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Pathway for Licensing Natural Health Products Making Modern Health Claims

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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.

These 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.

Document Change Log			
Document	Pathway for Licensing Natural Health Products Making Modern Health Claims, Version 1.0	Replaces	Evidence for Safety and Efficacy of Finished Natural Health Products, Version 2.0 Note: this document is also replaced by the following document: Pathway for Licensing Natural Health Products Used as Traditional Medicines, Version 1.0
Date	December 2012	Date	December 2006

Change	Location (section, paragraph)	Nature of and/or Reason for Change
Extensive revisions	There were extensive revisions to the content including the addition of revised appendices, annexes and an extensive reorganization of the document.	The December 2006 document, Evidence for Safety and Efficacy of Finished Natural Health Products, Version 2.0, was revised in order to reflect some of the recommendations of the Natural Health Product Program Advisory Committee which were posted on the Health Canada website under the name Report of the Natural Health Products Program Advisory Committee to the Natural Health Products Program, January 26, 2010. It was also split into two guidance documents.

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1.0 Introduction

This guidance document provides information to help product licence applicants determine the evidence (type and amount of data) to provide as part of a product licence application to support the safety (risk) and efficacy (benefit) of natural health products (NHPs) that make modern¹ health claims.

The intent of this document is to ensure that the levels of evidence are rigorous enough to protect public health and maintain consumer confidence, while providing industry with a clearly defined pathway to bring products to market.

While not specifically included in this guidance document, other options for supporting safety and efficacy may be considered depending on the circumstances of a particular NHP.

The *Natural Health Products Regulations* (NHPR) set out the requirements governing the sale, manufacture, packaging, labelling, importation, distribution and storage of NHPs. The objective of the NHPR is to provide reasonable assurance that products offered for sale in Canada are safe, efficacious and of high quality. Evidence submitted as part of a product licence application must support the requirements set out in section 5, paragraphs (a) to (j) of the NHPR.

1.1 Policy Objective

To provide reasonable assurance that NHPs offered for sale in Canada are safe and effective when used under their recommended conditions of use.

1.2 Policy Statement

The level of evidence (type and amount) that can be provided to support the safety and efficacy of an NHP varies depending on the proposed health claim(s) of the product and the overall risk profile of the product or its ingredients.

1.3 Scope and Application

This guidance document applies to product licence applications for NHPs that make modern health claims. It does not apply to product licence applications for:

- Traditional medicines;
- Homeopathic medicines;
- NHPs attesting to Natural Health Products Directorate (NHPD) Labelling Standards; and

¹ Modern is used to describe natural health products that are not used as traditional medicines

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- NHPs under the 60-day disposition clause (i.e., those citing a monograph from the NHPD's Compendium of Monographs as the sole source of information supporting the safety and efficacy of the product).

For traditional medicines, refer to the *Pathway for Licensing Natural Health Products Used as Traditional Medicines*.

For medicinal ingredients prepared in accordance with homeopathic pharmacy, refer to the *Evidence for Homeopathic Medicines Guidance Document*.

For more information on the 60-day disposition clause, refer to the *Compendium of Monographs Guidance Document*.

1.4 Background

The *Evidence for Safety and Efficacy of Finished Natural Health Products Guidance Document* (December 2006) is replaced by two new guidance documents: the *Pathway for Licensing Natural Health Products Making Modern Health Claims* and the *Pathway for Licensing Natural Health Products Used as Traditional Medicines*.

Looking for other [guidance documents relevant to NHPs?](#)

The current guidance document describes the risk-based levels of evidence for safety and efficacy of NHPs that make modern health claims. The document also includes two annexes:

- *Combination Ingredients* which defines the principles used for assessing multiple-ingredient products; and
- *General Health Claims* which outlines the pathway for using general health claims for NHPs with lower therapeutic impact.

1.5 Definitions

Natural Health Product

An NHP is a substance or a combination of substances described in Schedule 1 of the NHPR, a homeopathic medicine, or a traditional medicine, that is intended to provide a pharmacological activity or other direct effect in:

- diagnosing, treating, mitigating, or preventing a disease, disorder, or abnormal physiological state or its symptoms in humans;
- restoring or correcting organic functions in humans; or
- modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

Schedule 2 of the NHPR sets out substances which do not fall within the meaning of an NHP.

Medicinal Ingredient

A medicinal ingredient is a substance which is set out in Schedule 1 of the NHPR, is biologically active and is included in an NHP for the purposes of:

- diagnosing, treating, mitigating, or preventing a disease, disorder, or abnormal physical state or its symptoms in humans;
- restoring or correcting organic functions in humans; or

- modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

A medicinal ingredient is characterized by its physical form, its chemical attributes, its source, its preparation, as well as its dose and pharmacological action.

Non-medicinal Ingredient

A non-medicinal ingredient is defined as any substance that is added to a product to confer suitable consistency or form to the medicinal ingredients (suitable as per dosage form and route of administration). Non-medicinal ingredients:

- should not exhibit pharmacological effects;
- should not have any effect contradictory to the product's recommended purpose;
- should not exceed the minimum concentration required for the formulation;
- should not adversely affect the bioavailability, pharmacological activity, or safety of the medicinal ingredients; and
- should be safe.

Recommended Conditions of Use

The recommended conditions of use are defined as:

- recommended use or purpose;
- dosage form;
- recommended route of administration;
- recommended dose (including sub-population, amount, dosage unit, frequency, and directions of use);
- recommended duration of use, if any; and
- risk information, including cautions, warnings, contraindications, or known adverse reactions associated with the use of the product or its medicinal ingredients.

Modern Health Claims

Claims based on evidence from a range of sources, including (but not limited to) clinical studies, animal and *in vitro* studies, pharmacopoeias, textbooks, peer-reviewed published articles, and regulatory authority reports.

Traditional Health Claims

Claims based on the sum total of knowledge, skills, and practices based on theories, beliefs, and experiences indigenous to a specific culture, used in the maintenance of health, as well as prevention, diagnosis, improvement, or treatment of physical and mental illness. For a claim to be categorized as "traditional use," it should be founded upon the theories, experiences and beliefs embodying the respective ancient practice of medicine.

2.0 Guidance for implementation

2.1 Roles and Responsibilities

Product licence applicant:

It is the responsibility of the applicant to provide a complete product licence application, including evidence demonstrating that safety (risk) has been established and any risks

sufficiently mitigated; that efficacy (benefit) has been demonstrated; and that quality is supported.

Natural Health Products Directorate:

It is the responsibility of the NHPD to review the information provided as part of the product licence application in order to assess the safety, efficacy and quality of an NHP, to ensure benefits outweigh risks, and to clearly document the product licensing decision.

For further information on roles see the *Management of Product Licence Applications for Natural Health Products*. It explains how applicants can meet with the NHPD prior to submitting a product licence application and communicate with their submission coordinator throughout the application review process.

Did you know that you can meet with staff of the Natural Health Products Directorate before submitting your application if you have questions? For more information, see the [Management of Product Licence Applications for NHPs](#).

2.2 Health Canada Authorization Process

In order to obtain authorization to sell an NHP in Canada, a product licence application must be submitted to Health Canada. As part of this product licence application, evidence supporting the safety and efficacy of the NHP according to its recommended conditions of use must be included.

You may be able to get a product licence quickly by using our pre-cleared information: check out our monographs and labelling standards via the [Natural Health Products Ingredients Database](#)

The purpose of the assessment is to determine whether the evidence supports the safety and efficacy of the product, including whether there is reasonable assurance that benefits of the product outweigh any risk inherent in the product's ingredients or associated use of the product. The assessment of safety (risk) for a product depends on a variety of factors, including the conditions of use and the physical form and pharmacology of each ingredient in the product as well as the product as a whole. The benefit-to-risk profile of a product is always considered prior to a product licensing decision being made (i.e., licence issuance or refusal).

Refer to the [Management of Product Licence Applications for NHPs](#) for more information on the product application and assessment process.

2.3 Risk-Based Approach to Safety and Efficacy

Risks related to safety and efficacy includes potential risks due to:

- An ingredient's physical or chemical form;
- The seriousness of the health claim and the conditions of use implied; and
- The health impact from lower than expected performance of the product.

A risk-based assessment approach is used to categorize evidence recommendations into three levels of risk: low, medium, and high. These levels are proportionate to the standard of evidence necessary to support safety and efficacy of a product.

Figure 1 outlines the decision process for determining the category of safety and efficacy evidence recommended for NHPs making modern health claims.

Low Level of Risk:

This level applies to those products/ingredients that, through their intended use, present a low risk to health. This category includes NHPs with wide safety margins, including 1) NHPs used for treatment, cure, risk reduction or prevention of minor diseases or conditions (including symptoms or risk factors of those conditions), which naturally resolve in a timely manner or for which lower than expected performance of the product should not pose a major risk to the person taking it under the recommended conditions of use (refer to section 2.4.1. for the definition of minor disease/condition claims), 2) NHPs for the treatment of minor symptoms or risk factors of major conditions or the risk reduction of these conditions, and 3) NHPs for general health maintenance, support, or promotion that refer to modification of a biochemical or physiological function of a nutritional nature or imply benefit to a minor disease or health condition.

Medium Level of Risk:

This level applies to those products/ingredients that, through their intended use, present a significant risk to health. This category includes NHPs used for treatment, cure, or prevention of major diseases or health conditions which are not naturally resolved within a timely manner or have undesirable effects that may persist or worsen if proper care is not pursued in a timely manner (refer to section 2.4.1. for the definition of major disease/condition claims). It also includes NHPs for the treatment of risk factors of serious conditions or the risk reduction of these conditions.

Did you know that you can meet with staff of the Natural Health Products Directorate before submitting your application if you have questions? For more information, see the [Management of Product Licence Applications for NHPs](#).

