Health Canada Santé Canada

Canada

Monograph Combination Guide

Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. Health Canada is committed to improving the lives of all of Canada's people and to making this country's population among the healthiest in the world as measured by longevity, lifestyle and effective use of the public health care system.

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Foreword

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

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

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

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

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Overview

Purpose

The Natural and Non-Prescription Health Products Directorate (NNHPD) Monograph Combination Guide outlines NNHPD's expectations regarding best practices for attesting to multiple monographs in support of applications submitted for the licensing of natural health products (NHPs) in accordance with the Natural Health Product Regulations (NHPR). This guide aims to provide greater predictability and transparency for class II applications.

Scope

This guide is intended to help applicants determine the appropriate class of application for their products and situations in which a combination of monographs should be submitted as a class III application. While it aims to improve transparency and predictability regarding the class system, it cannot capture all specific scenarios that may occur. Depending on the product formulation and risk profile, NNHPD reserves the right to request additional information or reclassify a product.

Therefore, it should be used in conjunction with the Natural Health Products Management of Applications Policy (NHP MAP) for more information and guidance on the 3 application classes (**classes I, II and III**), which differ primarily in their use of NNHPD's monographs.

This guide does not apply to labelling standards, which are not considered equivalent to NNHPD's monographs. As such, they may only be used as part of the evidence to support class III applications.

Combinations of monograph

Specific qualifiers

For the purpose of this document, a specific qualifier is a word or phrase that associates a subpopulation or recommended use or purpose (that is, a claim) with a condition of use statement. Specific qualifiers should be used for products associated with conditions of use that do not apply to all subpopulations or claims to ensure consumers properly interpret the information. Although specific qualifiers cannot be selectable on the web-based Natural Health Product Licence Application Form (PLA form), this information can be added using the "other statements" text boxes rather than selecting the unqualified statement from the available options. It is important to avoid duplication of statements.

Examples of specific qualifiers:

- **As a diuretic**: For occasional use only (for example: Angelica - *Angelica archangelica* monograph):
    - A statement indicating the duration of use is required for products associated with a diuretic use. For products associated with other claims, a specific qualifier should be used on the label.
- **To aid digestion**: Ask a health care practitioner if symptoms persist or worsen (for example: Peppermint - *Mentha* x *piperita* monograph):
    - If a product is associated with symptomatic and non-symptomatic claims, the symptomatic claims should be associated with the cautionary statement.
- **Healthy mood balance**: Ask a health care practitioner before use if you have psychological disorders such as anxiety or depression (for example: Fish oil monograph):
    - A specific qualifier should also be used when a risk statement applies only to a specific use of a multi-use product.

Contradictory and/or conflicting conditions of use

Contradictory and/or conflicting information may exist when comparing the conditions of use between monographs. Such applications will not be considered as being entirely supported by a combination of 2 or more monographs and should be submitted as class III applications with supporting evidence. These scenarios include, but are not limited to:

a. The incompatibilities and/or conflicts cannot be resolved by omitting the statements required by the monographs to which the applicant attested;
b. The conditions of use required by a monograph exclude the conditions of use required by other monographs to which the applicant attested; and
c. The claimed effect of a product and/or its mechanisms of action, as required by and/or understood from the monographs to which the applicant attested, are contradictory and/or conflicting.

Table 1. Examples of (a) – the incompatibilities and/or conflicts cannot be resolved by omitting the statements required by the monographs to which the applicant attested

Statements	Incompatible
Take (1 hour) before bedtime, as needed	**Contradictory**

Table 1. Examples of (a) – the incompatibilities and/or conflicts cannot be resolved by omitting the statements required by the monographs to which the applicant attested	
Statements	**Incompatible**
Avoid taking before bedtime	
Use for at least 4 weeks to see beneficial effects	**Conflicting**
Ask a health care practitioner for use beyond 1 week	
Use for at least 12 weeks to see beneficial effects	**Conflicting**[1]
Ask a health care practitioner for use beyond 12 weeks	
For occasional use only[2]	**Contradictory**
Weight management claim (long-term use[3])	

[1] These statements are confusing to consumers and do not provide clear labelling information to help them make informed choices.
[2] NNHPD considers the statement “For occasional use only” to represent a duration of use that applies to products intended for supplementary use, when needed, (for example: on a specific occasion), but not typically to products intended for long-term continuous use. Products intended for occasional use may be used a few times per month (for example: caffeine at a dose higher than 400 mg/day to help temporarily promote alertness) or for a short, defined period of time (for example: bearberry as a mild diuretic to help relieve symptoms associated with minor urinary tract infections).
[3] Long-term use refers to claims requiring the regular use of a product for a duration of weeks or months. For example, claims supported by clinical trial evidence in which participants consume an ingredient daily for weeks or months are considered long-term uses. Similarly, general health claims that refer to maintaining good health or structure/function claims that imply maintaining or supporting a steady state may be considered long-term use.

Table 1. Examples of (a) – the incompatibilities and/or conflicts cannot be resolved by omitting the statements required by the monographs to which the applicant attested

Statements	Incompatible
Stimulant laxative[4]	**Conflicting**
Helps to support prostate health	

Table 2. Examples of (b) – the conditions of use required by a monograph exclude the conditions of use required by other monographs to which the applicant attested

Statements	Incompatible
Used in Herbal Medicine to assist healing of minor wounds such as cuts and burns, and minor skin irritations	**Contradictory**
Do not apply to open wounds or damaged skin	
Helps to support normal early fetal development (brain and spinal cord)	**Conflicting (with the warning statement)**
Ask a health care practitioner if you are pregnant or breastfeeding or **Do not use if** you are pregnant or breastfeeding	**Contradictory (with the contraindication statement)**

[4] Due to their limited duration of use and concerns about interfering with the absorption of co-administered ingredients, products containing stimulant laxatives at their therapeutic dose must be associated with laxative-related claims and cannot make any other claims except diuretic claims.

