Health Canada Santé Canada

COMPENDIUM OF MONOGRAPHS

NATURAL HEALTH PRODUCTS DIRECTORATE

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Canada

FOREWORD

Guidance documents are meant to provide assistance to industry and health care practitioners on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments and therefore allow for flexibility. Alternate approaches to the principles and practices described in this document may be acceptable; licence applicants are invited to discuss these with the Natural Health Products Directorate prior to submitting an application.

As a corollary to the above, it is equally important to note that Health Canada may request information or material, or define conditions not specifically described in this document, in order to enable the Department to adequately assess the safety, efficacy or quality of a health product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the *Natural Health Products Regulations* and relevant sections of other applicable guidance documents.

TABLE OF CONTENTS

INTRODUCTION

The Compendium is a compilation of monographs based on natural health product (NHP) ingredients. The Natural Health Products Directorate (NHPD) developed the *Compendium of Monographs* as a tool for the timely and efficient review of the safety and efficacy of many commonly used NHPs.

The NHPD allows applicants to reference NHPD monographs in support of the safety and efficacy of medicinal ingredients as part of their Product Licence Application (PLA). This process is efficient for both applicants and Health Canada, since there is no need to evaluate the safety and efficacy of NHP ingredients that are already known to be safe and efficacious when used under the conditions specified in the NHPD monographs.

For more information on the product licence application process and the evidence required to support the safety (risk) and efficacy (benefit) of NHPs, please refer to the *Pathway for Licensing Natural Health Products Making Modern Health Claims* and the *Pathway for Licensing Natural Health Products Used as Traditional Medicines*.

The Compendium consists of single ingredient monographs, product monographs and criteria for the combination of monographed ingredients.

For a list of published NHPD Single Ingredient and Product Monographs, see the Natural Health Product Ingredient Database (NHPID).

For acceptable non-medicinal ingredients that can be used in natural health products, see the NHPID.

1.0 ABOUT THE COMPENDIUM

1.1 Compendial Applications

Natural Health Products Regulations

Part 1: PRODUCT LICENCES
Sixty-Day Disposition
Section 6

6. (1) Subject to subsection (2), the Minister shall dispose of an application submitted under section 5 within 60 days after the day on which it is submitted if, in support of the application, the only information submitted by the applicant under paragraph 5(g) is that which is

a. in the case of an application respecting a natural health product that has only one medicinal ingredient, contained in a monograph for that medicinal ingredient in the Compendium; and

b. in the case of an application respecting a natural health product that has more than one medicinal ingredient, contained in a monograph for that combination of medicinal ingredients in the Compendium.

(2) If the Minister requests that additional information or samples be submitted under section 15, the 60-day period referred to in subsection (1) does not include the number of days beginning on the day on which the request is made and ending on the day on which the additional information or samples are received.

(3) For the purposes of this section, the Minister disposes of an application on the earlier of the day on which

a. the licence is issued in accordance with section 7; and

b. the applicant is sent a notice under subsection 9(1).

A compendial application cites NHPD monographs in the Compendium to support the safety and efficacy of medicinal ingredient(s) in a NHP. All other aspects of manufacturing and preparing the product for sale, including good manufacturing practices and labelling, must comply with the *Natural Health Product Regulations* (NHPR). For more information, see the *Quality of Natural Health Products Guide*, the *Labelling* guidance document, the *Good Manufacturing Practices* guidance document and the relevant sections of the *Product Licensing* guidance document.

1.2 Elements of a Monograph

When submitting a compendial application, several items on the PLA form must match the monograph content exactly or fall within its parameters, including the proper name, common name, source material, route of administration, dosage form and recommended dose. The remaining sections of the monograph - use or purpose, directions of use, duration of use and risk information - may use a “statement to the effect of”, unless otherwise stated on the monograph. This allows applicants to alter the

wording, but not the intent, of the monograph elements. Any ‘statement to the effect of’ wording may be evaluated to determine whether it has the same intent as the monograph.

The following are the parameters for the use of a NHPD monograph.