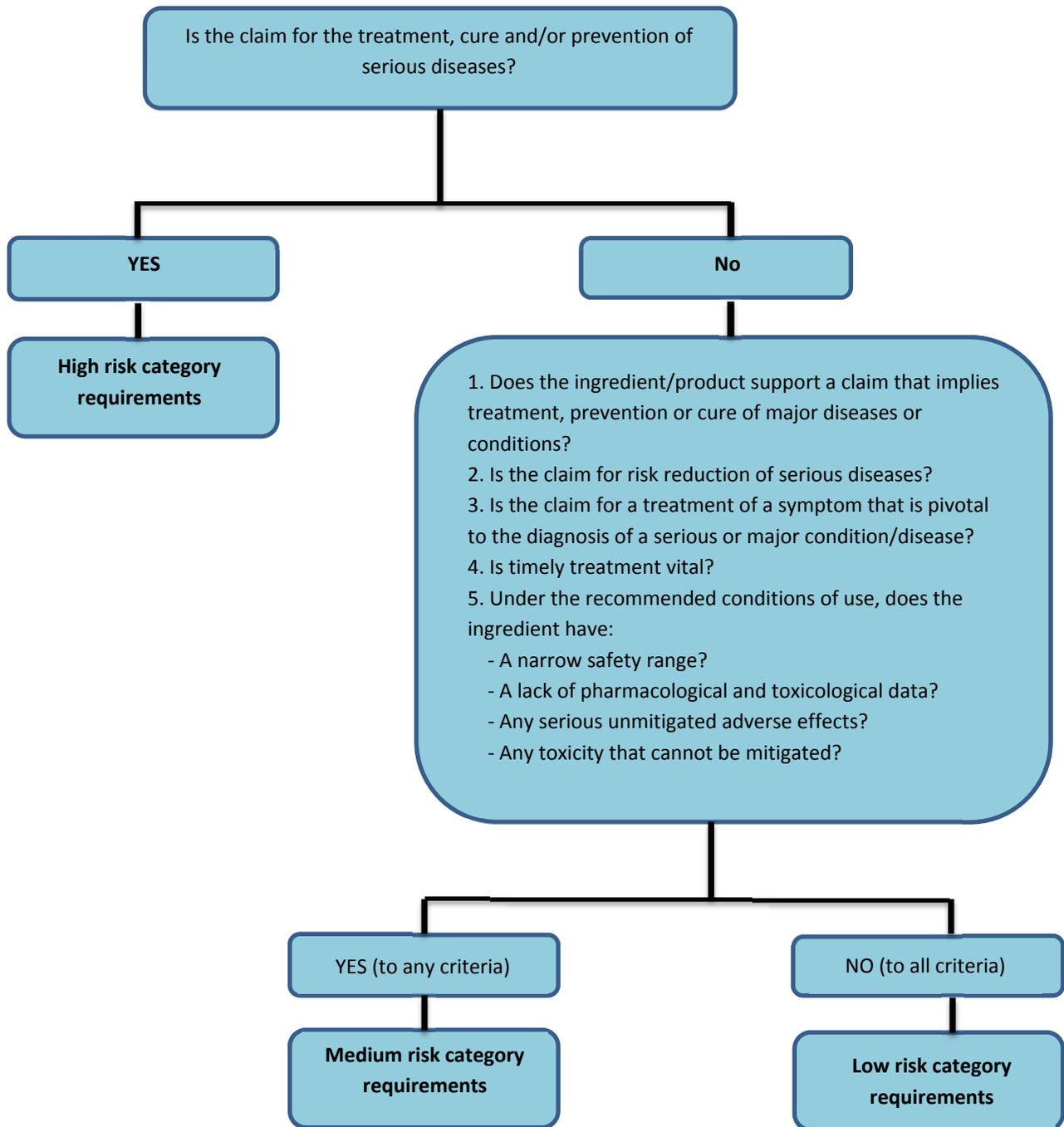
High Level of Risk:

This level applies to those products/ingredients that, through their intended use, present a serious health risk. This category includes NHPs with the narrowest safety margin and effective dose range, as well as those used for treatment, cure, and prevention of serious diseases that require supervision by a health care practitioner, or are debilitating or potentially life threatening without effective treatment (refer to section 2.4.1. for the definition of serious disease/condition claims). High level of risk includes, but is not limited to, schedule A disease/conditions.

At any level of risk, additional evidence may be necessary to substantiate safety and efficacy for:

- Vulnerable sub-populations (e.g., children, pregnant and breastfeeding women, elderly);
- Any known interaction among ingredients;
- Any known interaction with any other product/medication; and/or
- Any indication that the product/ingredient(s) may alter diagnostic testing.

Figure 1: Risk-Based Approach for Determining Safety and Efficacy Evidence for NHPs Making Modern Health Claims



Note: This decision process should be followed for each medicinal ingredient individually, for each claim individually, and for the product as a whole. Based on identified safety concerns for any ingredient, the evidence recommendations may be elevated to a higher category.

2.4 Types of Health Claims

A health claim is a statement that indicates the intended beneficial effect of a product when used in accordance with its recommended conditions of use. The term “recommended use or purpose” is often used interchangeably with “health claim” or “indications for use.”

2.4.1 Claim by Health Condition

NHP claims can be categorized into three main categories based on the characteristics of the health condition:

- **Serious disease/condition claims** are for products indicating treatment, prevention or cure of diseases/conditions that require supervision by a health care practitioner, or are debilitating or potentially life threatening without effective treatment. Treatment is vital to mitigate the health impact.
- **Major disease/condition claims** are for products indicating treatment, prevention, or cure of diseases/conditions that are not naturally resolved within a timely manner or have potentially undesirable effects that may worsen or persist if proper treatment or care is not pursued in a timely manner.
- **Minor disease/condition claims** are for products indicating treatment, prevention, risk reduction, or cure of diseases/conditions or symptoms that are expected to naturally resolve within a timely manner or for which lower than expected performance of the product should not pose a major risk to the person taking it under the recommended conditions of use.

Refer to Appendix A for examples of health claims by health condition.

2.4.2 Claim by Health Effect

Health claims can be further classified as those intended to help diagnose, treat or prevent a health condition or symptom, those intended to reduce the risk of a health condition or symptom, or those intended to have a more general health-related function:

- **Diagnostic claims** relate to the diagnosis of a disease, disorder, or abnormal physical state or its symptoms in humans (e.g., indicated for the detection of glucose intolerance in the diagnosis of diabetes mellitus).
- **Treatment claims** relate to the treatment or partial treatment and mitigation of a disease, disorder, or abnormal physical state or its symptoms (e.g., symptomatic relief claims) in humans.
- **Cure claims** describe a therapeutic effect that results in the elimination of a disease, disorder, or abnormal physical state in humans, either permanently or for a significant length of time.
- **Risk reduction claims** are based on significantly altering a major risk factor(s) for a disease or health-related condition. Diseases have multiple risk factors and altering one of these risk factors may or may not have a beneficial effect in preventing the health condition. The presentation of risk reduction claims should ensure that consumers do not interpret them as prevention claims. This can be accomplished, for example, by use of appropriate language and reference to other risk factors.
- **Prevention claims** relate to interventions which are proven to significantly reduce the incidence of the disease.

- **General health maintenance, support and promotion claims** describe the effect of a medicinal ingredient on restoration, correction, or modification of a structure or physiological function in the human body in a manner that maintains, supports or promotes health. Health function claims can vary from health maintenance (e.g., maintains healthy gums) to treatment of the symptoms or risk factors of a disease or condition (e.g., reduces plaque build-up along the gum line).
- **Antioxidant claims** are for products with at least one medicinal ingredient that has antioxidant properties. Antioxidant claims should be worded as general health support claims when the medicinal ingredient is an essential nutrient (e.g., “provides antioxidant(s) for the maintenance of good health”) or as “source of” claims for other types of antioxidant ingredients (e.g., “source of antioxidants”). If a more specific antioxidant claim is desired, the claim will be evaluated according to the conditions/diseases specified or implied within the claim.

A wide range of evidence can be used to support the safety and efficacy of an NHP – use the flow chart in Figure 1 to find the risk level of your product.

2.4.3 General Health Claims

Products with general health claims include those that have low therapeutic impact and are therefore subject to the appropriate evidence requirements.

Annex I outlines a regulatory pathway for NHPs with general health claims. These claims can be used provided that the health and safety of Canadians would not be at risk; this is consistent with a risk-based product approach where health claims are indexed against the level of evidence provided to support the safe use of the products. For more information on general health claims, see Annex I.

2.5 Safety Evidence Recommendations

All products should be safe under their recommended conditions of use. Safety evidence recommendations are based on the identified risks, including but not limited to:

- Severity and seriousness of adverse effects;
- Probability or frequency of adverse effects;
- Severity and seriousness of the disease or condition for which the product is indicated for use;
- Health impact associated with a lower than expected performance of the product;
- Use by potentially vulnerable sub-populations (e.g., infants, children, pregnant and breastfeeding women, elderly); and
- Inherent risks of the medicinal ingredients in the product.

When necessary, safety evidence may also need to support:

- Chemistry and manufacturing information;
- Characterization of the disease implicated in the recommended use or purpose;
- Characterization of the risk factors associated with the disease implicated in the recommended use or purpose;
- Assessment of the potential for interactions;
- An independent causality assessment of adverse reactions;
- A description of the post-market surveillance program (for active surveillance data);

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- Consumer research to support labelling; and/or
- A detailed benefit-to-risk assessment.

For additional information see the guidance document [Schedule A - Section 3 to the Food and Drugs Act](#)

Previous marketing data including summaries of adverse reaction reports and precautionary labelling may be submitted to support the safety of products but will not be accepted as the sole piece of evidence to support safety.