Table 2. Examples of (b) – the conditions of use required by a monograph exclude the conditions of use required by other monographs to which the applicant attested

Statements	Incompatible
Helps maintain development of brain, eyes and nerves in children up to 12 years of age	**Contradictory**
Adults 18 years and older	

Table 3. Examples of (c) – the claimed effect of a product and/or its mechanisms of action, as required by and/or understood from the monographs to which the applicant attested, are contradictory and/or conflicting

Statements	Incompatible
Intended to relieve joint or muscle pain by causing a superficial irritation of the skin (for example: ingredients from the Counterirritants monograph)	**Contradictory**
Intended to protect and help relieve skin irritation (for example: ingredients from the Medicated skin care products monograph)	
Sedative (for example: valerian)	**Contradictory**
Promotes alertness and wakefulness (for example: caffeine)	

Multiple conditions of use statements

Applicants who omit and/or select conditions of use in a class II application under the circumstances described below must still attest to the monograph for all applicable parameters. The same applies to applicants who choose to attest to a monograph in a class III application.

Duplicate statements

If the same conditions of use statement is required by more than one monograph, it should only be selected once on the PLA form; and therefore, displayed only once on the label.

Table 4. Example of duplicated statements

Statements	Statement to be selected on the PLA form
Take with food	Select only 1 statement
Take with food	

Multiple statements

If an applicant attests to 2 or more monographs with statements related to the same conditions of use, the less stringent statements should be omitted and only the most stringent statement should be included on the PLA form. If applicable, risk statements may be grouped together or modified using the free-text option on the PLA form to avoid repetition of similar statements.

This applies to maximum duration of use statements required to ensure the safety of a product. However, this does not apply to minimum duration of use statements required to see beneficial effects as these statements must all be kept when the associated claims are made and be associated with their respective claims, unless the claims are identical or at least comparable. This can be accomplished by adding the duration of use statements with their associated claims in the text boxes (“other statements”), rather than selecting the duration of use statements from the available options.

Multiple minimum duration of use statements for different claims

For example:

- For reduction of menopausal symptoms: use for at least 2 weeks to see beneficial effects; and
- For reduction of bone loss: use for at least 6 months to see beneficial effects

Multiple minimum duration of use statements for identical claims

Table 5. Example of multiple minimum duration of use statements for identical claims

Statements	Statement to be selected on the PLA form
For joint pain: Use for a minimum of 4 weeks to see beneficial effects	Use for a minimum of **4 weeks** to see beneficial effects (the shorter duration of use must be selected)
For joint pain: Use for a minimum of 8 weeks to see beneficial effects	

Multiple maximum duration of use statements

Table 6. Example of multiple maximum duration of use statements

Statements	Statement to be selected on the PLA form
Ask a health care practitioner for use beyond 4 weeks	Ask a health care practitioner for use beyond **4 weeks** (the shorter duration of use must be selected)
Ask a health care practitioner for use beyond 8 weeks	

Multiple directions for use statements

Table 7. Example of multiple directions for use statements

Statements	Statement to be selected on the PLA form
Take with a meal/food	Select only 1 statement. The most inclusive statement should be selected: • Take with a meal/food
Take with food	
Take with meal	

Multiple risk statements for the same condition or medication

If a condition or medication is mentioned in both a cautionary statement and a contraindication statement, it should only be listed in the contraindication statement. The cautionary statement should be updated to reflect this change.

Table 8. Examples of multiple risk statements for the same condition or medication

Statements	Statements to be listed on the PLA form
Ask a health care practitioner before use if you have a kidney disorder and/or diabetes	**Ask a health care practitioner before use if** you have a kidney disorder **Do not use if** you have cardiovascular disease (CVD), diabetes, metabolic syndrome or insulin resistance
Do not use if you have cardiovascular disease (CVD), diabetes, metabolic syndrome or insulin resistance	
Ask a health care practitioner before use if you are taking antidepressant medication, blood thinners or digoxin	**Ask a health care practitioner before use if** you are taking antidepressant medication or digoxin

Table 8. Examples of multiple risk statements for the same condition or medication	
Statements	**Statements to be listed on the PLA form**
Do not use if you are taking blood thinners or other health products that affect blood coagulation	**Do not use if** you are taking blood thinners or other health products that affect blood coagulation
Ask a health care practitioner if you are pregnant or breastfeeding	**Do not use if** you are pregnant or breastfeeding
Do not use if you are pregnant or breastfeeding	

Subpopulation-specific risk information

If the product is not recommended for a specific subpopulation, there is no obligation to include a risk statement for that subpopulation on the PLA form.

Table 9. Examples of subpopulation-specific risk information	
Statements	**Statements to be listed on the PLA form**
Ask a health care practitioner before use if you are pregnant or breastfeeding.	Subpopulation: **Adult male** Risk statements regarding pregnant, breastfeeding or women attempting to conceive are not required
Do not use if you are pregnant, breastfeeding, or attempting to conceive	
No subpopulation-specific risk statements	

Table 9. Examples of subpopulation-specific risk information	
Statements	**Statements to be listed on the PLA form**
Ask a health care practitioner before use if you are pregnant or breastfeeding.	Subpopulation: **Children 3-11 years**[5] Risk statement regarding pregnant or breastfeeding women is not required

Combinations with additive doses

If a product contains 2 or more ingredients (medicinal and/or non-medicinal) that are known to have the same or similar pharmacological effects, which could be concerning if these effects were additive, use **Table 10** to assess the potential additive dose of these ingredients in the product. Quantities of the ingredients of concerns, including non-medicinal ingredients, and the calculations must be provided as part of the cover letter. This requirement applies even to sub-therapeutic ingredients and/or when no related claim is made regarding such pharmacological effects. This also applies to maximum single doses when required.

