumin, dog hair extract, wasp venom, purified pork insulin and equine diphtheria antitoxin. The term “autologous” may be acceptable for certain products whose medicinal ingredients are, or are derived from, a patient’s own tissues or cells.

Examples where human or animal species would not be required are:

- virus or viral components fabricated in human or animal cell lines, primary animal cells or eggs
- recombinant proteins fabricated in human or animal cell lines
- mRNA consisting of human or animal sequences fabricated from plasmid DNA or by direct synthesis

#### *2.9.3.5. C.04.009(2)(g) – Safety statements*

C.04.009(2) is for the labelling of other information that is necessary to prevent injury to human health. Health Canada may require certain labelling statements for safety reasons on a case-by-case basis. Statements for safety reasons could cover situations such as:

- identification of dosage forms intended solely for pediatric or adult use
- indications for multi-dose vials where administration of the entire content could cause injury
- drugs that require dilution prior to administration
- differentiation between diluents and active components of a kit (for example, warning on a diluent vial that it is not for direct administration)
- statements related to the presence of specific allergens posing a safety risk

Specific and definitive guidance on how often safety statements are to be put on labels is out of scope of this guidance document. Statements depend on products. A safety statement may be required to be added throughout the life cycle of a product. It is recommended that sponsors consult the relevant guidance documents and discuss with Health Canada about their specific product as necessary.

#### *2.9.3.6. C.04.009(5)(c) and (d) – Storage and handling*

C.04.009(5)(c) and (d) are to address different situations:

- Under C.04.009(5)(c), the manufacturer is to label the approved storage conditions of the drug.
- Under C.04.009(5)(d), the manufacturer is to provide designated space on the label for those storing and handling the drug to record additional storage and handling information as the case may be.

C.04.009(5)(d) is to accommodate for space on the outer label where information may be recorded after packaging and labelling. For example, this addresses situations where a drug carries a label claim that allows the product to be stored under different temperature conditions for different lengths of time. In such cases, the label is to have a designated location for the end user to indicate the necessary information (such as new expiry date or discard time) to ensure the product is not used past its expiry based on different storage conditions.

#### *2.9.3.7. C.04.009(6) – Small containers*

C.04.009(6) is for the labelling of small containers.

Flexibilities on labelling for small containers outlined in Division 1, while not in the former Division 4, have historically also been extended to DIN holders of biologic drugs. Labelling of small containers in C.04.009(6) has been slightly tailored to biologic drugs.

Small container labelling set out in C.04.009(6) is based on current practice and takes into consideration Health Canada's guidance on all labelling for all biologic drugs in small containers.

#### *2.9.3.8. C.04.009(7) – Expiry date exemption on the label of stockpiled drugs*

C.04.009(7) is for an exemption of the expiry date on the label of drugs stockpiled by any level of government (federal, provincial, territorial, municipal) in Canada.

Although it is required that an expiry date be on a drug's label, there are situations involving stockpiles of biologic drugs that may be exempt from this requirement. Under C.04.009(7), there is:

- an exemption to not put an expiry date on the label of a drug that is stockpiled for use in emergency situations
- a requirement that the drug's expiry date be indicated by alternate means to communicate the date to those who administer the drug
    - Stability data are still required and an expiry date must be available.
    - The alternate means of conveying that expiry date can be proposed by the DIN holder and considered by Health Canada.

The expectation is that the alternate means of communication of the expiry date be kept up to date, and be easily accessible by most, if not all, persons. This includes the distribution chain to, and within, the community pharmacy.

- Manufacturers may consider a 24-hour phone number that is accessible for the hearing impaired, a publicly available website, or QR codes as alternate means of communicating expiry dates.
- Individuals who administer the drug is meant to be broad in scope. Those involved in distributing, administering or using the stockpiled drug are to be able to access up-to-date expiration date information in a timely manner. This includes a pharmacist, a pharmacy technician, those preparing the inventory for a public health administration of a vaccine and an individual person who self-administers a drug.