Only safety risks that can be mitigated by advisory information such as warning statements or contraindications for mild to moderately harmful outcomes are acceptable for licensed NHPs. Serious or severe outcomes that only occur in a very limited and specific population **and** which can be clearly contraindicated on the product licence application form and product label are the exception to this rule. All other risks should be mitigated by appropriate conditions of use. For instance, risk mitigation strategies may include:

Did you know that demonstrated food use of a medicinal ingredient can support the safety of that ingredient?

- Using a different method of preparation of the ingredients (e.g., choice of extraction solvent);
- Using an appropriate route of administration;
- Specifying a dose regimen;
- Qualifying health conditions with terms such as “mild,” “transient,” or “temporary” (to reflect the supporting evidence);
- Using more specific claims to more closely reflect evidence;
- Limiting to a sub-population who will benefit;
- Excluding vulnerable persons from the sub-population;
- Using clear directions of use so that the product can be used in a safe way;
- Not including ingredients with a lack of evidence for safety; and
- Limiting the amount of time that a product may be taken (including a specific duration of use).

As a general rule, risk statements should be based on human evidence or established risks and are necessary when the awareness of these risks is required to help consumers make an informed choice. Additionally, advisory information should be based on moderately intolerable or unexpected adverse reactions and not on mild transient reactions (e.g., nausea). Evidence of risk in animals can contribute to understanding the mechanism of action, but does not commonly form the basis for including a risk statement when non-corroborative human evidence is submitted. Risk statements based on animal evidence may be necessary when the risks are serious.

Within any risk category, the evidence may be sufficient to support both safety and efficacy when it is appropriate for the claim and when it fully reflects the product’s recommended conditions of use.

For the low and medium categories, methodologically weak safety evidence should be supplemented to demonstrate consistency in results and plausibility.

For the high risk category, product specific evidence is recommended. Additionally, the evidence package should include a complete critical summary reflecting the totality of evidence and should usually reflect more than one type of evidence.

The minimum safety and efficacy evidence for each risk category – high, medium, low – is outlined in Table 1.

2.5.1 Safety Evidence Recommendations for Non-Medicinal Ingredients

It is important to note that non-medicinal ingredients listed in the Natural Health Products Ingredient Database (NHPID) have not necessarily been reviewed for safety or suitability in NHPs. Additional information may be requested to support the safety or nature of any non-medicinal ingredient. Information to support the recommended conditions of use for all non-medicinal ingredients should be available upon request, such as quantity, purpose in formulation, alternative formulations and specifications, identity information, safety information or other manufacturing information.

When evidence to support safety is requested, it should reflect the daily dose and purpose of the non-medicinal ingredient, should be appropriate to the route of administration, and should consider exposure. Non-medicinal ingredients should not be indiscriminately included within a product's formulation. The safety requirements for non-medicinal ingredients generally mirror those of medicinal ingredients. However, when risk or uncertainty is identified, additional evidence may be requested to help characterize the risk.

Manufacturers may add substances to their medicinal ingredients to aid stability or manufacturing processes. If these remain in significant quantities in the finished NHP (e.g., including any quantity that still provides a technical effect), they must be declared as non-medicinal ingredients on the product licence application form and label. It may be necessary to communicate with the manufacturer directly in order to identify these types of ingredients.

The individual components of mixtures should be listed separately except when the mixture has a common name in the NHPID (exceptions may be made when the NHPID does not adequately describe the components of the mixture) or the mixture is a proprietary blend of flavours that may be qualitatively described (e.g., artificial strawberry kiwi flavour).

Did you know that you can provide evidence to support non-medicinal ingredients that are not present in the Natural Health Products Ingredient Database with the [NHPID Issue Form](#)?

2.6 Efficacy Evidence Recommendations

All products must have at least one health claim. Efficacy evidence should support the reasonable association of the medicinal ingredient(s) with the health claim(s) and demonstrate that therapeutic efficacy of the product will be supported by at least one medicinal ingredient or the combination of more than one.

To do this, the evidence should support the claim with respect to the specific target population intended, the specific directions of use and the specific system of medicine, when appropriate.

The efficacy evidence should be able to support the health context of the product and, when necessary, provide enough background information to describe the characterization of the health condition implied by the claim and the health context of the recommended use.

Within any risk category, the same evidence may be sufficient to support both safety and efficacy when it is appropriate for the claim and when it fully reflects the product's recommended conditions of use.

The minimum type of evidence from a higher risk category may be used to support a claim in a lower category as long as it is appropriate for the condition.

For the low and medium categories, methodologically weak efficacy evidence should be supplemented to demonstrate consistency in results and plausibility.

Table 1 outlines the minimum safety and efficacy evidence for each risk category (high, medium, low).

2.6.1 Efficacy Evidence for the High Risk Category

NHPs making claims for the treatment, prevention or cure of serious health conditions should meet the evidence criteria for the high risk category.

The evidence package should include a complete critical summary reflecting the totality of evidence. Evidence should be presented in the form of a systematic review outlining the validity and causality elements for each reference by providing a critical analysis of the study design types, and the quality and quantity of each evidence type that supports and refutes the claim. Product-specific evidence is recommended. Evidence provided should demonstrate statistically significant outcomes, clinically meaningful differences, relevance to the target population, and overall consistency of the results across all studies of acceptable quality. Data should support the characterization of the disease.

Additional evidence to support interactions and a complete summary reflecting the totality of evidence should be provided in addition to evidence recommendations listed in Table 1.

2.6.2 Efficacy Evidence for the Medium Risk Category

NHPs making claims for major health conditions and diseases should meet the evidence criteria of the medium risk category. The evidence for products or ingredients in this category can be submitted as individual references, although additional information or evidence is recommended to help support: the recommended conditions of use, the health context of the product, and the comparability of the ingredient forms. Evidence should ideally demonstrate:

- A well described study population;
- A record of the flow of subjects through the trial;
- Power analysis to determine proper number of subjects;
- Random allocation;
- Blinded assessment of outcome;
- Intention to treat analysis;
- Should usually be assessed compared to current standard therapy; and
- In addition to validity, evidence should demonstrate reasonable causality supporting the efficacy of the product.

2.6.3 Efficacy Evidence Requirements for the Low Risk Category

NHPs making claims for minor health conditions and diseases should meet the evidence criteria of the low risk category. This risk category also includes NHPs for the treatment of symptoms or risk factors of serious or major conditions or the risk reduction of these conditions; and NHPs for general health maintenance, support, or promotion that refers to modification of a biochemical or physiological function of a nutritional nature or implies benefit to a minor disease or health condition. Evidence requirements for this category reflect the low risk nature of these products; however, evidence should still demonstrate key aspects of validity and be appropriate for the recommended conditions of use.

This category includes most vitamins, minerals, essential nutrients, and other nutrients recommended for use by healthy adults. These types of ingredients are often associated with NHPD pre-cleared information.

For additional guidance on appropriate claims for low risk products, refer to Annex I: General Health Claims.

Table 1. Acceptable Minimum Safety and Efficacy Evidence by Risk Category

For a description of each risk category, refer to section 2.3. For each medicinal ingredient and claim associated with the risk category, at least one of the following types of evidence meets the minimum criteria.

High Risk Category:	
Evidence type	Considerations
NHPD published monographs	N/A
Phase III or phase IV clinical trials (randomized, controlled, well-designed)	For treatment, cure, and prevention claims or for health support claims when they imply treatment, cure, prevention, and risk reduction claims if the study is not multi-centred, at least two studies are required.
Meta-analysis (controlled and well-designed)	Conclusions should be based primarily on phase III trials, not phase II trials; primary evidence may be requested.
Prospective observational studies or combinations of one prospective study and one retrospective study	Evidence only meets minimum requirements for prevention and risk reduction claims. Two pieces of evidence of equivalent ranking or higher are required to support efficacy.
Evidence of a positive decision from another regulatory agency	Documentation in the form of an authorization letter or positive decision must be submitted that includes details on what was approved. A description of the regulatory requirements from the other regulatory agency should be provided.
Medium Risk Category:	
All acceptable minimum evidence requirements for the high risk category	N/A
Systematic review other than meta-analysis	Conclusions should be based primarily on phase III trials, not phase II trials; primary evidence may be requested.
Published, peer-reviewed, detailed narrative reviews which cite detailed primary evidence	Detail should include: defining characteristics of the ingredient; primary endpoints/outcomes with statistical and clinical significance; the studied sub-population's age, gender, and health state; the dosing regimen and dosage form; the route of administration; the directions of use; any restrictions to study entry of participants based on interactions/risk; any identified adverse reactions

Phase II clinical trials	Two pieces of evidence of equivalent ranking or higher are required to support efficacy. When the evidence provided to support the claim is methodologically weak, it should be supplemented to demonstrate consistency in results and plausibility.
Epidemiological studies	Evidence only meets minimum requirements for prevention and risk reduction claims. Two pieces of evidence of equivalent ranking or higher are required to support efficacy.
Published compilations referring to traditional use	Evidence can be used to support safety only.
Low Risk Category:	
All acceptable minimum evidence requirements for the high and medium risk categories	N/A
Phase II clinical trials	One piece of evidence of equivalent ranking or higher is required to support efficacy. When the evidence provided to support the claim is methodologically weak, it should be supplemented to demonstrate consistency in results and plausibility.
Epidemiological studies	Evidence only meets minimum requirements for prevention and risk reduction claims. One pieces of evidence of equivalent ranking or higher are required to support efficacy.
Pilot and open label studies	Two pieces of evidence of equivalent ranking are required to support efficacy. The two different studies may be of equivalent or higher ranking. When the evidence provided to support the claim is methodologically weak, it should be supplemented to demonstrate consistency in results and plausibility.
Reputable textbooks	Textbook should reflect human in vivo data if the ingredient is an essential nutrient.
Demonstration of food use	Evidence can be used to support safety only.