- **Proper name:** The proper name must be chosen from one of the proper name options provided in the monograph.
- **Common name:** The common name must be chosen from one of the common name options provided in the monograph.
- **Source material:** The source material must be chosen from the options provided in the monograph. More than one source material is acceptable, provided that all source materials listed in the PLA form reflect the same dose and/or use or purpose on the referenced monograph.
- **Route of administration:** The route of administration must be chosen from the options provided in the monograph. Please see the Controlled Vocabulary section of the NHPID for a description of the routes of administration.
- **Dosage form:** The dosage form must be chosen from the options provided on the monograph and must reflect the route of administration for the product. The dosage form must be chosen from the list of recognized dosage forms, found in the NHPID under the Controlled Vocabulary section.

  Please note that an NHP in a liposomal formulation is not considered equivalent to an NHP in a non-liposomal formulation. Therefore applicants cannot attest to a monograph for safety and efficacy of an ingredient unless the monograph specifically states that liposomal formulations are acceptable. Products with liposomal formulations must be submitted through the appropriate non-compendial assessment stream with specific evidence to support the liposomal formulation.
- **Recommended use or purpose:** Claims have been identified for each monographed ingredient based on NHPD’s evaluation of the safety and efficacy data. Applicants may choose one or more claims provided in the monograph or create an alternative using a “statement to the effect of”, unless otherwise stated. Applicants must ensure that any conditions surrounding the claim (dose, source material, etc.) are met.
- **Dose:** The total daily dose must be equal to that noted in the monograph, or, when a range is specified, fall within the range indicated in the monograph. The dose indicated on the monograph may be specific to:
  - **Subpopulation:** All monographs are intended for adults, unless otherwise specified.
  - **Method of preparation:** Must be chosen from the list of acceptable methods, if indicated. Furthermore, to make a traditional use claim, the method of preparation must be one that was traditionally used. Please see

the *Pathway for Licensing Natural Health Products Used as Traditional Medicines* guidance document for a list of traditional methods of preparation.

- **Potency:** When a monograph includes potency, it must be included in the PLA, unless otherwise specified.
- **Frequency:** The frequency must be the same as or fall within the range of the frequency on the monograph, when specified. When the monograph specifies a divided dose the frequency must be more than once daily. If no frequency is specified, the applicant may select an appropriate frequency.
- **Directions of use:** Where specified, all directions of use must be included in the PLA. The directions of use may be identical to that on the monograph or may be a "statement to the effect of", unless otherwise stated.

- **Duration of use:** When the monograph includes a duration of use, it must be included on the PLA.
- **Risk information:** All risk information contained in the monograph must be included in the PLA, as applicable. The risk information may be identical to that on the monograph, or may be a "statement to the effect of", unless otherwise stated.
- **Non-medicinal ingredients:** Only non-medicinal ingredients listed in the NHPID may be used with an appropriate excipient purpose. Any applicable restrictions indicated in the database must be met.

  The presence of non-medicinal ingredients without conditions on the List of Prohibited and Restricted Cosmetic Ingredients (the Cosmetic Ingredient Hotlist), indicates that there are potentially significant safety issues with these ingredients. If the hotlist indicates that additional evidence is required for an ingredient or if an ingredient is listed with no specified conditions, it is not permitted in a topical product submitted in the compendial stream. If the hotlist specifies certain conditions for an ingredient, or label requirements, it is the responsibility of the license holder to ensure that the ingredient meets the conditions outlined.

  Requirements for non-medicinal ingredients are outlined in the *Quality of Natural Health Products Guide*, *Pathway for Licensing Natural Health Products Making Modern Health Claims* and *Pathway for Licensing Natural Health Products Used as Traditional Medicines* guidance documents.
- **Storage conditions:** When the monograph includes storage conditions, they must appear on the product label as per Section 87 of the *NHPR*.
- **Specifications:** Note that certain monographs include additional specifications relevant to that ingredient or product. This information should be considered when establishing product specifications.

1.3 References Used in NHPD Monograph Development

The Compendium is comprised of monographs based on information obtained from modern and traditional sources with regard to the safety and/or efficacy associated with the use of NHPs.

Developing the monographs involves considering information gathered from sources such as:

- published compendia such as those of the World Health Organization, European Scientific Cooperative on Phytotherapy, British Herbal Pharmacopoeia, Pharmacopoeia of the People's Republic of China, European Medicines Agency: Committee on Herbal Medicinal Products (HMPC), and the German Commission E;
- articles published in peer-reviewed journals;
- information published in national pharmacopoeias such as the *United States Pharmacopeia*, *British Pharmacopoeia*, *European Pharmacopoeia, Pharmacopée Française*;
- other published expert committee reports such as the Dietary Reference Intakes (1997-2011), and the U.S. Agency for Health Care Research and Quality (ongoing); and
- Health Canada publications such the Therapeutic Products Directorate's *Category IV Monographs* and *Labelling Standards*.