Refer to **Appendix I** for a list of ingredients grouped by pharmacological effects considered by NNHPD when monographs are combined.

[5] Pregnant or breastfeeding risk statement is required for adolescents 12 to 17 years old.

Table 10. Combination table to assess potential additive dose						
Potential additive effect	For example: Sedative					
Recommended dose	For example: X dosage unit(s), X time(s) per day					
Ingredients (Source)	**On the monographs[6]**		**On the PLA form**		**Results**	
	A. Minimum Daily Reference Dose	**B. Maximum Daily Reference Dose**	**C. Quantity per Dosage Unit**	**D. Maximum Daily Dose**	**E. Percentage of the Minimum Daily Reference Dose (%)**	**F. Percentage of the Maximum Daily Reference Dose (%)**
Ingredient 1 (Source)	XX g	XX g	XX g	XX g	XX%	XX%
Ingredient 2 (Source)	XX g	XX g	XX g	XX g	XX%	XX%
Ingredient 3 (Source)	XX g	XX g	XX g	XX g	XX%	XX%
Sum of Percentages:					**XX%**	**XX%**

[6] For non-medicinal ingredients in a product that are also monographed as medicinal, such as those that contribute to water and/or electrolyte imbalance as listed in Appendix I (that is, licorice, dandelion, and angelica), the monograph dose(s) should be used for calculations. Other supporting evidence should be used for ingredients that are not supported by a monograph.

Notes:

- Each ingredient must comply with the parameters specified in its respective monograph (for example: no single ingredient can exceed 100% of the maximum daily reference dose) for class II applications.
- **For extracts:**
    - If the monograph specifies the minimum and maximum daily doses in terms of “dry” or “fresh” source materials, the quantities in **Columns C and D** should represent the appropriate quantity crude equivalent (QCE) instead of the quantity per dosage unit for such ingredients.
    - The quantity per dosage unit should only be used when the monograph specifies the minimum and maximum daily doses in terms of extract amount, which is typically reserved for standardized extracts. In such cases, the quantity of the potency constituent(s) must be considered in the calculations.

The calculations are performed as follows:

- Percentage of the minimum daily reference dose (E) = [(Maximum daily recommended dose (D)) / (Minimum daily monograph reference dose (A))] x 100%; and
- Percentage of the maximum daily reference dose (F) = [(Maximum daily recommended dose (D)) / (Maximum daily monograph reference dose (B))] x 100%

Refer to **Appendix II** for examples of calculations.

The next sections provide some guidelines for specific ingredient classes with known additive effects. Unless supporting evidence is provided as part of a class III application, **Column F (sum)** (sum of the percentage of the maximum daily reference dose) must not exceed 120% when there are no specific rule captured below.

Ingredients contributing to water and/or electrolyte imbalance

The following ingredients must all be included into the same combination table for safety:

- Diuretics
- Licorice; and
- Stimulant laxatives

Bulk-forming laxatives, that promote bowel movements by increasing bulk volume and water content (for example: psyllium, or flaxseed), are not to be included in the combination table. Products containing these medicinal ingredients typically take 1 to 3 days to be effective, whereas the ingredients to be included in this combination table typically work in shorter time frames. Therefore, water loss due to bulk-forming laxatives is not expected to have an additive effect when combined with other ingredients that have a quicker impact on water and/or electrolyte balance.

Note: Licorice and stimulant laxatives are permitted in combination provided that the licorice is deglycyrrhizinated (that is: contains less than 3% glycyrrhizin), or the glycyrrhizic acid dose from the licorice does not exceed 16 mg/day. The glycyrrhizin content must be provided in the cover letter to demonstrate deglycyrrhizination.

Products containing 1 or more stimulant laxatives at therapeutic doses

Products containing 1 or more stimulant laxatives at therapeutic doses must be associated with a stimulant laxative claim. However, they cannot be associated with other claims unless supporting evidence is submitted as a class III application. This is due to their limited duration of use and concerns regarding interference with the absorption of co-administered ingredients. However, a diuretic claim may be made if the product also contains a diuretic ingredient.

Table 11. Rules for class II applications: 1 or more stimulant laxatives at therapeutic doses – no diuretic

Examples of monographs	Combination Table[7]	To be listed on the PLA form
Senna – *Senna alexandrina* Cascara sagrada – *Frangula purshiana*	**Column E (sum) (stimulant laxatives)**: More than 100%[8] **Column F (sum) (all ingredients contributing to water and/or electrolyte imbalance)**: 120% or less Note that at least one of the stimulant laxatives must meet the minimum therapeutic amount and no single ingredient can exceed 100% of its maximum daily reference dose	• Claims from the stimulant laxatives must be listed on the PLA form; and • No other claim can be made in class II applications
Products that do not meet the above requirements must be submitted with supporting evidence as **class III applications**		

[7] Conditions under which the information in the column to the right applies.
[8] Column E = 100% or more, if the product contains only 1 stimulant laxative.

Products containing 1 or more stimulant laxatives at therapeutic doses and 1 or more diuretics

Diuretics should not be included in the calculations for Column E, but they should be included in the calculations for Column F.

