

# **EVIDENCE FOR SAFETY AND EFFICACY OF FINISHED NATURAL HEALTH PRODUCTS**

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**NATURAL HEALTH PRODUCTS DIRECTORATE**

December 2006  
**Version 2.0**

“Our mission is to help the people of Canada maintain and improve their health, while respecting individual choices and circumstances.”

*Health Canada*

“Our role is to ensure that Canadians have ready access to natural health products that are safe, effective and of high quality while respecting freedom of choice and philosophical and cultural diversity.”

*Natural Health Products Directorate*

Également offert en français sous le titre :

*Preuves attestant l'innocuité et de l'efficacité des produits de santé naturels finis*

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## ABOUT THIS DOCUMENT

This guidance document provides the information to help product licence applicants determine the evidence (amount and type of data) required to support the safety and efficacy of finished natural health products (NHPs).

The intent of this document is to ensure that the requirements are rigorous enough to protect public health and increase consumer confidence, yet flexible enough for industry to develop useful NHPs while accommodating changing scientific developments.

The information in this guidance document is based on the *Natural Health Products Regulations* (the Regulations) published in the Canada Gazette, Part II, on June 18, 2003.

Boxes with the Regulations appear in relevant locations throughout the document and a complete version of the Regulations is available on the Internet (see [http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/regs\\_cg2\\_cp\\_e.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/regs_cg2_cp_e.html)).

The information in this document applies to all applications submitted for a product license under the Regulations except those that:

- belong to the 60-day disposition clause (i.e. cite a monograph from the NHPD's *Compendium of Monographs* as the sole source of information that supports the safety and efficacy of the product);
- are homeopathic medicines; or
- are NHPs that carry a drug identification number (DIN) issued by Health Canada.

For the requirements of the 60-day disposition clause, homeopathic medicines, and NHPs with DINs issued by Health Canada, the applicant must refer to the Natural Health Products Directorate's (NHPD's) *Compendium of Monographs* guidance document, *Evidence for Homeopathic Medicines* guidance document and *Transition Guidance Document*.

The NHPD uses the evidence submitted by the applicant to critically assess the safety and efficacy of finished NHPs prior to approving the product for sale in Canada. For information on the quality requirements for NHPs, the applicant should refer to the NHPD's *Evidence for Quality of Finished Natural Health Products* guidance document.

The definitions of terms used in this guidance document are provided in the **Glossary**.

This guidance document was developed in consultation with individuals from the NHP industry, as well as academics, researchers, and consumers.

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## 1.0 GENERAL OVERVIEW

Section 5 of the *Natural Health Products Regulations* (the Regulations) outlines the requirements of a product licence application. The safety and efficacy evaluation of a natural health product (NHP) includes an assessment of its recommended conditions of use, its appropriateness for self-care and the existing totality of evidence related to the NHP.

### 1.1 Recommended Conditions of Use

Part 1: PRODUCT LICENCES  
Licence Application  
Section 5

An application for a product licence shall be submitted to the Minister and shall contain the following information and documents:

- (f) the recommended conditions of use for the NHP;
- (g) information that supports the safety and efficacy of the NHP when it is used in accordance with the recommended conditions of use.

The recommended conditions of use, as defined in the Regulations, include the following six elements that provide the necessary information to enable consumers to make informed choices about using an NHP:

- its recommended use or purpose;
- its dosage form;
- its recommended route of administration;
- its recommended dose;
- its recommended duration of use, if any; and
- its risk information, including cautions, warnings, contraindications or known adverse reactions associated with its use.

### 1.2 Self-Care

Self-care involves the activities individuals undertake for the prevention, treatment, and symptomatic relief of diseases, injuries or chronic conditions that individuals can recognize and manage on their own behalf, either independently or in participation with a health care practitioner. This includes the use of self-care products, such as NHPs, that are safe, effective and of high quality.