The labelling exemption for the expiry date is limited to the requirement to have expiry dates directly on the outer and inner labels. This exemption is not expected to be widely used. It is foreseen only for biologic drugs that are to be stockpiled for emergency use by Canadian governments, where the need for the drug is sporadic and infrequent.

- The regulation is not for foreign or internationally labelled drugs. These labels do not meet several of the labelling requirements set out in the FDR. Thus, broadening the scope of this clause does not relieve the

current barriers to bring such products to the Canadian market. This regulation is intended for drugs carrying Canadian labels that are stockpiled by Canadian governments only.

#### *2.9.3.9. C.04.010 – Labelling of prescription drugs*

C.04.010(1) is for the labelling of prescription drugs. It applies to manufacturers' labels.

C.04.010(2)(b) is the exemption in prescription drug labelling to address the practice of pharmacy. It is for labels created by pharmacies. Prescription labelling requirements are part of the practice of pharmacy and regulated at the provincial and territorial level. Each province or territory has its own specific requirements and standards around what is expected of pharmacy professionals for the labelling of prescription drugs.

In regulation, Health Canada uses:

- "adequate directions for use" for manufacturer labelling (for example, C.04.009, A.01.015(2))
- "suitable directions for use" for labelling determined by a pharmacist for an individual patient (for example, C.04.010(2)(b), C.01.004(5)(b))

# 3. REQUIREMENTS – OTHER

## 3.1. C.02.012.1 – STORAGE

### 3.1.1. Regulation

**C.02.012.1** Every lot or batch of a drug shall be fabricated, packaged/labelled, tested and stored, including during transportation, in a manner that assures the quality of the drug.

(Refer to Food and Drug Regulations in section 4.1.2.2)

C.02.012.1:

- replaces the former C.04.050 to C.04.683 because they are overly prescriptive, product-specific or outdated
- maintains the original intent behind approximately 17 regulations about storage from the former C.04.050 to C.04.683

### 3.1.2. Explanation in comparison to current practice

There is no change to current practice or expectations.

The regulation makes explicit the understanding that drugs should be prepared, stored and transported in a manner that preserves their quality. Storage includes transportation. The inclusion of "including during transportation" is for greater clarity and certainty.

As part of the renewal of Division 4, the regulation about storage is included in Division 2 as it relates to good manufacturing practices.

For further guidance on assuring the quality of drugs during storage, including during transportation, consult the Guidelines for Environmental Control of Drugs During Storage and Transportation (GUI-0069) (refer to References in section 4.1).

## 3.2. C.08.003.1 – INFORMATION OR MATERIAL OBTAINED FROM SITES FOR THE REVIEW OF DRUG SUBMISSIONS

### 3.2.1. Regulation

**C.08.003.1** In examining a new drug submission, an extraordinary use new drug submission, an abbreviated new drug submission, an abbreviated extraordinary use new drug submission or a

supplement to any of those submissions, the Minister may, for the purpose of assessing the safety and effectiveness of the new drug for which the submission or supplement was filed, examine

**(a)** information or material provided by any person under the Act;

**(b)** information or material obtained from sites at which the new drug or any *active ingredient*, as defined in subsection C.01A.001(1), of the new drug is or is proposed to be *fabricated* or *packaged/labelled* within the meaning of those terms in that subsection, or tested; and

**(c)** information or material obtained directly or indirectly from a *foreign regulatory authority*, as defined in subsection C.10.001(1).

(Refer to Food and Drug Regulations in section 4.1.2.2)

### 3.2.2. Explanation in comparison to current practice

There is no change to current practice or expectations.

In general:

- C.08.003.1 is revised to reflect activities under current practice.
- In line with current practice, C.08.003.1 clarifies the Minister's authority to consider information or material that could be examined on a risk-based, case-by-case basis during Health Canada's assessment of a drug submission. The authority is to flexibly use discretionary activities as optional tools to help ensure product quality and thus product safety.
- C.08.003.1 provides greater transparency for the current practices of potentially considering information or material obtained from sites, information filed under the FDA (for example, Divisions 1, 5 and 8) and information from foreign regulatory partners for assessing drug submissions.
- Health Canada currently applies a risk-based approach when deciding if additional information on the implementation of the manufacturing process in proposed sites is required. This information supports decision-making related to a submission or its supplement for a biologic drug. The regulation provides transparency on the consideration of information obtained directly at, or indirectly from, manufacturing sites in the decision-making process for the market authorization of biologic drugs. This approach allows for the use of flexible, discretionary, risk-based, case-by-case activities that support changes in current practice in the review of drug submissions, now and in the future, as needed.
- An on-site evaluation (OSE) is one tool used to obtain additional information from a manufacturing site. It is a product-specific evaluation that the Biologic and Radiopharmaceutical Drugs Directorate (BRDD) conducts at the site of manufacture of a Schedule D drug (intermediate or finished product). The evaluation assesses how the drug is manufactured, the process, conditions and control of manufacture, and conformity with the information submitted.
- Most of the content in Division 4 relates to requirements that extend throughout the life cycle of biologic drugs. However, OSEs are a point-in-time activity directly related to pre-market review. As a result, the regulation

supporting OSEs is included in Division 8 because OSEs are used to assess the following:

- a new drug submission (NDS)
- an extraordinary use new drug submission (EUNDS)
- an abbreviated new drug submission (ANDS)
- an abbreviated extraordinary use new drug submission (AEUNDS) **or**
- a supplement to any of those submissions

This point-in-time information is for consideration in the context of drug submission review and is distinct from GMP inspections.

- Stakeholders may additionally discuss with BRDD the OSE for their particular product.

## 3.3. EXPIRY DATE

### 3.3.1. Regulation

No regulation is added to Division 4.

The approach is to rely on 5 current regulations (C.01.001(1), C.02.027, C.02.028, C.08.002(2)(f) and C.08.002(2)(g)) to:

- replace the former C.04.050 to C.04.683 because they are overly prescriptive, product-specific or outdated
- maintain the original intent behind approximately 23 regulations about expiry date from the former C.04.050 to C.04.683
- support that the drug shall have an expiry date and that the drug shall be labelled with the expiry date, as is done for pharmaceutical drugs

### 3.3.2. Explanation in comparison to current practice

The 5 current regulations are:

- C.01.001(1): defines "expiration date"
- C.02.027: requires the DIN holder to establish the period that each packaged drug in dosage form and active ingredient will comply with the drug's specifications, which is interpreted to include data in support of the expiry date
- C.02.028: requires the DIN holder to monitor the stability of the packaged drug in dosage form and its active ingredient, which is interpreted to include data in support of the expiry date

- C.08.002(2)(f): requires the manufacturer to submit details of tests that control the potency, purity, stability and safety of the drug, which is interpreted to include data in support of the expiry date
- C.08.002(2)(g): requires the manufacturer to submit information to establish the safety of the new drug, which is interpreted to include information to support shelf-life, which is part of the "conditions of use recommended"

## 3.4. CORRESPONDING REGULATIONS

### 3.4.1. Regulations and explanation

The repeal of the product-specific regulations from the former C.04.050 to C.04.683 is not expected to affect currently marketed biologic drugs. Two other regulations are also repealed in that context, the former C.04.002 and C.04.003.

- The former C.04.002 set out that the former Division 4 does not apply to a drug in oral dosage form that contains microorganisms if the drug is recommended solely for restoring, normalizing or stabilizing intestinal flora.
    - This regulation is no longer needed because such products are covered by the Natural Health Products Regulations (NHPR), which did not exist when the former C.04.002 was included in the former Division 4.
- The former C.04.003 is no longer needed because the corresponding product-specific regulations in the former Division 4 that rely on "date of issue" are replaced.
    - The requirements on "date of issue" are outdated because the temperature ranges are incorrect.

## 3.5. CONSEQUENTIAL AMENDMENTS

### 3.5.1. Explanation

The consequential amendments update regulations that refer to the amended regulations, such as updates to the references to Division 4 numbering.

### 3.5.2. Regulations

Part A:

- A.01.015(2) is about bilingual labelling for directions for use for drugs available for sale without prescription in an open self-selection area.
    - The regulation is updated with new Division 4 numbering, C.04.009(2)(f). This is in case there will be this type of non-prescription biologic drug in the future. The same labelling rule for directions for use

applies to non-biologic drugs (Division 1 through C.01.004(1)(c)(iii)) and biologic drugs (Division 4 through C.04009(2)(f)).