Table 12. Rules for class II applications: 1 or more stimulant laxatives at therapeutic doses + 1 or more diuretics

Examples of monographs	Combination Table[9]	To be listed on the PLA form
Senna – *Senna alexandrina* Cascara sagrada - *Frangula purshiana* Burdock – *Arctium lappa* – Oral	**Column E (sum) (stimulant laxatives)**: More than 100%[10] **Column F (sum) (all ingredients contributing to water and/or electrolyte imbalance)**: 120% or less Note that at least one of the stimulant laxatives must meet the minimum therapeutic amount and no single ingredient can exceed 100% of its maximum daily reference dose	• Must include a laxative claim; • May include a diuretic claim; and • No other claim can be made in class II applications
Products that do not meet the above requirements must be submitted with supporting evidence as **class III applications**		

Products containing 1 or more stimulant laxatives at sub-therapeutic doses, singly or when combined – no laxative claim

The inclusion of stimulant laxatives at sub-therapeutic doses in products not intended for use as laxatives should be avoided. However, this may be permitted for short-term use in

[9] Conditions under which the information in the column to the right applies.
[10] Column E = 100% or more, if the product contains only 1 stimulant laxative.

related products, such as cleansing health products that support the body's natural detoxification processes.

Table 13. Rules for class II applications: 1 or more stimulant laxatives at sub-therapeutic doses – no laxative claim

Examples of monographs	Combination Table[11]	To be listed on the PLA form
Senna – *Senna alexandrina* Cascara sagrada – *Frangula purshiana*	Sub-therapeutic - no laxative claim **Column E (sum) (stimulant laxatives)**: 10% to less than 100%[12] **Column F (sum) (all ingredients contributing to water and/or electrolyte imbalance)**: 120% or less Note that no single ingredient can exceed 100% of its maximum daily reference dose	• The monographed stimulant laxative directions for use statements should be removed except "Take a few hours before or after taking other medications or health products"; and • The following risk statements must be included in addition to the monographed statements unless already part of the monographed statements. **It is important to avoid any duplication**: ○ **When using this product**, a laxative effect may occur; and ○ **Stop use if** you experience abdominal pain, cramps, and/or spasms
Products that do not meet the above requirements must be submitted with supporting evidence as **class III applications**		

Products containing 2 or more diuretics, including any non-medicinal ingredient contributing to water and/or electrolyte imbalance, associated with a diuretic claim, but not containing licorice (see examples in Appendix I)

[11] Conditions under which the information in the column to the right applies.
[12] Also applies if the product contains only 1 stimulant laxative.

Table 14. Rules for class II applications: 2 or more diuretics (including any non-medicinal ingredient contributing to water and/or electrolyte imbalance) – with a diuretic claim

Examples of monographs	Combination Table[13]	To be listed on the PLA form
Burdock – *Actium lappa* – Oral Juniper – *Juniperus communis*	**Column E (sum) (diuretics):** More than 100% **Column F (sum) (all ingredients contributing to water and/or electrolyte imbalance**): 120% or less Note that at least one of the diuretics must meet the minimum therapeutic amount and no single ingredient can exceed 100% of its maximum daily reference dose	• A diuretic claim is listed on the PLA form. • The duration of use "For occasional use only" must always be associated with a diuretic claim; and • The following risk statements must be included[14] in addition to the monographed statements and adjusted to keep the most stringent option as per Table 8 if conditions or medications are already mentioned as per the respective attested monographs. **It is important to avoid any duplication**: ○ **Ask a health care practitioner before use if** you have a liver or biliary disorder or an intestinal obstruction; ○ **Do not use if** you have diabetes or a blood pressure, kidney or cardiovascular disorder; ○ **Do not use if** you are taking heart medications or other

[13] Conditions under which the information in the column to the right applies.
[14] Additional risk statements are required on the PLA form because the product contains multiple diuretics. The risk of dehydration and electrolyte imbalance increases as the number and dose of diuretics increases. Diuretics can act at multiple sites in the kidneys, resulting in excessive loss of sodium, potassium and water when reabsorption is blocked at multiple sites. The mechanisms of action and/or the dose-response relationship of (NHP) diuretics are generally unknown, and there is no safety evidence (in the form of clinical trials) supporting the combination of these diuretics.

Table 14. Rules for class II applications: 2 or more diuretics (including any non-medicinal ingredient contributing to water and/or electrolyte imbalance) – with a diuretic claim		
Examples of monographs	**Combination Table[13]**	**To be listed on the PLA form**
		○ products containing diuretics; and ○ **Stop use and ask a health care practitioner if** you experience dizziness, confusion, muscle weakness or pain, abnormal heartbeat and/or difficulty breathing
Products that do not meet the above requirements must be submitted with supporting evidence as **class III applications**		

Products containing 2 or more diuretics, including any non-medicinal ingredient(s) contributing to water and/or electrolyte imbalance, not associated with a diuretic claim, and not containing licorice (see examples listed in Appendix I)

Table 15a. Rules for class II applications: 2 or more diuretics (including any non-medicinal ingredient contributing to water and/or electrolyte imbalance). Column E (sum): 10% or more – no diuretic claim

Examples of monographs	Combination Table[15]	To be listed on the PLA form

Burdock – *Actium lappa* – Oral
 	
Juniper – *Juniperus communis*
	Column E (sum) (diuretics): 10% or more
	
	Column F (sum) (all ingredients contributing to water and/or electrolyte imbalance): 120% or less
	
	Note that no single ingredient can exceed 100% of its maximum daily reference dose
		• No diuretic claim listed on the PLA form.
		• The conditions of use statements listed in Table 14 apply except:
		  ○ The duration of use "For occasional use only"; and
		  ○ The statement "**Ask a health care practitioner if** symptoms persist or worsen", which is listed on the monographs with a diuretic claim, unless it is required for another claim and
		• The following risk statements must be included when no diuretic claim is made:
		  ○ **When using this product** diuretic effect may occur

Products that do not meet the above requirements must be submitted with supporting evidence as **class III applications**		

[15] Conditions under which the information in the column to the right applies.