2.6.4 Qualifying Claims

When necessary, qualifying statements may be necessary to add context to support a claim and to help consumers make informed decisions. The need to qualify a claim is based on the characteristics of the ingredients, the seriousness and severity of the health claim, the need for specificity within the claim, as well as the value that the wording will provide to the consumer.

Examples of claims that should be qualified include:

- When the evidence refers to one risk factor in a risk reduction claim, the claim should be qualified with other modifiable factors that should be considered (e.g., “calcium intake, when combined with sufficient Vitamin D, a healthy diet, and regular exercise, may reduce the risk of developing osteoporosis”); and
- Risk reduction claims in which a biomarker was used should indicate that the biomarker, the factor which contributes to the efficacy of the claim, is only one of many that may contribute to the development of the disease to which it has been linked.

For additional guidance on claim qualifiers, refer to Annex I: General Health Claims.

Traditional Use Claims may appear in all Natural Health Products

Traditional use claims may appear on non-traditional use products; these products should be formulated based on the following principles:

- The medicinal ingredient(s) supporting the traditional claim(s) should meet the requirements for traditional use claims as per the *Pathway for Licensing Natural Health Products Used as Traditional Medicines*.
- Evidence should support the dose information and the method of preparation as those traditionally used within the given traditional system of medicine.
- To prevent the product from being represented as a “traditional medicine,” any indicated traditional use claim should refer to the specific medicinal ingredient(s) and recognized traditional system of medicine from which the claim originates.
 - This includes products with claims based on modern evidence and claims supported by traditional use. E.g., “Helps to promote sleep” (*based on modern evidence*). “Passionflower is traditionally used in Herbal Medicine as a sleep aid” (*based on evidence for traditional use*).
 - It also includes products with claims from multiple systems of traditional medicine. E.g., “Ashwagandha is traditionally used in Ayurveda to balance aggravated Vata (nervine tonic, sedative)” and “Passionflower is traditionally used in Herbal Medicine as a sleep aid.”
- When an additive combination of ingredients within a single traditional system of medicine has been used to support the traditional use claim(s), all ingredients supporting the traditional use claim should be disclosed in the recommended use or purpose(s). E.g., “Passionflower, hops, and chamomile are traditionally used in Herbal Medicine as sleep aids”

2.7 Combination Ingredients

For information on products with multiple ingredients, including sub-therapeutic ingredients, and combinations of medicinal ingredients individually supported by NHPD pre-cleared information, see Annex II.

2.8 Linking Evidence to Conditions of Use, Ingredient Form and Use of Extracts

Refer to Appendix B for recommendations on how to link safety and efficacy evidence to a product's conditions of use.

Refer to Appendix C for recommendations on how to link safety and efficacy evidence to an ingredient's chemical and physical form.

Refer to Appendix D for information on linking safety and efficacy evidence to the use of an extract (i.e., comparability of an extract to the evidence).

2.9 Additional Guidance

More information can be found in Appendix E.

2.10 Final Check before Submitting Product Licence Application

Refer to Appendix F for evidence criteria, which can be used as a final check before submitting a product licence application to ensure that the application is not critically deficient and meets a minimum level of validity.

Health Canada

Pathway for Licensing Natural Health Products Making Modern Health Claims v1.0

Appendices

Appendix A: Examples of Health Claims by Health Condition

Appendix B: Linking Evidence to Conditions of Use

Appendix C: Linking Evidence to Ingredient Form

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Appendix G: Expert Opinion

Annexes

Annex I: General Health Claims

Annex II: Combination Ingredients

Appendix A: Examples of Health Claims by Health Condition

Table 2: Examples of Health Claims by Health Condition

Health Condition	Examples
Serious disease/ condition	<p>Helps prevent rheumatoid arthritis. For the treatment of cerebrovascular disease. For the treatment of depressive disorders. Used to prevent diabetic neuropathy. For the treatment of prostate cancer. For the treatment of high blood pressure. Used to treat diabetes.</p>
Major disease/ condition	<p>Helps to reduce serum triglycerides/triacylglycerols. Helps to lower blood/plasma cholesterol levels. For reducing acid reflux during pregnancy. Helps to restore cognitive function/memory. Helps in the prevention of nausea and vomiting associated with conventional cancer management (chemotherapy and radiation treatment). Helps attenuate the rise in blood sugar levels following a meal. Helps improve insulin sensitivity. Helps to regulate blood glucose levels. Helps prevent glucose intolerance. Helps prevent osteoporosis. Improves joint function in osteoarthritis of the knee. Helps prevent recurrent urinary tract infections. Prevents against cavities. Helps cure migraine headaches. Helps prevent macular degeneration. Helps treat erectile dysfunction.</p>

Health Condition	Examples
<p>Minor disease/ condition</p>	<p>Reduces the number and severity of acne pimples. Helps relieve nervousness. Helps relieve minor pain associated with menstruation. Used as a mild sedative (for jet lag). Soothes sore throat. Short-term relief of occasional constipation/laxative. Helps relieve minor burns including sunburn. Used for the temporary relief of muscle and joint pain associated with rheumatoid arthritis or osteoarthritis (symptom). Helps to relieve the symptoms (e.g., sore throat, runny nose) of the common cold. Used as a decongestant to relieve nasal congestion due to hay fever. Helps to reduce the recurrence of cold sores. Relieves symptoms such as heartburn and dyspepsia associated with gastric hyperacidity (i.e. antacid). For the removal of corns and calluses. Helps prevent nausea and vomiting associated with motion sickness and seasickness.</p>

Appendix B: Linking Evidence to Conditions of Use

Evidence is required to support the claim and all of the recommended conditions of use. Table 3 provides a summary of important recommendations.

Table 3: Linking Evidence to the Conditions of Use

Condition of Use	Safety Requirements	Efficacy Requirements
Dosage form	<ul style="list-style-type: none"> Evidence specific to less common dosage forms should be provided when possible or when ingredients have stability concerns (i.e., extended-release dosage forms or immediate-release dosage forms). 	<ul style="list-style-type: none"> When pharmacokinetics may be influenced by dosage form, information may be required regarding the potential impact of the efficacy of the product. The reference dosage form should be comparable to that recommended, unless an acceptable justification is provided to show that the difference in dosage form is unlikely to affect product efficacy.
Route of administration	<ul style="list-style-type: none"> The reference route of administration should be the same as that recommended (except for throat sprays/lozenges for which swallowed dosage forms will be considered). Topical use in adults should not be extrapolated to children; evidence should support specific use by children unless an acceptable justification is provided. Evidence for other routes of administration may be considered when specific knowledge of the ingredient mechanism of action is known, (e.g., sublingual use may help support oral use, if evidence of the specific mechanism of action is provided). 	<ul style="list-style-type: none"> The route of administration in the evidence should be the same as that recommended. A minimum concentration for efficacy should be assumed.

Condition of Use	Safety Requirements	Efficacy Requirements
<p>Dosing Information (including dose frequency, daily dose)</p>	<ul style="list-style-type: none"> • The reference daily dose should be equal to or greater than the recommended daily dose. • The dose should be appropriate for the vulnerability of the target population; • The reference frequency of use should be the same as that recommended if the frequency of use has an effect on the safety profile (e.g., consuming 4 x 200 mg of caffeine per day is likely to induce different physiological effects than 1 x 800 mg of caffeine per day). • Evidence supporting use in children or infants should either be clinical or represent a long-standing history of safe use. • The product risk profile, including the nature of the ingredient and how it is being used, should be considered when deciding how closely the safety evidence should match the ingredient. For example, the higher the risk profile, the more closely the dosing information should match the evidence. 	<ul style="list-style-type: none"> • The reference daily dose should be less than or equal to the recommended daily dose. • The reference frequency of use should be the same as that recommended when frequency of use and circulating concentrations over time is required for achieving specific pharmacological effects. • A reference dose by weight is more appropriate than a reference dose by age for children. • For children, age brackets should also include a weight (e.g., “children aged 1 to 2 years of age, weighing at least 9 kg”).
<p>Duration of use</p>	<ul style="list-style-type: none"> • A duration of use statement based on the conditions in the evidence should be provided when the evidence demonstrates a risk to health that supports occasional use only or if the nature of the condition requires a limited duration of use. • The duration of use should be limited in cases where there is an established risk to health due to the long-term use of an ingredient/product. • For ingredients with uncertainty relating to risk (e.g., novel ingredients), an unlimited duration of use without sufficient 	<ul style="list-style-type: none"> • A duration of use statement should be provided when the efficacy evidence suggests a minimum duration of use is necessary before an effect can be seen. If evidence demonstrates that efficacy is consistently observed at the first time point studied, a minimum duration of use is not usually necessary.

Condition of Use	Safety Requirements	Efficacy Requirements
	<p>advisory information should be supported by at least 6 months of use without significant identified adverse effects.</p>	
<p>Target population</p>	<ul style="list-style-type: none"> • The risk of using a specific sub-population in the evidence to support a wider population should be justified by the product's benefit-to-risk profile. This includes consideration of the ingredient's risk profile, the method of action, the quality and type of evidence and the specificity of the recommended target population. • Evidence (particularly for treatment claims) for <u>adults</u> should not be extrapolated to <u>children or infants</u> (age 0-11 years), and evidence for <u>children</u> (age 2-11 years) should not be extrapolated to <u>infants</u> (under age 2 years). • As necessary, specific evidence may be needed to support the dosing of vulnerable groups such as infants, children and elderly (over 65 years of age) and other vulnerable groups. • Specific evidence should be provided for pregnant or breastfeeding women. • A history of food use may not support safety in infants; evidence supporting a history of safe food use specifically in infants may be required. • Extrapolation of evidence to adolescents from adults or children or vice versa should be considered on a case-by-case basis, depending on the type of product, the conditions of use, and the quality of the evidence. • The age range should be restricted when the age group in 	<ul style="list-style-type: none"> • The dose should be appropriate for the recommended population. • The recommended age bands for infants, children and adolescents should reflect the ages specified in the evidence. For example, evidence for use in children age 2-10 years of age is insufficient to support the use in children under age 2. • The age bands should appear on the label even when the evidence does not specify an age range. • The health impact of lower than expected efficacy should be considered when deciding if extrapolation from a specific health condition to a more general use in healthy consumers would be acceptable. • The pathology and aetiology of the health condition in the evidence should be considered before extrapolating to healthy consumers.

