Health Canada Santé Canada

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

Annex 1 to the Current Edition of the Good Manufacturing Practices Guidelines - Selected Category IV Monograph Drugs

GUI-0066

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Disclaimer
This document does not constitute part of the Food and Drugs Act (Act) or its associated Regulations and in the event of any inconsistency or conflict between that Act or Regulations and this document, the Act or the Regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the Regulations and the applicable administrative policies. 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.

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1.0 Introduction

Although the *Food and Drug Regulations* (http://laws.justice.gc.ca/eng/C.R.C.-c.870/index.html) and their rationale as well as the quality management principles outlined in the "Good Manufacturing Practices (GMP) Guidelines (GUI-0001)" (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php) apply to all drugs, it is recognized that some of the interpretations provided in the "GMP Guidelines (GUI-0001)" may not always be applicable or appropriate in certain situations (e.g., for some personal care products). Therefore, this Annex to the current edition of the "GMP Guidelines (GUI-0001)" was developed by Health Canada in consultation with their stakeholders. It is intended to clarify certain aspects that have relevance to the manufacture of selected Category IV monograph drugs. For more details regarding Category IV monographs, please consult the Therapeutic Products Directorate's guidance documents. For each monograph, the following are specified: ingredients, strengths, indications, directions for use, and warnings.

The guidance included in this Annex, when placed in context with the "GMP Guidelines (GUI-0001)", should facilitate compliance with Part C, Division 2 of the *Food and Drug Regulations*. In order to avoid repetition, only those interpretations that are different from the ones included in the "GMP Guidelines (GUI-0001)" are contained in this Annex. The numbering of each interpretation used in this Annex corresponds to that of the interpretation being modified from the "GMP Guidelines (GUI-0001)". **Therefore, unless otherwise stated in this Annex, all interpretations included in the "GMP Guidelines (GUI-0001)" are applicable to selected Category IV monograph drugs.**

For imported products, the exemptions granted under the scope of the Mutual Recognition Agreement (MRA) are limited to products that are considered drugs/medicinal products in their country of origin. It is the responsibility of the importer to support classification of the product in the country of origin.

The content of this Annex should not be regarded as the only interpretation of Division 2 of the *Food and Drug Regulations* (GMP) nor does it intend to cover every conceivable case. Alternative means of complying with these *Regulations* can be considered with the appropriate scientific justification. Different approaches may be called for as new technologies emerge.

2.0 Purpose

To provide additional interpretive guidance for Part C, Division 2, of the *Food and Drug Regulations* for Category IV monograph drugs. These guidelines are designed to facilitate compliance by the regulated industry and to enhance consistency in the application of the regulatory requirements.

3.0 Scope

The modified interpretations from the "GMP Guidelines (GUI-0001)" contained in this Annex apply to the following non-sterile, over-the-counter (OTC) drugs for which a Drug Identification Number (DIN) is issued based on compliance with a Category IV monograph:

- -Acne Therapies (topical)
- -Antidandruff Products
- -Antiseptic Skin Cleansers
- -Athletes Foot Treatments
- -Medicated Skin Care Products

-Sunburn Protectants
-Throat lozenges

Products regulated by the *Natural Health Product Regulations* (http://laws.justice.gc.ca/eng/SOR-2003-196/index.html) are excluded from the scope of this document.

4.0 Modified Interpretations from the Good Manufacturing Practices Guidelines (GUI-0001)

Personnel
C.02.006

1a. The individual in charge of the quality control department of a fabricator, packager/labeller, and tester; and the individual in charge of the manufacturing department of a fabricator or packager/labeller;

1.1 holds a Canadian university degree or a degree recognized as equivalent by a Canadian university or Canadian accreditation body in a science related to the work being carried out;

1.2 has practical experience in their responsibility area;

1.3 directly controls and personally supervises on site, each working shift during which activities under their control are being conducted; and

1.4 may delegate duties and responsibility (e.g., to cover all shifts) to a person in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a course of study at a university, college or technical institute in a science related to the work being carried out combined with at least two years of relevant practical experience, while remaining accountable for those duties and responsibility.

1b. The individual in charge of the quality control department of an importer, and distributor;

1.1 are qualified by pertinent academic training and experience (possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a course of study at a university, college or technical institute in a science related to the work being carried out combined with at least two years of relevant practical experience); and

1.2 while remaining accountable for those duties and responsibility, can delegate their duties and responsibilities to a person who is qualified by pertinent academic training and experience.