Table 15b. Rules for class II applications: 2 or more diuretics (including any non-medicinal ingredient contributing to water and/or electrolyte imbalance). Column E (sum): Less than 10% – no diuretic claim		
Example of Monographs	**Combination Table[16]**	**To be listed on the PLA form**
Burdock – *Actium lappa* – Oral	**Column E (sum) (diuretics):** Less than 10%	No diuretic claim listed on the PLA form. No additional risk information is required beyond the monographed statements
Juniper – *Juniperus communis*		
Products that do not meet the above requirements must be submitted with supporting evidence as **class III applications**		

Products containing 2 or more diuretics and including any non-medicinal ingredient contributing to water and/or electrolyte imbalance, and containing licorice (see examples listed in Appendix I)

Table 16. Rules for class II applications: 2 or more diuretics (including any non-medicinal ingredient contributing to water and/or electrolyte imbalance), and containing licorice		
Examples of monographs	**Combination Table[17]**	**To be listed on the PLA form**
Licorice		

[16] Conditions under which the information in the column to the right applies.
[17] Conditions under which the information in the column to the right applies.

Table 16. Rules for class II applications: 2 or more diuretics (including any non-medicinal ingredient contributing to water and/or electrolyte imbalance), and containing licorice

Examples of monographs	Combination Table[17]	To be listed on the PLA form
Burdock – *Actium lappa* – Oral Juniper – *Juniperus communis*	**Column E (sum) (diuretics only – excluding licorice):** 10% or more **Column F (sum) (all ingredients contributing to water and/or electrolyte imbalance including licorice):** 120% or less Note that no single ingredient can exceed 100% of its maximum daily reference dose	• The duration of use "For occasional use only" must be associated with a diuretic claim if made (for example: As a diuretic: For occasional use only); • The duration of use "Ask a health care practitioner for use beyond 4 weeks" is required due to the presence of licorice; • The following risk statements must be included[18] in addition to the monographed statements and adjusted to keep the most stringent option as per Table 8 if conditions or medications are already mentioned as per the respective supporting monographs. **It is important to avoid any duplication**: ○ **Ask a health care practitioner before use if** you have a liver or biliary disorder or an intestinal obstruction; ○ **Do not use if** you have heart disease, high or low blood

[18] Additional risk statements are required on the PLA form because the product contains multiple diuretics and licorice. The risk of dehydration and electrolyte imbalance increases as the number and dose of diuretics and licorice increases. Diuretics and licorice can act at multiple sites in the kidneys, resulting in excessive loss of sodium, potassium and water when reabsorption is blocked at multiple sites. The mechanisms of action and/or the dose-response relationship of (NHP) diuretics are generally unknown, and there is no safety evidence (in the form of clinical trials) supporting the combination of these diuretics and licorice.

Table 16. Rules for class II applications: 2 or more diuretics (including any non-medicinal ingredient contributing to water and/or electrolyte imbalance), and containing licorice

Examples of monographs	Combination Table[17]	To be listed on the PLA form
		pressure, kidney or liver disorder, hypokalemia, diabetes or edema (swelling of hands, face and feet); and ○ **Stop use and ask a health care practitioner if** you experience dizziness, confusion, muscle weakness or pain, abnormal heartbeat and/or difficulty breathing; and • The following risk statements must be included when no diuretic claim is made: ○ **When using this product** diuretic effect may occur
Products that do not meet the above requirements must be submitted with supporting evidence as **class III applications**		

Sedative effect

Table 17. Rules for class II applications: 2 or more ingredients with sedative effects (see examples listed in Appendix I)

Examples of monographs	Combination Table[19]	To be listed on the PLA form
Melatonin – Oral	**Column F (sum)**: 120% or less (applies to all products containing sedatives, regardless of whether the product attests to the Cognitive Function Products monograph) Note that no single ingredient can exceed 100% of its maximum daily reference dose	No additional risk information is required beyond the monographed statements
Valerian – *Valeriana officinalis*		
Products that do not meet the above requirements must be submitted with supporting evidence as **class III applications**		

Glucose-modifying effect

Products containing 2 or more ingredients with glucose-modifying effects (excluding chromium), with or without an associated glucose-related claim

[19] Conditions under which the information in the column to the right applies.

Table 18. Rules for class II applications: 2 or more ingredients with glucose-modifying effects (excluding chromium; see examples listed in Appendix I)

Examples of monographs	Combination Table[20]	To be listed on the PLA form
Fenugreek – *Trigonella foenum-graecum* Panax ginseng	**Column F (sum)**: 120% or less Note that no single ingredient can exceed 100% of its maximum daily reference dose	The following risk statements are required if ingredients in Appendix I (glucose modifying) are combined and not already covered by identical or more stringent monograph statements: **Column E (sum):** 10% or more • **Ask a health care practitioner before use if** you have diabetes; **Column E (sum):** At any dose • **Ask a health care practitioner before use if** you are pregnant or breastfeeding (unless a monograph already requires: "**Do not use if** you are pregnant or breastfeeding")
Products that do not meet the above requirements must be submitted with supporting evidence as **class III applications**		

Products making a medium-level risk glucose claim and containing free sugars. The ingredient quantity must be declared on the PLA form as free sugars are known to increase blood glucose

The glucose-modifying ingredients "beta-glucan" and "white kidney bean extract" are included in the rules for free sugars because their monograph contains medium-level risk glucose claims, such as "Helps improve". This is not required for other monographed medicinal ingredients with low-level risk glucose claims on their

[20] Conditions under which the information in the column to the right applies.

monographs; however, a non-medicinal ingredient should not have any effect contradictory to the product's recommended claim.