Condition of Use	Safety Requirements	Efficacy Requirements
	<p>the evidence does not match that of the product.</p> <ul style="list-style-type: none"> The use by the target population should not be considered too risky based on the assessment of the benefit-to-risk profile of the product. 	
Direction of use	<ul style="list-style-type: none"> The vulnerability of the target population should be considered when deciding how the directions of use should be specified on the label. Additional safety evidence should be provided when there is uncertainty regarding a product's safety based on the recommended directions of use (e.g., when a nasal spray uses a high pressure nasal bulb for delivery). When necessary, the directions of use should be clear enough to allow a third person, such as a parent, to safely administer the product. 	<ul style="list-style-type: none"> The directions of use should be specific enough to provide the guidance for the proper administration of the product (e.g., "take before going to bed," "take on an empty stomach"). When necessary, the directions of use should be clear enough to allow a third person, such as a parent, to effectively administer the product (i.e. specific instructions to crush a tablet or empty contents of a capsule into food or drink to ensure administration to young children or groups who cannot swallow a whole capsule).
Precautionary labelling	<ul style="list-style-type: none"> As necessary, the risk information should be appropriate for ingredients with a therapeutic dose; ingredients with a sub-therapeutic dose; and for non-medicinal ingredients. All precautionary labelling should be based on human evidence or established risks; however certain statements based on theoretical evidence may be necessary when the risks are serious. A precaution for use with other medications and or conditions/diseases should be included when one or more ingredient(s) in the product is known to alter the effectiveness of the medication or progression of the disease (e.g. alters 	<ul style="list-style-type: none"> Risk information should prevent over medication when pharmacological effects are additive.

Condition of Use	Safety Requirements	Efficacy Requirements
	effectiveness of treatment, increases risk of developing the disease, worsen the course of the disease or mask symptoms of the disease)	

Appendix C: Linking Evidence to Ingredient Form

Table 4 provides recommendations for ensuring that evidence will support the ingredient's chemical and physical form.

Table 4: Linking Evidence to Ingredient Form

Ingredient Characteristic	Recommendations for Safety and Efficacy Evidence
Identity	<p>Evidence should support:</p> <ul style="list-style-type: none"> • The unambiguous Latin binomial name or chemical name; • The part or derivative used; and • The specificity of the ingredient's action. <p>For example, for probiotics the evidence should be specific to the organism strain number as well as the genus and species; for botanicals, the evidence should be specific to the part of the plant used; if the evidence indicates "leaf" then "aerial parts" would not likely be supported unless evidence was provided to show that stem and other relevant components have the same ingredient at the same concentration.</p>
Source material	<p>Evidence should:</p> <ul style="list-style-type: none"> • Support the source material when changing the source material might influence the safety or efficacy of the ingredient; • Describe the source material for isolates when there is a known safety concern; • For isolates that represent a defined molecule (e.g., caffeine), pharmacological activities do not vary depending on their biological source. Therefore, the evidence for these isolates does not need to be source specific. • Isolates that are either polymers (like collagen and hyaluronic acid) or groups of molecules (like polyphenols) have variable pharmacological activity depending on the biological source. Therefore, source-specific evidence is required for these isolates.
Blends of ingredients	<p>Efficacy evidence should:</p> <ul style="list-style-type: none"> • Describe a blend of medicinal ingredients (X, Y, Z) only when X, Y, Z are all present in the recommended product at a similar dose.
Chemical form	<p>Evidence should :</p> <ul style="list-style-type: none"> • Support the ingredient form as much as possible when the ingredient has undergone chemical processes that could affect its safety or efficacy (e.g., oxidation, reduction, purification, emulsification, etc.).

Physical form	Evidence should: <ul style="list-style-type: none">• Support the ingredient form as much as possible when the ingredient has undergone physical processes that could affect its safety or efficacy (e.g., micronization, extraction, binding, stabilization, microencapsulation, etc.).
Dosage form	Evidence should: <ul style="list-style-type: none">• Support the ingredient form as much as possible when the dosage form has been altered in a way that could affect safety or efficacy (e.g., addition of coatings, etc.)

Types of evidence that may be useful to describe the form of the ingredient in the evidence or in the recommended product include: technical information sheets, raw material specifications, bioequivalence studies, other details obtained directly from the author of a clinical trial, information describing the method of preparation, phytochemical composition studies.

Appendix D: Linking Evidence to Use of Extracts

To support the comparability of an extract to the evidence, whether it is of plant, animal or microbial origin, information about the extract standardization or extract solvent system and the extract ratios should be provided. Considerable discrepancy in the methods of preparations could mean that the extracts are not comparable. Also, in order to compare scientific studies on whole materials, or to relate the applicability of a study material to a commercial product, the study materials have to be adequately characterized.

In general, if the extract is standardized, the evidence provided to support the safety and efficacy of the extract should be of the same standardization. In this case, the Quantity Crude Equivalent (QCE) and solvent system is not required to support safety and efficacy but may be provided as additional information. The QCE, extract ratio and solvent system can be used to support a standardized extract when the quantity of the extracts match and the extract ratio and extraction solvents used are comparable.

If the extract is not standardized and is prepared from a known QCE or extract ratio, starting material, solvent and method of preparation (e.g., decoction), the evidence provided to support the safety and efficacy of the extract should match.

An evidence-based justification may be required to support comparability of extracts to one another. This rationale may include the methods of manufacture (e.g., comparisons of the solvents used), the characterization of the extracts (e.g., comparisons of phytochemical profiles), and different studies that compare different extract types.

Appendix E: Additional Guidance

Refer to Table 5 for additional guidance on a variety of topics. This table will be updated on a regular basis.

Table 5: Additional Guidance

Issue	Source of Information	Web Link
Antiseptics	Human Use Antiseptic Drugs Guidance Document	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/antiseptic_guide_ld-eng.php
Nanotechnology	Policy Statement on Health Canada's Working Definition for Nanomaterial	http://www.hc-sc.gc.ca/sr-sr/pubs/nano/pol-eng.php
Schedule A	Schedule A and Section 3 of the <i>Food and Drugs Act</i> Guidance Document	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/scha_guide_ld-eng.php
Health Canada's Decision-Making Framework for Identifying, Assessing, and Managing health Risks- August 1, 2000	Health Canada Guidance Document on how to Identify, Assess and Manage Health Risks	http://hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/risk-risques_tc-tm-eng.php#aa

Appendix F: Evidence Criteria for Modern Health Claims

Prior to submitting evidence-based Product Licence Applications (PLAs), cross check supporting evidence against the evidence criteria below to ensure that it meets a minimum level of validity.

1. Evidence must be provided for all the medicinal ingredient(s) [XXX and YYY].

Example of missing evidence:

- The PLA indicates that the product is composed of medicinal ingredients X, Y and Z. However, the evidence provided supports the safety and efficacy of medicinal ingredients X and Y, but no evidence has been provided to support the safety of medicinal ingredient Z.

2. The product and/or medicinal ingredient on the PLA form must be comparable to the product and/or medicinal ingredient included in the evidence.

Examples where the medicinal ingredient(s) in the evidence does not adequately represent the medicinal ingredient(s) listed on the PLA form, may include differences in:

- Medicinal ingredient (e.g., collagen vs. hydrolyzed collagen)
- Chemical derivative (e.g., glucosamine HCl vs. glucosamine sulphate);
- Source organism or species (e.g., protease sourced from *Aspergillus niger* vs. protease sourced from *Aspergillus oryzae* or *Panax quinquefolius* vs. *Panax ginseng*);
- Bacterial strain (e.g., *Lactobacillus rhamnosus* AB-123 vs. *Lactobacillus rhamnosus* GG);
- Source material (e.g., *Echinacea angustifolia* leaf vs. *Echinacea angustifolia* root);
- Extract/isolate vs. crude material (e.g., Green tea leaf extract standardized to 15% EGCG vs. Green tea leaf); and,
- The evidence provided is for a blend of medicinal ingredients X, Y, Z, but the medicinal ingredients listed on the PLA are A, B, C.

3. Some evidence is not considered adequate on its own to support safety and efficacy of the product and/or the medicinal ingredient.

Examples of evidence that is not considered adequate as sole support for the safety and efficacy of products include:

- Compilations of evidence that have not been critically reviewed (e.g., Natural Medicines Comprehensive Database, Physicians' Desk Reference (PDR) Health, general information websites);
- Evidence without relevance to, or that cannot support safety of the medicinal ingredient(s)/product and/or efficacy of the product for use in humans (e.g., biochemical characterization study, pharmacokinetic study)

4. Animal or in vitro evidence is provided as the sole source of safety or efficacy evidence for the product and/or medicinal ingredient.

At least some evidence should come from human use; animal or in vitro experimental evidence may be considered as additional, supporting information but is not recommended to form the basis for product authorization. While animal and *in vitro* studies can provide plausible

explanations of how a medicinal ingredient will work, they are not sufficient evidence on their own to support efficacy in humans.