- A.01.048(d) is about the exports and transshipments of drugs.
    - The regulation is updated with new Division 4 numbering, C.04.001 to C.04.006.

Part C:

- Division 1 - C.01.004(5) is about labelling.
    - The regulation excludes Schedule D drugs from some Division 1 labelling.
    - The exclusion, which was in Division 4 (the former C.04.019), is moved to Division 1 (C.01.004(5)(c)).
    - For the explanation that ties C.01.004(5)(b) and C.04.010(2)(b), refer to C.04.010 – Labelling of prescription drugs in section 2.9.3.9.
- Division 2
    - The heading "Quality Control Department" before C.02.013(1) is replaced with the heading "Quality Control".
    - C.02.019(4.1) is about finished product testing. The regulation is updated with new Division 4 numbering, C.04.007(2).
- Division 3 - C.03.206 is about labelling with respect to the exclusion of Schedule C drugs from Division 4 labelling.
    - The regulation is updated with new Division 4 numbering, C.01.005 and C.04.009.
- Division 8
    - C.08.009.04 is about COVID-19 drugs. The regulation is updated with new Division 2 numbering, C.02.012.1.
    - C.08.011.2(2) is about Special Access Program (SAP) release drugs. The regulation is updated with new Division 2 numbering, C.02.012.1.
- Division 10
    - C.10.001(5) is about drugs for an urgent public health need. The regulation is updated with new Division 2 numbering, C.02.012.1.
    - C.10.002(2) is about drugs for an urgent public health need. The regulation is updated with new Division 2 numbering, C.02.012.1.

Regulations Amending the Food and Drug Regulations (Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19):

- 20(e) is about COVID-19 drugs. The regulation is updated with new Division 4 numbering, C.04.004, C.04.005, C.04.007, C.04.009, and C.04.010.

# 4. REFERENCES, CONTACTS

## 4.1. REFERENCES

### 4.1.1. Guidance documents

This guidance document refers to 4 Health Canada guidance documents. Sponsors should refer to the most up-to-date versions of these 4 references.

The documents are listed alphabetically, followed by the regulation to which they are relevant:

- Good manufacturing practices guide for drug products (GUI-0001) for C.04.004
- Guidance document - Post-notice of compliance (NOC) changes: Quality document (refer to Appendix 3) for C.04.004 and C.04.006
- Guidance for sponsors: Lot release program for Schedule D (biologic) drugs for C.04.007 and C.04.008
- Guidelines for environmental control of drugs during storage and transportation (GUI-0069) for C.02.012.1

### 4.1.2. Legal references

#### 4.1.2.1. Food and Drugs Act

Schedule D in the Food and Drugs Act sets out biologic drugs.

#### 4.1.2.2. Food and Drug Regulations

Division 4 in Part C of the Food and Drug Regulations (FDR) sets out regulations that are specific to biologic drugs.

- For the official version of all new and revised regulations explained in this Guidance document (such as Division 4, Division 2, and Division 8), refer to the Food and Drug Regulations.
- For the official version of the regulation **amending** the FDR, refer to Canada Gazette Part II, Date 2024-12-18, Volume 158, Number 26, titled Regulations Amending Certain Regulations Made Under the Food and Drugs Act (Agile Licensing).

## 4.2. CONTACTS

The contact information is correct at the time of writing and may change over time.