Table 19. Rules for medium-level risk glucose claims from beta-glucan and white kidney bean extract monographs – with free sugar

Examples of monographs	Combination[21]	To be listed on the PLA form + Appropriate class

beta-Glucan
 	
and/or
 	
White kidney bean extract
	A medium-level risk glucose claim from these monographs is listed on the PLA form
	
	+
	
	Free sugar(s) (see examples listed in Appendix I)
		• The quantity of the free sugars must be provided on the PLA form; and
		• Products must be submitted with supporting evidence and/or rationale as **class III applications**:
		  ○ to support safety (free sugars may be of concern for specific subpopulations where tracking sugar intake is an important step in managing their disease(s) – for example: diabetes, prediabetes, metabolic syndrome, obesity, non-alcoholic fatty liver disease); and
		  ○ to support efficacy (glucose claims may be affected by the presence of free sugars in a product); and
		• The risk statement “This product contains XX g of sugars” should be added, similarly to Health Canada nutrient table. This statement is intended to alert all subpopulations where sugar intake may be of concern, rather than adding a contraindication for specific subpopulations that may not be inclusive of all potentially relevant diseases.

[21] Conditions under which the information in the column to the right applies.

Blood pressure-lowering effect

Table 20. Rules for class II applications: 2 or more ingredients with blood pressure-lowering effects (see examples in Appendix I)

Examples of monographs	Combination Table[22]	To be listed on the PLA form
Green coffee bean extract Coenzyme Q10	**Column F (sum):** More than 100% and up to 120% Note that no single ingredient can exceed 100% of its maximum daily reference dose	The following risk statements are required in addition to the monographed statements and adjusted to keep the most stringent option as per Table 8 if conditions or medications are already mentioned as per the respective attested monographs. **It is important to avoid any duplication**: • **Ask a health care practitioner before use if** you have low blood pressure, or if you take blood pressure medication; and • **Stop use and ask a health care practitioner if** you experience headaches or confusion, or feel faint, dizzy or light-headed
Products that do not meet the above requirements must be submitted with supporting evidence as **class III application**		

Estrogenic or anti-estrogenic effect

Specific combination rules apply to medicinal ingredients with estrogenic (for example: red clover isoflavone extract, soybean extracts and isolates and dong quai – *Angelica sinensis*) or anti-estrogenic effects [(for example: indole-3-carbinol (I3C) and, diindolylmethane (DIM)].

For combination of estrogenic and anti-estrogenic ingredients

Combinations of estrogenic and anti-estrogenic ingredients should be submitted as **class III applications**. Combining these ingredients is expected to lead to reduced efficacy for

[22] Conditions under which the information in the column to the right applies.

all ingredients involved, at any dose. Additionally, products that recommend unstudied combination of counteracting ingredients are likely to have unintended and/or unknown effects. While some combinations may make sense for a particular product, they nevertheless require assessment to minimize any unintended risks to consumers.

For estrogenic ingredients

Soy isoflavones, red clover isoflavones, and dong quai either are or contain estrogen mimics (that is, agonists) that can directly interact with estrogen receptors. These types of ingredients can act primarily as weak estrogen-mimics. As such, under certain scenarios, they can also act in an anti-estrogenic capacity (for example: by competing with estradiol in a pre-menopausal state).

Table 21. Rules for class II applications: 2 or more ingredients with estrogenic effects (see examples in Appendix I)

Examples of monographs	Combination Table[23]	To be listed on the PLA form
Soybean extracts and isolates	**Column F (sum):** 100% or less Note that no single ingredient can exceed 100% of its maximum daily reference dose	No additional risk information is required beyond the monographed statements
Dong quai – *Angelica sinensis*		
Products that do not meet the above requirements must be submitted with supporting evidence as **class III applications**		

For anti-estrogenic ingredients

Ingredients such as I3C and DIM are primarily considered to be associated with anti-estrogenic effects due to altered metabolism. Although indirect effects on estrogen receptors can still occur, these isolates elicit conventional drug-like effects by enhancing

[23] Conditions under which the information in the column to the right applies.

the production of 2-hydroxyestrone and decreasing the production of 16-α-hydroxyestrone, resulting in a less active estrogenic state.

Table 22. Rules for class II applications: 2 or more ingredients with anti-estrogenic effects (see examples in Appendix I)

Example of Monographs	Combination Table[24]	To be listed on the PLA form
DIM	**Column F (sum):** 100% or less Note that no single ingredient can exceed 100% of its maximum daily reference dose	No additional risk information is required beyond the monographed statements
I3C		
Products that do not meet the above requirements must be submitted with supporting evidence as **class III applications**		

For medicinal ingredients containing isoflavones

Ingredients such as soy, soy isoflavone extract, soy protein and red clover contain isoflavones. The Workout Supplements monograph currently permits 2.6 – 35 g of protein per day, with a maximum of 30 mg aglycone isoflavone equivalents (AIE). Up to 30 mg AIE is not currently considered to elicit estrogenic effects; however, additive effects are possible when combined with other estrogenic ingredients. A maximum of 125 mg AIE per day should considered from all sources (as specified in the Soybean Extracts and Isolates monograph).

[24] Conditions under which the information in the column to the right applies.

Table 23. Rules for class II applications: 2 or more ingredients with AIE

Examples of monographs	Maximum daily dose[25]	To be listed on the PLA form
Soybean extracts and isolates	**Total Maximum daily dose:** 125 mg total AIE Note that no single ingredient can exceed its respective maximum daily monographed dose The potency for isoflavones must be listed on the PLA form	No additional risk information is required beyond the monographed statements
Red clover isoflavone extract		
Products that do not meet the above requirements must be submitted with supporting evidence as **class III applications**		

Combination rules within monographs

Many NNHPD monographs include additional notes and combination rules applicable to ingredient combinations within 1 or more monographs. Therefore, products that do not comply with all the parameters of the monograph(s), including the combination rules, should be submitted as class III applications with supporting evidence.