Sanitation
C.02.007

3.1 Cleaning procedures for all primary contact surfaces for manufacturing and filling equipment should consistently result in the absence of any visible product or cleaning agent residues.

The equipment should be kept clean and dry and protected from contamination. For throat lozenges, the level of microbial contamination should be controlled and there should be no objectionable micro-organisms.

3.4 If analytical methods are used to detect residues or contaminants, they have been shown to provide accurate and consistent results.

C.02.008

1.1 Personnel who have access to any area where a drug is exposed during its fabrication or packaging / labelling must undergo health examinations prior to employment.

Raw Material Testing
C.02.009

2. Specifications of active pharmaceutical ingredients (API) are of pharmacopeial or other equivalent standards and are in compliance with the marketing authorization. Specifications of other raw materials may be based on a house standard provided that they are in compliance with the current marketing authorization of the drug.

4. Water used in the formulation of any drug product for which there is a pharmacopeial (Schedule B of the *Food and Drugs Act*) (http://laws.justice.gc.ca/eng/F-27/page-4.html) monograph meets the requirements of the applicable monograph.

   For drugs not appearing in a pharmacopeial (Schedule B of the *Food and Drugs Act*) monograph, water used in the formulation must meet appropriate specifications based on sound physical and chemical principles. In addition, specifications should include requirements for total microbial count, which should not exceed 100 colony forming units (cfu)/ml, and for absence of *Escherichia coli* and *Salmonella* for oral preparations and *Staphylococcus aureus* and *Pseudomonas aeruginosa* for topical preparations.

5. Test methods provide accurate and consistent results.

   6.1 In addition, each container of a lot of an active pharmaceutical ingredient (API) is tested for the identity of its contents using a specifically discriminating identity test.

Manufacturing Control
C.02.011

2. All critical production processes have been shown to produce consistent results and are approved by the person in charge of the quality control department. Demonstration of consistency should include a satisfactory evaluation of completed batch documents, in-process controls, finished product test results, and additional testing as appropriate for at least 3 consecutive batches.

3. A written report recording results and conclusions of the evaluation of critical production processes is prepared, evaluated, approved, and maintained.

4. Changes to production processes, equipment, or materials that may affect product quality and/or process reproducibility are evaluated for suitability prior to implementation following the change control procedure.

9. Provided that changeover procedures are evaluated and approved prior to implementation, similar non-medicinal products may be fabricated or packaged/labelled in areas or with equipment that is also used for the production of pharmaceutical products.

Finished Product Testing
C.02.018

2. All test methods have been shown to provide accurate and consistent results.

Stability Testing
C.02.027

1. The stability of the drug is determined prior to marketing and prior to adoption of significant changes in formulation, fabrication procedures, or packaging materials that may affect the shelf life of the drug. Stability samples should be stored at conditions supportive of the intended label storage conditions.

    1.1 Accelerated stability data and/or data from similar product formulations are considered to be preliminary and supportive information only. The assignment of the expiry date is based on systematic stability studies as described in the "International Conference on Harmonisation (ICH) documents (Q1 A-E)" (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/index-eng.php). Information on accelerated data and data from similar formulations, may support a reduced stability study (reduced number of lots and/or frequency of testing) and is supported by long term testing.

    1.3 For existing chemical entities, one commercial-scale batch of each strength is sampled. The principle of bracketing and matrixing designs may be applied if justified.

    1.7 Analytical test procedures used in stability evaluation have been shown to provide accurate and consistent results. Assays are to be stability-indicating, (e.g., sufficiently specific to detect and quantify degradation products and to distinguish between degraded and non-degraded materials). Limits for individual specified, unspecified, and total degradation products are included.

C.02.028

1.2 A minimum of one batch of every strength of the drug is enrolled in the continuing stability program at all times. The principle of bracketing and matrixing designs may be applied if justified in accordance with the Health Canada document entitled "Stability Testing of Existing Drug Substances and Products" (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/stabt_stabe-eng.php).

2. Minor changes (e.g., addition, deletion, or substitution of a fragrance, flavour, or colour) to the formulations may be acceptable without new stability data, provided that ongoing stability studies are conducted on the revised formulation to demonstrate that the proposed change does not affect the quality of the drug product. These studies may be conducted concurrently with the marketing of the modified product.