5. The daily dose indicated on the PLA form for the product and/or medicinal ingredient is not captured within the safety and efficacy evidence provided.

Example of missing evidence:

- The recommended daily dose of Medicinal Ingredient X in the PLA is 300 mg; however, the evidence provided supports a daily dose of 60 mg. The evidence may support efficacy but would not support safety.

Example of missing evidence:

- The recommended daily dose of Medicinal Ingredient Y in the PLA is 50 mg; however, the evidence provided supports a daily dose of 150 mg. The evidence may support safety but would not support efficacy.

6. Dosing information must be provided/contained within the evidence submitted.

Example of missing evidence:

- The evidence provided is a general review article that discusses a variety of studies but does not indicate the doses used in the studies.

7. The claim(s) supported by the safety and efficacy evidence must have direct relevance to the claim(s) for the product OR the evidence does not support at least one of the claims.

Examples of missing evidence:

- The evidence provided supports the safety and efficacy of product X when used to relieve osteoarthritic pain. However, the PLA indicates that the product is to be used for cognitive function.
- The evidence provided supports the safety and efficacy of product X when used for headache relief. However, the PLA indicates that the product is to be used to aid digestion.

Example of relevance:

- The evidence describes the effect of treatment on LDL cholesterol whereas the claim indicated on the PLA is for "Cardiovascular health." This is acceptable.

8. The route of administration supported by the safety and efficacy evidence must be the same as the route of administration indicated in the recommended conditions of use section of the PLA.

Example of missing evidence:

- The evidence provided supports the safety and efficacy of product X/medicinal ingredient(s) when taken as an intravenous solution/injection but the PLA indicates that the route of administration for the product is oral. Furthermore, as per Schedule 2 of the *Natural Health Products Regulations*, products administered by injection are prohibited.

Appendix G: Expert Opinions

An expert opinion may be used to supplement information that is not available in the literature, (e.g., duration of use for an ingredient) or as supplementary information to support a new use for a previously approved ingredient. When using expert opinions, factors such as experience, education, the number of experts, and conflicts of interest should be considered. These factors, along with any other relevant information provided, will contribute to the weighting of the expert opinion.

An expert should have:

- Training in the field or healing paradigm related to the proposed NHP or medicinal ingredient(s);
- Scientific qualifications, including experience in research methods and/or training in evidence-based health care; and
- No conflicts of interest or must disclose all conflicts of interest.

Annex I: General Health Claims

Intent:

This annex outlines a regulatory pathway for natural health products (NHPs) with general health claims. These claims can be used provided that the health and safety of Canadians would not be at risk; this is consistent with a risk-based product approach where health claims are indexed against the level of evidence provided to support the safe use of the products.

What is meant by a general health claim? There are several types of general health claims. The main type of general health claim is known by the fact that the claims are more limited in describing the effect of the NHP and present the component as having a therapeutic effect as it relates to a disease or health condition without classical definition of the effect or outcome. As such, the first type of general health claims does not address mitigation, treatment, prevention or cure of serious or major conditions. Instead, they relate to modifying organic functions in a manner that maintains or promotes health, including nutrient structure-function and quality of life health claims.

What type of evidence is required for a general health claim? The information or data used to support a general health claim should be appropriate to the strength of the health claim. This includes the fact that the evidence standards could be different than those presented in the main body of the 'Pathway for Licensing Natural Health Products Making Modern Claims' or 'Pathway for Licensing Natural Health Products Making Traditional Claims' guidance documents.

General health claims must not be false or misleading and their accuracy must be established through an established methodology to meet the appropriate standard of evidence. Further, the claims must not lead to unsafe or inappropriate use of an NHP, nor to the sale or advertising of NHPs for use outside of their approved indications and conditions of use.

An NHP, its associated claim(s) and its packaging, labelling and advertising must be consistent with the terms of market authorization. Additionally, a claim made through the product name, the brand name or the name of the manufacturer will be considered false or misleading if it indicates or implies an unauthorized indication and/or use of the NHP that was not included in the terms of market authorization.

Types of general claims that have low therapeutic impact include:

- For health maintenance (e.g., maintains healthy gums)
- For relief of minimally bothersome symptoms (e.g., runny nose)
- For self-limiting conditions (e.g., colds)
- For purposes that will cause little or no harm if an NHP is ineffective in a particular consumer (e.g., anti-flatulent).

It is important to note that while the previous paragraphs focus on the main types of general health claims, there are also a few other types of general health claims for which there is a different relationship between the claim and the intended therapeutic effect. In these other types, the information used to support the claim exists, but there are challenges in determining the therapeutic effect, leading to the need for generalization.

- *Pattern of evidence:* In some instances it is not a single trial, text, or study that suggests that the product has a therapeutic effect. Rather, there is a positive pattern of evidence of benefit from the product. In these instances, because

information on the product's benefit is drawn from multiple sources, there needs to be generalization in the claim to assure that it is accurate to the patterns of demonstrated benefit(s). As such, the claim will be generalized to a therapeutic effect that is evidenced throughout the sources used to support the benefit of the product.

- *Specific end-points:* In some instances there is some certainty regarding the health benefits of a given ingredient, but the therapeutic outcome is either less clear or is very specific and not readily relatable or understandable. As it relates to specificity, this could include a situation whereby the information shows a mechanism of action for which the therapeutic benefit of that action is not readily known or understood. For instance, information relating to a benefit provided to support a health claim shows benefits on a health system rather than a more common treatment, prevention or cure claim for a specific disease. As such, generalization may be necessary to support the licencing of the product. As another example, the information showing a benefit to support licencing of a product may relate to a specific mechanism of action within the human body, but the health outcome of that mechanism of action may not be clearly known or understood by a consumer.
- *Qualifications:* In some other cases qualification of the claim may be necessary in order to support the addition of a claim. Qualification should be reserved for occasions where there could be concern of a benefit not being achieved, creating a known risk. In these cases, a qualifier such as "could," or "likely," or "when used in addition to x or y" may be added to the claim to convey that a benefit was not as strong as other instances whereby a qualifier was not used. An example of this includes a situation where the product is treating a symptom of a disease that, if not treated, could have an impact on health and safety. This also assures that there is fairness in the strength of a claim for a product licence being directly proportional to the strength of the benefit. More direction on qualification of claims can be found within the body of the annex and in Section 2.6.4 of the 'Pathway for Licensing Natural Health Products Making Modern Claims' guidance document.

Qualification can also occur in instances whereby the product is intended to be used within a system of medicine, such as within the context of traditional medicine. Refer to the main body of the annex for more direction on these types of claims.

This demarks an important distinction between the main types of general health claims, such as source of claims, and the three types of general health claims listed above. While a "source of" claim has a lower therapeutic effect and a less specific general health claim as a result of that, other general health claims could be supported by higher levels of evidence.

1.0 Purpose

The purpose of this annex is to provide guidance on the use of general health claims for NHPs, such as those demonstrating a lower therapeutic effect, to ensure that the standards of evidence for those NHPs reflect the therapeutic outcome and the allowable health claim.

The approach follows these principles:

- Evidence requirements are proportional to the level of risk of the NHP:
 - Higher intrinsic risk, higher therapeutic impact, higher level claim NHPs must be supported by evidence that is of a higher standard and level of certainty.
 - Conversely, lower intrinsic risk, lower therapeutic impact, lower health claim NHPs can be supported by lower level or less certain evidence of efficacy so long as there is high certainty of safety under the recommended conditions of use.
- Mitigate risks to the health of consumers and support access to NHPs that are safe and are likely to do what the health claim on the label states.
- Focused decision making, grounded in a risk-benefit analysis that recognizes degrees of appropriate evidence in relation to the NHP's safety and positive health outcomes.
- Provide stakeholders (internal and external) with predictability and transparency in evidence requirements for health claims.

2.0 Scope

The following list outlines NHPs that fall outside the scope of this annex:

- NHPs that contain ingredients that are intrinsically higher risk. This includes NHPs associated with a higher level of uncertainty and/or seriousness of effect, as well as safety concerns that cannot be mitigated sufficiently through the authorized conditions of use (e.g., with dosage and duration limitations, cautionary labelling, etc.).
- NHPs that have a demonstrated lack of quality control as evidenced by inspection or complaints made to Health Canada and could be contaminated with bacteria, adulterated or hyper potent.
- NHPs that have been the subject of controversial or inconclusive science related to the safety of the ingredient(s).
- NHPs that have been identified through post-market monitoring as having potential safety concerns, such as the number of reported adverse drug reactions for a given ingredient or product.
- Licensed NHPs that have a demonstrated history of being advertised outside their terms of market authorization (e.g., through internet advertising).

NHPs marketed with statements that are not considered to be health claims under the *Natural Health Products Regulations* (NHPR) could fall outside of the scope of this annex. Any other consideration that negatively changes the risk/benefit profile of the NHP could lead to a decision that an NHP is outside of scope of this annex.

NHPs that are intended for use in vulnerable sub-populations, such as children and pregnant/breastfeeding women, would not be categorically excluded from this annex; however, a greater attention to risk mitigation may be required (including appropriate cautionary statements or dosage limitations) to allow for a general health claim.

This annex should only apply to those general claims not already specified in other NHPD recognized forms of pre-cleared information (PCI). This guidance is intended to support and not supplant or supersede any other policies or guidance documents related to standards of evidence or health claims.

3.0 Background

Although Health Canada has developed PCI to support efficient authorization of many products and/or claims, there are NHPs that do not meet the current evidence requirements within the established PCI and as such require a full review.

General health claims can provide a clearer pathway to market through a streamlined application process while remaining consistent with the principles of the risk-based approach to NHP licensing.