Proteins and/or amino acids

The rules from the Workout Supplements monograph apply to all proteins and/or amino acids, including those not included in the monograph. For example:

- Products must provide at least 2.6 g of total protein and/or amino acids to support protein-related claims, with a maximum of 90 g total protein and/or amino acids.
- For safety, the maximum allowable quantity of amino acids is specific to free amino acids. The quantity of amino acids as sub-ingredients is only taken into account if they are free. For example, amino acids that are components of proteins are not

[25] Conditions under which the information in the column to the right applies.

free. However, highly hydrolyzed proteins may contain free amino acids. It is the applicant's responsibility to know the composition of their ingredient.
- For efficacy, the total amino acid content (from amino acids as protein sub-ingredients and as individual medicinal ingredients) can be used to support 'Source of' claims. However, this does not apply to more specific amino acid claims which are based on studies that administer individual amino acids to participants as the pharmacokinetics and effects of free amino acids may differ from those of amino acids as protein sub-ingredients.
- Soy protein concentrate and/or soy protein isolate must not exceed 35 g of protein per day with a maximum of 30 mg of AIE per day.

The following risk statements must be listed on the PLA form for products providing more than 30 g total protein and/or amino acids per day:

- **Ask a health care practitioner before use if** you have a liver or kidney disorder; and
- **When using this product** you may experience gastrointestinal discomfort/ disturbances.

Other combination rules

Considerations regarding total amount of constituents and/or ingredients in a product formulation

Some ingredient combinations, including non-medicinal ingredients, may affect the safety and/or efficacy of a product. In these cases, the amount of the ingredient and/or constituent must be declared for all medicinal and non-medicinal ingredients, and the total amount per single dose and/or per day must meet the evidence requirements. The total amount of the ingredient and/or constituent in the product formulation may also be listed as additional information in the directions for use (for example: This product provides XX mg of total caffeine per dose or per day).

They include, but are not limited to, the following:

- Caffeine
- Iodine
- Stimulant laxatives
- Diuretics

The total daily amount of an ingredient and/or constituent (or the total single dose if applicable) must be declared in the cover letter. If the cover letter does not provide this information, NNHPD may request clarification via an Information Request Notice.

Recommended conditions of use for sub-therapeutic ingredients (10% criterion)

NNHPD has adopted a standard for applying recommended conditions of use based on the minimum known therapeutic dose of an ingredient or when a known risk exists.

In most cases, a product supported by a combination of monographs only requires recommended conditions of use (for example: duration of use, directions for use, and risk information) for the maximum daily (and/or single, if applicable) dose of the ingredient in the product if it is **equal to or greater than 10%** of the minimum therapeutic dose, unless otherwise specified in a monograph.

If duration of use, directions for use or risk statements are already outlined by dosage range in monographs, these conditions of use only apply within that dosage range. They are not required below the minimum of that dosage range and should not appear on the PLA form. In some cases, a combination of ingredients at quantities less than 10% of their respective minimum therapeutic doses may require additional conditions of use based on a combination table (see section **Combination with additive dose** of this guide for examples).

When the therapeutic dose is between zero and a maximum amount (for example: antioxidants), the associated conditions of use should be included on the PLA form for all doses.

The following are examples of situations in which the 10% criterion would not apply. Some statements are required regardless of ingredient quantity:

Risk statements:

- For pregnant, breastfeeding, or women planning to conceive;
- For children and adolescents;
- For allergic reactions, hypersensitivity or skin reactions;
- Known adverse reaction statements. These are often not associated with a specific dose and may be required at any dose;
- For liver toxicity (for example: Malabar tamarind, hydroxycitric acid, turmeric, curcuminoids including curcumin, green tea extract, and black cohosh);
    - **Ask a health care practitioner before use if** you have a liver disorder, if you are taking medications.
    - **Stop use and ask a health care practitioner if** you experience any new symptoms including yellowing of the eyes or skin, dark urine, nausea, vomiting, stomach pain.
- Keep out of reach of children;
- Linked to phototoxicity or sensitization;

Topical products:

- For external use only;

- **When using this product** avoid contact with the eyes and mucous membranes. If contact occurs, rinse thoroughly with water;
- If swallowed, call a poison control centre or get medical help right away.
- Do not apply to wounds, or damaged, broken, irritated, or sensitive skin;

Conditions of use:

- Where conditions of use for an ingredient are required, regardless of the dose;
- Where multiple ingredients have additive effects and the cumulative minimum therapeutic doses exceed 10%, the inclusion of conditions of use should be considered.

This list is not exhaustive, and NNHPD may request the addition of recommended conditions of use based on the product's formulation and overall risk profile.

If any statement is omitted based on the 10% criterion, the reason for the omission and the omitted statements must be specified in the cover letter.

Glossary

For the definition of key terms, refer to the NHP MAP and the guidance document Pathway for Licensing Natural Health Products Making Modern Health Claims.

Appendix I: Ingredients and pharmacological effects

Table 24. Examples of ingredients grouped by pharmacological effects. This list includes most of the monographed ingredients, but it is not exhaustive. Some non-medicinal ingredients that contribute to electrolyte imbalances and free sugars are also listed.

Diuretics

- *Angelica archangelica*
- *Arctium lappa*
- *Arctostaphylos uva-ursi*
- *Armoracia rusticana*
- *Betula pendula*
- *Betula pubescens*
- *Boswellia sacra*
- *Caffeine (from any source)*
- *Glechoma hederacea*
- *Juniperus communis*
- *Olea europaea (leaf)*
- *Pulmonaria officinalis*
- *Sambucus nigra subsp. canadensis*

- *Sambucus nigra subsp. nigra*
- *Scrophularia nodosa*
- *Taraxacum officinale*
- *Tribulus terrestris*
- *Urtica dioica*
- *Wolfiporia extensa*

Stimulant laxatives

- *Aloe vera/ferox* (leaf latex)
- *Frangula purshiana* (Cascara sagrada)
- *Senna alexandrina*