The evidence applicants provide with the product licence application allows the Natural Health Products Directorate (NHPD) to determine whether the NHP is appropriate for self-care. When there are risks associated with the use of a NHP (for example, use by a particular group of people, such as seniors), the applicants should take certain measures to manage the risk. This includes putting advisory information on the product label or restricting the dose, route of administration, subpopulation, source, preparation or form in which the NHP is presented.



However, if the risk cannot be mitigated (i.e. the NHPD considers the NHP unsafe for use in humans according to the recommended conditions of use or is inappropriate as a self-care product), the NHPD will not approve the application for a product licence under the Regulations.

Section 7(d) of the Regulations states that Health Canada will not approve products that may injure the health of consumers. In developing the Regulations, Health Canada's intent was to cover products that consumers can select and use themselves without the need to consult a health care practitioner and obtain a prescription. Accordingly, products with ingredients required to be sold pursuant to a prescription (listed in Schedule F to the *Food and Drug Regulations*) are not NHPs, except for homeopathic medicines. In reviewing all other product applications for safety and efficacy, the NHPD will keep this intent in mind.

### **1.3 Totality of Evidence**

Applicants must submit evidence from all relevant sources to support the safety and efficacy of the NHP according to its recommended conditions of use. That evidence must come from human use; animal or in vitro experimental evidence may be considered as additional, supporting information but cannot be the basis for approval. The required evidence will vary depending on the product and type of claim being made (see **Chapter 2.1**). Applicants are encouraged to undertake a systematic, well-constructed literature search (see **Chapter 4**) to review the totality of evidence relevant to the product, including both favourable and unfavourable data from published and unpublished literature (e.g. an expert opinion report), regulatory authority reports, and pre- and post-market experience, when applicable.

A referenced, critical analysis of all relevant information must be included in the Evidence Summary Report and Safety Summary Report to reflect the totality of evidence related to the safety and efficacy of the NHP (see **Chapter 3**). All conditions of use must be supported by suitable references submitted to the NHPD in full text hard copy. When experience with human use provides sufficient evidence to support safety and efficacy, animal or in vitro studies are not required. The evidence will be assessed as outlined in **Chapter 5**.

### **1.4 Definition of a Natural Health Product**

A natural health product is defined as a substance, or a combination of substances, described in Schedule 1 of the *Natural Health Product Regulations*, 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.

In other words, the ingredient is considered medicinal in nature if it contributes to the pharmacological activity associated with the recommended use or purpose.

## 2.0 HEALTH CLAIMS

### 2.1 Types of Health Claims

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

Claims are assessed by the NHPD based on the credibility, strength and quality of evidence provided to support the claim. Different types of claims require different levels of evidence. Depending on the product and strength of the claim, the supporting evidence may not have to include clinical trials. For example, clinical evidence may be required to support a claim to treat a specific health problem while a more non-specific claim for health maintenance can be supported by a lower level (strength) of evidence (see **Chapter 5.2**).

The totality of evidence (see **Chapter 1.3**) must be in support of the benefits of the product outweighing any risks. The level of risk depends on several considerations including, but not limited to, the following:

- whether the ingredient is intended to be the sole therapy or an adjunct therapy;
- whether the ingredient is intended to help with symptom management or to cure/treat the condition; and
- the seriousness of the condition to be treated.

The NHPD permits therapeutic, risk reduction and structure-function claims.

**Therapeutic claims** relate to the diagnosis, treatment and mitigation or prevention of a disease, disorder, or abnormal physical state or its symptoms in humans.

**Risk reduction claims** describe the relationship between using a medicinal ingredient and reducing the risk of developing a specific disease or abnormal physiological state. This is achieved by significantly altering a major risk factor or factors recognized to be involved in the development of the chronic disease or abnormal physiological state.

Most risk reduction claims are based on observational (epidemiological) studies (see **Chapter 3.1.4**), such as prospective cohort studies. Therefore, well-designed observational studies may be the bulk of the supporting evidence submitted.