1.4 Revising and Adding Monographs

Monographs are revised periodically. If new information is published or if a safety or efficacy issue is identified, a monograph will be updated accordingly. A notice to affected stakeholders requesting information may be issued when a monograph is revised for safety reasons and a risk has been identified. Regarding any other monograph revisions, product licence holders are expected to align products affected by the revision(s) with the current monographs, as applicable. This can be accomplished by submitting a post licensing change. Please see the *Post Licensing* guidance document for more information on these types of changes and how to submit such changes to the NHPD. Any new PLA's referencing a NHPD monograph will be expected to comply with the current version of the monograph published in the Compendium, found in the NHPID.

The NHPD considers the following when determining which monographs may be developed or revised:

- High proportion of applications in queue with NHPD that contain specific ingredients.
- Changes to safety and/or efficacy profile of an ingredient.
- Amount of safety and/or efficacy data available for a particular ingredient.
- Directorate, Department and/or Government strategic priorities.

- Signals from international associations, agencies and/or regulatory bodies.
- Suggestions from stakeholders.

Suggestions for revisions to currently published monographs and suggestions for ingredients that should be the subject of a monograph and included in the Compendium can be submitted to NHPD at ingredient_support@hc-sc.gc.ca via the *Ingredient Database Issue Form*. The form should include the name of the monograph being amended along with the rationale and supporting scientific data for consideration.

2.0 TYPES OF MONOGRAPHS

2.1 Single Ingredient Monographs

Applicants may reference a single ingredient monograph that supports the safety and efficacy of a NHP as part of their PLA in the compendial stream.

Safety-only monographs address only the safety of the medicinal ingredient. No recommended uses or purposes are associated with these monographs and on their own cannot support the licensing of a product via the compendial stream. The NHPD strives to revise safety-only monographs periodically. When the available body of evidence supports the inclusion of a recommended use or purpose, safety-only monographs will be revised. Applicants cannot reference safety-only monographs in the compendial application stream for single ingredient products; however safety-only monographs, like all monographs, can be used to support the safety of individual ingredients in non-compendial PLA's, provided that the conditions of use on the monographs are met.

2.2 Product Monographs

Product monographs are composed of more than one medicinal ingredient and may outline the conditions of use based on a product category (e.g. antiseptic hand cleansers, diaper rash products, Multi-Vitamin/Mineral Supplements, etc.) and not the ingredient. As such, a single ingredient may appear on several product monographs. Therefore, the conditions of use for that ingredient, such as dose, recommended use or purpose and risk information, will differ depending on the product category.

Upon the coming into force of the *NHPR* and the classification of certain ingredients as NHPs, the NHPD adopted relevant Therapeutic Product Directorate (TPD) *Category IV Monographs* and *Labelling Standards (LS)* into NHPD product monographs, and has incorporated them in the NHPD *Compendium of Monographs*. Work is ongoing to convert all relevant Category IV monographs and LS to compendial monographs.

2.3 Combination of NHPD Pre-cleared Information

Please refer to the Pathway for *Licensing Natural Health Products Making Modern Claims* for more information regarding combining pre-cleared information.

3.0 SPECIFICATIONS

The submission of a signed PLA will be regarded as an attestation acknowledging the licence holder's responsibility to meet the requirements set out in the *NHPR* and associated guidance documents relating to quality and Good Manufacturing Practices.

The *Quality of Natural Health Products Guide* and the *Good Manufacturing Practices* guidance document outline expectations and approaches relating to the quality requirements for NHPs. Furthermore, individual monographs and the NHPID may also include ingredient specific considerations pertinent to the quality of the product.

By submitting a PLA, the applicant is attesting to meeting the general specifications included in the *Quality of Natural Health Products Guide.* If the product specifications fall outside the general specifications provided in the *Quality of Natural Health Products Guide*, the applicant must submit their own product specifications. Any product specifications submitted should be established in accordance with the requirements and principles described in the *Quality of Natural Health Products Guide*. Applicants are responsible for ensuring that all information is documented, maintained, relevant, accurate, and sufficient to support the quality of their NHPs. This documentation could be requested by the NHPD at any time.