Non-medicinal ingredients contributing to water and/or electrolyte imbalance

- Angelica root dry (diuretic)
- Dandelion root dry (diuretic)
- Castor oil - hydrogenated (stimulant laxative)
- Heavy mineral oil (stimulant laxative)
- Light mineral oil (stimulant laxative)
- Mineral oil (stimulant laxative)
- Liquorice dry (licorice)
- Licorice flavour (licorice)

Blood-pressure lowering

- Coenzyme Q10
- *Crataegus laevigata*
- *Crataegus monogyna*
- Green coffee bean extract
- *Ocimum tenuiflorum* (Holy basil)
- *Olea europaea* (leaf)
- *Tribulus terrestris*
- Ubiquinol

Glucose-modifying

- DL-alpha-Lipoic acid
- R-alpha-Lipoic acid
- American ginseng
- beta-Glucan
- *Cinnamomum aromaticum*
- Glucomannan
- *Glycine max*
- Inulin
- *Irvingia gaborensis*

- *Moringa oleifera*
- *Ocimum tenuiflorum*
- Panax ginseng
- *Phaseolus vulgaris*
- Propolis
- *Trigonella foenum-graecum*
- *Vaccinium myrtillus*

Free sugars (Reference: Diabetes Canada)

- Agave syrup
- Barley malt
- Brown rice syrup
- Brown sugar
- Corn syrup
- Dextrose
- Fructose
- Fruit juice concentrates
- Glucose
- High fructose corn syrup
- Honey
- Invert sugar
- Lactose
- Maltodextrins
- Maltose
- Maple syrup
- Molasses
- Sucrose

Iodine from kelp

- *Ascophyllum nodosum*
- *Fucus vesiculosus*
- *Laminaria digitata*
- *Saccharina japonica*

Estrogenic effects or anti-estrogenic effects

Associated with estrogenic effect

- Dong quai - *Angelica sinensis*
- Red clover isoflavone extract
- Soybean extracts and isolates
- *Tribulus terrestris*

Associated with anti-estrogenic effects

- 3,3'-Diindolylmethane (DIM)
- Indole-3-carbinol (I3C)

Sedatives

- *Eschscholzia californica*
- *Humulus lupulus*
- Melatonin
- *Passiflora incarnata*
- *Valeriana officinalis*

Weight management

- Green tea extract
- Chitosan
- Conjugated linoleic acid
- Green coffee bean extract
- African wild mango
- 5-HTP
- White kidney bean extract

Appendix II: Examples of calculations

Table 25. Example #1 of a combination table to assess potential additive dose - diuretics

Potential additive effect	Diuretic (no diuretic claim)					
Recommended dose	1 capsule, 2 times per day					
Ingredients (Source)	**On the monographs**		**On the PLA form**		**Results**	
	A. Minimum Daily Reference Dose	**B. Maximum Daily Reference Dose**	**C. Quantity per Dosage Unit**	**D. Maximum Daily Dose**	**E. Percentage of the Minimum Daily Reference Dose (%)**	**F. Percentage of the Maximum Daily Reference Dose (%)**
Burdock (Root)	1.2 g	18 g	0.2 g	0.4 g	0.4/1.2 = 33.3%	0.4/18 = 2.2%
Dandelion (Leaf)	1.2 g	30 g	0.1 g	0.2 g	0.2/1.2 = 16.7%	0.2/30 = 0.67%
Caffeine	0.1 g	1 g	0.01 g	0.02 g	0.02/0.1 = 20%	0.02/1 = 0.02%
Sum of Percentages:					**70%**	**2.89%**

Columns A and B: In accordance with the Burdock - *Arctium lappa* - Oral monograph, Dandelion – *Taraxacum officinale* monograph, and Caffeine monograph, respectively.

Conclusions:

This product contains 3 diuretics and is not associated with a diuretic claim. The sum of the percentages of the minimum daily reference doses is greater than 10% and the sum of the maximum daily reference doses is lower than 120%.

The following risk statements must be included in addition to the monographed statements and adjusted to keep the most stringent option as per **Table 8** if conditions or medications are already mentioned as per the respective supporting monographs:

- **Ask a health care practitioner before use if** you have a liver or biliary disorder or an intestinal obstruction;
- **Do not use if** you have diabetes or a blood pressure, kidney or cardiovascular disorder;
- **Do not use if** you are taking heart medications or other products containing diuretics;
- **Stop use and ask a health care practitioner if** you experience dizziness, confusion, muscle weakness or pain, abnormal heartbeat and/or difficulty breathing.

The monographed statement "**Ask a health care practitioner if** symptoms persist or worsen" would only be kept if required for one of the product claims.

Table 26. Example #2 – Combination table to assess potential additive dose - blood pressure-lowering ingredients						
Potential additive effect	Blood pressure-lowering					
Recommended dose	1 capsule per day					
Ingredients (Source)	**On the monographs**		**On the PLA form**		**Results**	
	A. Minimum Daily Reference Dose	**B. Maximum Daily Reference Dose**	**C. Quantity per Dosage Unit**	**D. Maximum Daily Dose**	**E. Percentage of the Minimum Daily Reference Dose (%)**	**F. Percentage of the Maximum Daily Reference Dose (%)**
Coenzyme Q10	0.03 g	0.3 g	0.2 g	0.2 g	0.2/0.03 = 667%	0.2/0.3 = 67%
Crataegus laevigata (Fruit)	0.6 g	3.5 g	0.8 g	0.8 g	0.8/0.6 = 133%	0.8/3.5 = 0.23%
Sum of Percentages:					**799%**	**67.23%**

Columns A and B: In accordance with the Coenzyme Q10 monograph and the Hawthorn monograph, respectively.

Conclusions:

The sum of the percentages of the maximum daily reference doses is less than 100%; therefore, safety of this combination of ingredients with potential blood pressure-lowering effect is supported for a class II application with no additional risk statements.