### 4.2.1. Drug submissions

Office of Regulatory Affairs (ORA)
Biologic and Radiopharmaceutical Drugs Directorate (BRDD)
Health Products and Food Branch (HPFB)
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100 Eglantine Driveway
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Telephone: 613-957-1722
Teletypewriter (TTY): 1-800-465-7735 (for people who have a hearing or speech impairment)

### 4.2.2. This guidance document

Centre for Policy, Pediatrics and International Collaboration (CPPIC)
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# 5. COMPARISON OF DIVISION 4 – FORMER AND NEW

## 5.1. OVERVIEW COMPARISON OF DIVISION 4 TO CURRENT PRACTICE

Table 1: New Division 4 compared to former Division 4 and to current practice

| Number | A. Div 4 /2/8 | B. Subject | C. Former Div 4 | D. Explanation | E. Change to current practice |
|---|---|---|---|---|---|
| 1. | C.04.001 | Definitions | C.04.001 | A1 **replaces** C1 | No |
| 2. | C.04.002, C.04.003 | Prohibitions on sale | C.04.001.1 | A2 **replaces** C2 | No |
| 3. | C.04.004 | Biological source material | C.04.016 to C.04.018 | A3 incorporates the concepts from, then **replaces**, C3 | No |
| 4. | C.04.004 | Biological source material | approximately 31 regulations about biological source materials from the former C.04.050 to C.04.683 | A3 maintains the original intent of, then **replaces**, C4 | No |
| 5. | C.04.005 | Prevention of contamination | C.04.013 and C.04.014 | A5 is based on, then **replaces**, C5 | No |
| 6. | C.04.005 | Prevention of contamination | approximately 10 regulations about the prevention of contamination from the former C.04.050 to C.04.683 | A5 maintains the original intent of, then **replaces**, C6 | No |
| 7. | C.04.006 | Reference preparations | approximately 70 regulations about reference preparations from the former C.04.050 to C.04.683 | A7 maintains the original intent of, then **replaces**, C7 | No |
| 8. | C.04.007 | Lot release | C.04.015 | A8 is the equivalent of, then **replaces**, C8 | No |
| 9. | C.04.007 | Lot release | approximately 20 regulations about lot release from the former C.04.050 to C.04.683 | A8 maintains the original intent of, then **replaces**, C9 | No |
| 10. | C.04.008 | Periodic quality reporting | None | N/A | Yes - increased flexibility = |

| Number | A. Div 4 /2/8 | B. Subject | C. Former Div 4 | D. Explanation | E. Change to current practice |
|---|---|---|---|---|---|
| | | | | | longer than 1 year |
| 11. | C.04.009, C.04.010 | Labelling, labelling exemption, labelling of prescription drugs | C.04.019 and C.04.020 | A11 is the equivalent of, then **replaces**, C11 | No |
| 12. | C.04.009, C.04.010 | Labelling, labelling exemption, labelling of prescription drugs | approximately 28 regulations about labelling from the former C.04.050 to C.04.683 | A11 maintains the original intent of, then **replaces**, C12 | No |
| 13. | C.02.012.1 | Storage | approximately 17 regulations about storage from the former C.04.050 to C.04.683 | A13 maintains the original intent of, then **replaces**, C13 | No |
| 14. | C.08.003.1 | On-site evaluations | None | N/A | No |
| 15. | Status quo | Expiry date | approximately 23 regulations about expiry date from the former C.04.050 to C.04.683 | The status quo is 5 current regulations - C.01.001(1), C.02.027, C.02.028, C.08.002(2)(f), C.08.002(2)(g).<br><br>A15 maintains the original intent of, then **replaces**, C15 | No |
| 16. | None | Corresponding regulations | 2 regulations | C16 is repealed in the context of the repeal of all product-specific regulations | No |

### 5.2. FORMER DIVISION 4 AS REFERENCE

The current Food and Drug Regulations (FDR) is updated with the Agile Regulations as each part of the Agile Regulations comes into force.

To find the former Division 4 in the previous version of the FDR:

- Search for “Justice Canada”, then “Laws”. Under “Find a title”, search for “Food and Drug Regulations”.

- In the header area, look for “Regulations are current to YYYY-MM-DD and last amended on YYYY-MM-DD. Previous Versions”. Open “Previous Versions” for a list of previous versions of the FDR. Choose any time frame to make available the legislation in force for that selected period.
- Choose the date range of the FDR **before** the coming into force date of the new Division 4, which is 2025-07-01.
- Use Control-F to search for Division 4. Do not use the box for “Search within these regulations”. The correct Division 4 (for drugs, not food) is the one with the heading “Schedule D drugs”.