**Structure-function claims** describe the effect of a medicinal ingredient on a structure or physiological function in the human body, or a medicinal ingredient’s support of an anatomical, physiological, or mental function.

Structure-function claims vary widely from health maintenance (for example: “maintains healthy gums”) to the treatment of disease or conditions (for example: “reduces blood cholesterol”).

Structure-function claims synonymous with therapeutic claims will be evaluated as therapeutic claims.

The NHPD will also consider certain non-specific claims (generally structure-function type), but only in cases where there is adequate evidence to demonstrate safety. These claims consist of a broad statement that the product will promote overall health. It should be noted that the NHPD favours the use of specific claims that provide consumers with more information to help them make better choices.

Evidence supporting non-specific claims, whether from traditional (see **Chapter 2.2.1**) or scientific (see **Chapter 3**) literature, will be required. Examples of non-specific claims that may be accepted are:

- “a factor in the maintenance of good health”;
- “digestive tonic in TCM”;
- “adaptogen”; and
- “immuno-modulator”.

However, traditional products or ingredients may only be called tonics provided the system or organ on which the tonic acts is identified (e.g. “digestive tonic” or “lung tonic”). As well, the healing paradigm or system of medicine in which the product or ingredient is traditionally used should be identified (e.g. “traditionally used in Chinese Medicine to tonify Qi”) if it is being used differently than in Western tradition.

The health claim “adaptogen” requires scientific evidence to demonstrate that the product or medicinal ingredient has a normalizing action. Likewise, the health claim “modulator” requires scientific evidence and should be associated with the system or organ on which the ingredient acts.

Certain general claims, such as “source of essential fatty acids” are unacceptable because they do not indicate a health context. Such claims should be modified to include a health context, e.g. “source of essential fatty acids for the maintenance of good health”. The claim “dietary supplement” is unacceptable on its own, but may be included in addition to at least one other, more specific claim for certain nutrient-type products, such as vitamins and minerals.

## **2.2 Categories of Health Claims**

Products are divided into two categories according to the claim:

- traditional use claims; and
- non-traditional use claims.

### **2.2.1 Traditional Use Claims**

Traditional medicine represents the sum total of knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, used in the maintenance of

health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness. This definition is based on the one used by the World Health Organization Traditional Medicine Program.

The NHPD further requires a history of at least 50 consecutive years of traditional use of a medicinal ingredient within a cultural belief system or healing paradigm (e.g. Traditional Chinese Medicine) for the product to be considered traditional. This time span was chosen to represent two generations, allowing possible reproductive side effects to be identified.

To make a traditional use claim, the dose information and the method of preparation must be those traditionally used. Traditional methods of preparation include:

- the use of a whole organism or specific parts (leaf, root, fruiting body, etc.), whether fresh, dried or freeze-dried, or preserved with alcohol, honey or sugar;
- extracts produced by the application of pressure to the source material;
- aqueous extracts such as infusions, decoctions and syrups;
- ethanol-based extracts such as tinctures, fluid extracts and succi;
- glycerine-based extracts;
- vinegar-based extracts;
- oil, grease or fat-based infusions; or
- beeswax salves and ointments.

Other methods of preparation may be considered traditional if supported by at least one reference, assessed as acceptable by NHPD, describing the method's use within the practice of traditional medicine. Depending on the evidence available, applicants may submit a traditional use claim for treatment, risk-reduction or structure-function purposes.

Claims for traditional use must be prefaced with qualifiers such as “traditionally used...”. If the claim uses terminology specific to a particular culture or system of medicine, that culture or healing paradigm of medicine should be specified in the claim (e.g.: “In Traditional Chinese Medicine used to replenish Qi...”, “traditionally used in Ayurvedic medicine to treat over-active agni”).

If traditional and scientific evidence are available to support a proposed claim, the applicant may choose whether to use the wording “traditionally used...”. If a health claim is solely supported by scientific evidence, it must not include the words “traditionally used...”.