A general health claim is one that applies broadly to a set of circumstances where there may be a benefit to health, but that benefit may not relate to a specific structure or function being affected, and may not indicate a disease, disorder or abnormal physical state or its symptom(s) that is/are being treated or prevented. Instead, general health claims relate to modifying organic functions in a manner that maintains or promotes health, including nutrient structure-function and quality of life health claims.

4.0. General Health Claims

The following categories are those general health claims that may be authorized if all required conditions/considerations are met.

"Source of/Provides/Contains" Claims

A "source of" claim is a factual representation that identifies a constituent or ingredient within a product. This approach is already utilized for food. Thus, the recommended use or purpose to be authorized for the NHP is as a source of that substance. A health benefit is generally implied by identifying the product as a source of the constituent/ingredient, and this must not be false or misleading, i.e., such claims will relate to nutrients or other constituents/ingredients generally known to be beneficial to health and should not be in reference to inert or ubiquitous substances. These claims can be prefixed by "source of," "provides" or "contains."

Examples

- Source of fibre
- Provides antioxidants
- Source of probiotic
- Source of protein
- Source of a vitamin or mineral
- Source of an essential fatty acid
- Source of an essential amino acid
- Contains digestive enzymes
- Provides non-essential amino acid
- Contains non-essential fatty acid
- Source of carbohydrates

Evidence requirements

Applicants wishing to apply for a “source of” claim are required to test for the presence of the constituent or ingredient (i.e., identification testing) and may be asked to provide evidence for quantification such as an assay at the finished product or raw material stage; however, this will not be a requirement upon submission. Applicants should have the results of the aforementioned tests maintained such that they could be provided to Health Canada in a timely manner upon request.

The NHPD is adopting a standard with respect to essential nutrient content in NHPs modelled after the Food and Drug Regulations’ (FDR) vitamin and mineral minimum dose requirements as per Sections D.01.004 and D.02.002. If a Recommended Dietary Allowance (RDA) or an Adequate Intake (AI) exists for the nutrient (excluding chloride, fluoride, potassium, sodium and sulphate), the daily dose of the NHP should contain at least 5% of the RDA or AI and the NHP would qualify for a “source of” claim.

When the constituent is not an essential nutrient, data does not need to be provided to support the dose as any amount greater than zero will confer efficacy. Evidence is required to support the safety of each ingredient at the specified dose.

Claims Based on Constituents

Many medicinal ingredients of NHPs have constituents that on their own can support a specific health claim. Products that are standardized as a source of such a constituent at a relevant quantity can have a more specific claim based on that constituent.

Examples

- Helps maintain eyesight, skin membranes and immune function
 - Cod liver oil is known to contain vitamin A (palmitate), vitamin D3 (cholecalciferol), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
- Helps to support eye health in conditions (associated with sunlight damage), such as cataracts and age-related macular degeneration
 - Marigold extracts that are standardized to lutein

Evidence requirements

Applicants applying for these types of claims must provide evidence in the form of identification testing (for the constituent) as well as assays to determine the quantity of the constituent. To support the more specific claim, applicants can attest to a Natural Health Product Monograph such as the Multi-Vitamin-Mineral Supplement Monograph. The applicant can also provide clinical evidence as well as supporting evidence from animals or *in vitro* evidence to support the more specific claim. Applicants should include the name of the constituent in the claim or list it as a constituent of the medicinal ingredient so that consumers know the claim is not false or misleading and can make informed choices.

Claims for the Maintenance of Good Health

Applicants can apply for the claim “for the maintenance of good health” providing the product contains an essential nutrient. These essential ingredients may be isolated ingredients or constituents of ingredients.

Examples

- A source of vitamin x for the maintenance of good health
- A source of mineral x for the maintenance of good health

- A source of dietary fibre for the maintenance of good health
- Provides essential fatty acid x for the maintenance of good health
- A source of essential amino acid x for the maintenance of good health

Evidence requirements

To apply for one of these claims the ingredient must be present in the product and will be identified and assayed for in the product. If the essential nutrient is a constituent of an ingredient, the applicant will be asked to identify through constituent testing (identification testing and assay) which ingredient contains the specific nutrient at the finished product stage; however this will not be a requirement upon submission. An applicant can also apply, for the product as a whole, to use the claim "for the maintenance of good health" without identifying the essential nutrient in the claim if it is listed as a constituent of the medicinal ingredient so that it is clear to the consumer that the product contains that nutrient.

General Claims to Help/Support/Maintain/Promote Health

Structure-function health claims imply the modification of an organic function related to a specific body structure. These general health claims are prefixed by either "supports," "maintains" or "promotes" versus "treats," "prevents" or "cures." "Supports" and "maintains" are claims usually referring to the maintenance of a steady state whereas "promotes" usually implies an improvement to the state or condition. The low therapeutic impact claim qualifier "helps" is used to indicate that the product addresses or treats only one/some components of the disease or intended health benefit. These claims must not be to treat or cure Schedule A diseases but may support mechanisms of action associated with reduction of the risk of a Schedule A disease. These claims differ from general health maintenance claims in that there is an implied relationship between the claim and the product, and the claim and health outcome, whereas the general health maintenance claim does not contain such a relationship. It should be noted that a general health maintenance claim does not necessarily equate to poor evidence; on the contrary, most general health maintenance claims are supported by higher levels of evidence including clinical trials and text book evidence.

Examples

- Supports the immune system
- Promotes liver function
- Supports cognitive function
- Maintains vision
- Supports digestion
- Supports glucose metabolism
- Supports cardiovascular health

Evidence requirements

These claims are often supported by clinical trials and observational or epidemiological studies in humans, but other forms of evidence could be considered acceptable. The minimum evidence required to support these types of claims includes at least some human evidence (clinical and/or epidemiological), clinical text books that describe how constituents work in the body, and supporting evidence such as animal and *in vitro* studies that provide more information surrounding the mechanism of action.

Where supported by the evidence, it is beneficial to the consumer to provide more detail on the mechanisms of action by relating that to a body system or function.

Examples

- Support liver function by aiding in carbohydrate metabolism
- Helps support digestion by adding to the body's natural micro flora

Generalized claims based on mechanism of action

When clinical endpoints/markers discussed in the evidence are not clearly recognizable, are not well known, or could not be easily understood by the public, claims must be generalized for the average consumer to understand. In the case of biomarkers, evidence should be provided for the validation of the biomarker.

Examples

- Helps to reduce blood C reactive protein levels, a clinical marker of inflammation.

When evidence to support a claim describes a biochemical pathway the claim may be generalized to discuss organ function or health. It should be noted that a generalized claim based on a mechanism of action does not necessarily equate to poor evidence.

General Claims for the Relief or Resolution of Low Therapeutic Impact Conditions

General claims are also appropriate for the resolution of less serious conditions (self-diagnosable, self-treatable and/or self-resolving) where a consumer can easily tell if a product is effective. These claims cannot be for the treatment of serious conditions such as those outlined in Schedule A but may be for relief of non-unique symptoms of such serious diseases such as treatment of the pain from osteoarthritis. These claims can be prefixed by "Helps to."

Examples

- Relieves dry eyes
- Helps to relieve the pain associated with osteoarthritis
- Reduces the symptoms associated with the common cold
- Helps to relieve runny nose
- Helps to relieve upset stomach

Evidence requirements

The minimum evidence required to support these types of claims includes at least some human evidence (e.g., clinical and/or epidemiological), clinical text books that describe how constituents work within the body, and supporting evidence such as animal and *in vitro* studies that provide more information surrounding the mechanism of action. The clinical evidence provided to support these claims may be weak in methodological design and may represent trends in evidence.

General Claims for Risk Reduction of Low Therapeutic Impact Conditions

General claims are also appropriate for the prevention of less serious conditions (self-diagnosable, self-treatable and/or self-resolving) where a consumer can easily tell if a product is effective. These claims cannot be for the treatment of serious conditions such as those outlined in Schedule A. These claims are usually prefixed by "Helps to prevent" or "Reduces the risk of."

Examples

- Helps to prevent dry eyes
- Helps to prevent drowsiness

Evidence requirements

The minimum evidence required to support these types of claims includes at least some human evidence (clinical and/or epidemiological), clinical text books that describe how constituents work within the body, and supporting evidence such as animal and *in vitro* studies that provide more information surrounding the mechanism of action. The clinical evidence provided to support these claims may be weak in methodological design and may represent trends in evidence.

Herbal Medicine

When the primary support for treatment of minor conditions comes from a specified paradigm of medicine such as herbalism, the claim should be prefixed with the paradigm such as "Used in Herbal Medicine."

Examples

- Used in Herbal Medicine to help relieve upset stomach
- Used in Herbal Medicine as a sleep aid
- Used in Herbal Medicine to help relieve pain and/or inflammation in muscles and joints (e.g., sprains, bruises, joint pain)

Evidence requirements

In order to apply for a "used in herbal medicine" claim, an applicant must provide two independent references that support the product's use within the specified healing paradigm. At least one of the references must support the product's extraction information and the recommended conditions of use such as dose, duration, sub-population and specified risk statements.

The paradigm of Herbal Medicine may also be appropriate for both the treatment and prevention of self-limiting conditions where all requirements as previously described are met.

Aromatherapy- Essential Oils

The NHPD has adopted the following definition as a basis for decision-making regarding essential oil products: *Aromatherapy is a branch of botanical medicine which uses essential oils and other volatile/aromatic plant extracts for therapeutic or medicinal effect.*

There are three routes by which essential oils are commonly administered:

1. Topical: external skin via massage, compress, bath, creams/ointments
2. Internal: mucous membranes via inhalation, mouthwashes, douches, pessaries, suppositories
3. Oral: ingestion in gelatin capsules, on activated charcoal tablets or diluted in honey or alcohol

The general claims for these classes of products are "Used in Aromatherapy" or "Aromatherapy product." When the evidence to support a more specific claim becomes available in the paradigm of Aromatherapy, the claim should be prefixed by "Used in Aromatherapy."

Evidence requirements

In order to apply for an Aromatherapy claim, an applicant must provide two independent references that support the product's use within Aromatherapy. The references should be route of administration-specific. At least one of the references must support the product's

extraction information and the recommended conditions of use such as dose, duration, directions of use, sub-population and specified risk statements.

General Claims for Traditional Products

The NHPD definition of a traditional product is outlined in the guidance document *Pathway for Licensing Natural Health Products Used as Traditional Medicines*. In the cases where the product meets the requirements for a traditional medicine, the product may make a claim “For use in traditional XXX Medicine” where the paradigm of the traditional medicine is included in the general claim. Additionally, these claims can be used for products where there has been a modification from the original formula. Essentially, this may represent a personalized formula or manufacturer/practitioner-specific formula.

Examples

- Remedies/Products based on Herbal Medicine
- Remedies/Products based on Traditional Ayurvedic Medicine
- Remedies/Products based on Traditional Chinese Medicine

Evidence requirements

In order to apply for a general traditional health claim, an applicant must provide two independent references that support the medicinal ingredient’s use within the specified traditional paradigm. At least one of the references must support the product’s extraction information and the recommended conditions of use such as dose, duration, sub-population and specified risk statements.

Claims that are Only Effective When Used in Combination with Other Treatments

When the clinical evidence provided to support claims demonstrates that a product is only efficacious when used in conjunction with an activity or other constituents, the claims should reflect those additional requirements.

Examples

- Helps in weight maintenance when used in conjunction with adequate exercise and a calorie-reduced diet
- Helps reduce the risk of developing osteoporosis when taken with adequate amounts of calcium and vitamin D
- When used in conjunction with good oral hygiene helps reduce the risk of developing gingivitis

Evidence requirements

The minimum evidence required to support these types of claims includes limited human evidence (clinical and/or epidemiological), clinical text books that describe how constituents work within the body, and supporting evidence such as animal and *in vitro* studies that provide more information surrounding the mechanism of action.

Building Health Claims

Licensees are encouraged to seek greater specificity and strength in the health claims for their products as additional evidence becomes available. Additionally, consumers seeking

a higher therapeutic impact should be directed to health claims that are more specific and strong, as the specificity of the claim relates to the sufficiency of the evidence provided in the product licence application.

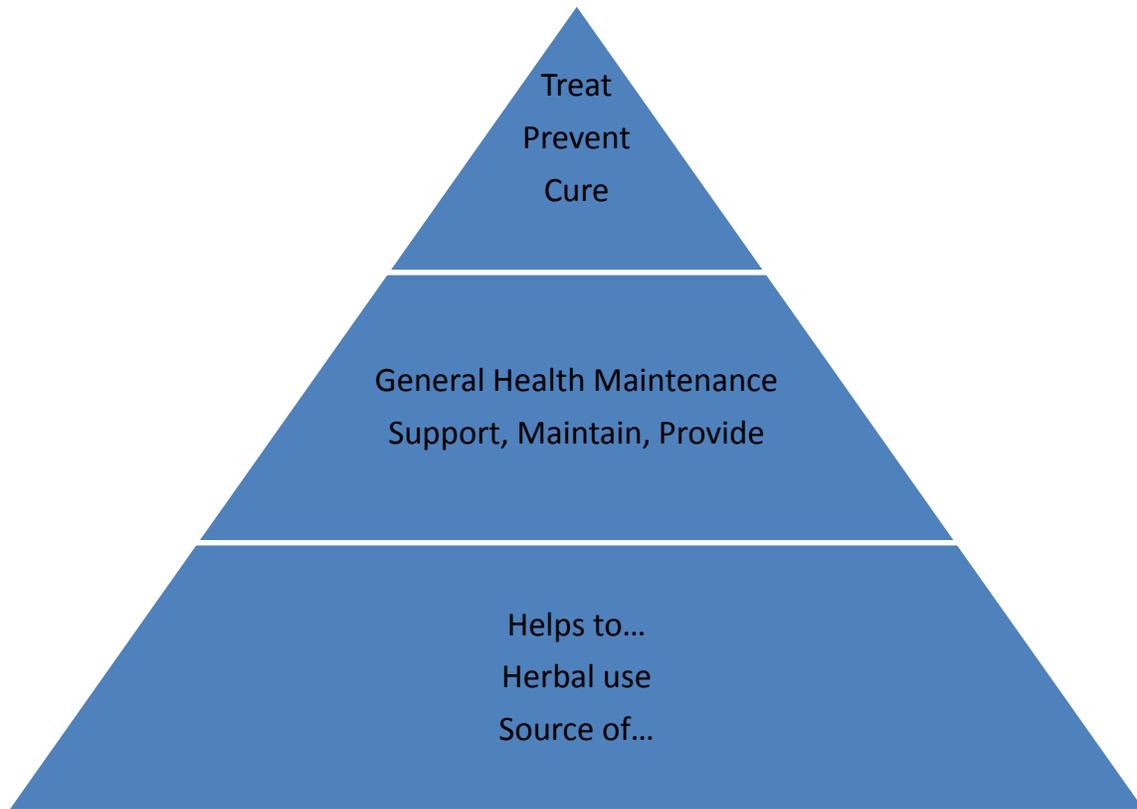


Figure 2. Building Health Claims

As such, through product licence amendments, the claim for a lower therapeutic impact product can evolve over time as additional studies, supplemental literature, clinical use, and other sources of evidence provide more conclusiveness as to the benefits of the product. As the link between the condition, the NHP and the therapeutic outcome becomes more definitive, the applicant can provide that evidence to modify the product licence to allow for more specific and stronger health claims.

Applicants providing evidence that supports a stronger or more specific health claim will be supported. This annex applies more specifically to situations whereby the evidence supports a more general health claim. As science and available evidence evolves, a stronger health claim could be applied for, and if the evidence is sufficient, received.

Having a General Health Claim Revoked

An NHP with a general health claim could be affected if the low risk nature of the product changes, effectively making a product or ingredient ineligible for a general health claim.

The reasons for removing a general health claim can be found in section 3 of this annex. Additionally, a general health claim may be invalidated if:

- There is heightened uncertainty regarding the safety of the ingredient or product.
- New evidence suggests the product could pose a risk to health.
- New evidence indicates that the product is not conforming to the general nature of the claim authorized in the product licence.
- Post-market evidence effectively elevates the risks of the product above the benefits conferred by use of the NHP.

In the event of a potential need to revoke a general health claim, the following process will be adhered to so that immediate steps are taken to address the potential safety concern.

1. Issuance of a non-regulatory letter to affected stakeholders providing an opportunity for the impacted parties to address Health Canada's concerns of a potential risk to health, including a risk assessment by the impacted stakeholder. For the issue to be resolved, evidence would be required to show that Health Canada's safety concerns are groundless or to provide appropriate risk mitigation measures.
2. If the safety concern persists, Health Canada will move forward with the issuance of a regulatory letter requesting information from the impacted party (or parties) to address the safety concern. Acceptable outcomes at this stage could include a withdrawal of the concern due to sufficient evidence provided by the regulated party, risk mitigation measures to address potential safety concerns, or additional steps required by Health Canada.
3. If a significant risk to health and safety is identified, section 17 notices could be issued effectively mitigating the risks. As such, the general health claim would no longer be acceptable for such a product.

This annex documents the current practice, and it will continue to be in effect. However, during the consultation period, stakeholders provided differing viewpoints about how the practice is represented to consumers. These important viewpoints will be considered in the on-going modernization efforts for health products. Any future changes to this annex will be made available for consultation.

Annex II: Combination Ingredients

Combinations of the substances listed in Schedule 1 of the *Natural Health Products Regulations* (NHPR) are permitted, provided that:

- There is no increased risk (e.g., additive risk, over-medication, altered bioavailability or pharmacological activity) that cannot be mitigated;
- There is no decrease in efficacy (e.g., contradictory effects); and
- There are no incompatible recommended conditions of use (e.g., contradictory claims, durations of use, risk information).

Sub-therapeutic Ingredients

Sub-therapeutic ingredients are those that are commonly recognized to have medicinal properties but are present in a product below known effective doses. These ingredients can be classified as follows:

- A sub-therapeutic ingredient should be listed as non-medicinal when it is added to confer suitable consistency or form to the medicinal ingredients as per the definition of a non-medicinal ingredient.
- A sub-therapeutic ingredient should be listed as medicinal:
 - When its combination with other ingredients supports the recommended use or purpose(s) of the product as demonstrated by evidence of an additive effect; or
 - When an additive effect cannot be demonstrated and it does not meet the definition of a non-medicinal ingredient.

Combinations of Medicinal Ingredients Individually Supported by Natural Health Products Directorate (NHPD) Pre-Cleared Information (PCI)

When NHPD PCI is cited for all individual medicinal ingredients in a multiple medicinal ingredient product, licensing will be facilitated. Certain basic criteria should be met, such as, but not limited to:

- All of the elements reflecting the conditions of use of the PCI being cited should be the same or compatible (i.e., route of administration, dosage form, use or purpose, dose,

sub-population, potency, frequency, directions of use, duration of use, risk information). In cases where specific recommended conditions of use are required for efficacy, these should be clearly represented for each of the different uses or purposes of the product.

- **Recommended use or purpose:** Efficacy of at least one medicinal ingredient is required while safety of all medicinal ingredients is required within a multiple-ingredient product. Restrictions from risk statements for the product should not conflict with the product's claims.

The NHPD may request additional evidence in support of the safety and/or efficacy of any multiple ingredient products when necessary, when adverse reactions are reported, when new evidence becomes available or when consumer concerns are raised.