### **Evidence to Support Traditional Use**

Products with traditional use claims are divided into two sub-categories according to the evidence provided:

- pharmacopoeial evidence for traditional use claims; and
- other evidence for traditional use claims

The following sections provide the safety and efficacy requirements for these two categories of evidence.

### **Pharmacopoeial Evidence for Traditional Use Claims**

Products meeting this stream's criteria only require one reference. Using the example of a product intended as a Traditional Chinese Medicine, this reference may be from one of two sources: the *Pharmacopoeia of the People's Republic of China* or the *State Drug Standard*. To meet these requirements, the application must show that the following items in the Product Licence Application are identical to the *Pharmacopoeia of the People's Republic of China* or the *State Drug Standard*:

- medicinal ingredients;
- quantity of crude material equivalent (see Product Licensing Guidance Document for definition);
- recommended use or purpose;
- recommended dose;
- recommended route of administration;
- recommended duration of use;
- dosage form;
- directions of use;
- risk information; and
- method of preparation (traditional).

Applicants must ensure that copies of the relevant pages from a recognized pharmacopoeia (e.g. the *Ayurvedic Pharmacopoeia of India*) are included as supporting evidence and accompanied by an English or French translation when the language of publication is neither English nor French.

To assist applicants in determining whether or not the product fits the pharmacopoeial stream, and therefore only requires one approved reference, applicants should use the checklist provided (see **Appendix 6**) as a self-assessment tool. This checklist is for applicant's use and does not need to be included in the application. However, responding "no" to any of the questions posed on this checklist excludes the product from being assessed within the pharmacopoeial stream.

For those applications that are suitable for assessment within the pharmacopoeial stream, an Evidence Summary Report (see **Chapter 9.1**) is *not* required.

### **Other Evidence for Traditional Use Claims**

Applicants who make a traditional use claim but do not meet the requirements of the pharmacopoeial stream must provide at least two independent references (i.e. references that do not cite the same source, or each other, as the main source of information regarding the traditional use) that support the recommended conditions of use (see **Chapter 1.1**). The references must be authoritative and from a reputable source. Some examples of such references are provided in **Appendix 1** under the heading "References to Traditional Use."

In the case where only one written reference exists, or where multiple references refer back to a single original source, an expert opinion report based on practitioner experience and knowledge of use over a period of at least 50 years would be considered as a possible substitute for a second reference. An expert opinion is *not* acceptable as the sole source of evidence supporting safety and efficacy. **Chapter 3.5** outlines the requirements for expert opinion reports.

In the case of oral traditions, the NHPD requires that an indigenous, ethnographic, professional and/or scientific authority prepare a written account of relevant information from recognized authorities on traditional healing who have knowledge and experience with the product. As an example, three or more herbalists or aboriginal elders may serve as the source of information. Their evidence must provide information supporting the traditional use of the product and the remaining conditions of use (i.e. information on dose, dosage form, route of administration, duration of use and any risk information). They must also indicate that the traditional use of the ingredient extends back to at least 50 years.

### **Substantiating Traditional Use Claims**

The NHPD recognizes that it may be difficult to find references that state an ingredient has been used for at least 50 consecutive years. In this case, applicants should consider the following when determining whether the submitted information adheres to the definition of traditional use:

- Does the reference describe the use in the context of a particular cultural belief system or healing paradigm? For example, the book *Native American Ethnobotany* refers to the use of herbs by specific Native North American cultures. Other relevant sources are pharmacopoeias of Ayurveda, Unani, Kampo, Traditional Chinese Medicines, etc., and reference textbooks referring to other cultures such as African or Ukrainian.

If the reference refers to a particular cultural belief system or paradigm (e.g. a specific culture such as the Chinese culture), and it is apparent that the cultural system has been in existence for at least 50 years, the NHPD will assume that the group has used the medicinal ingredient for that particular purpose for 50 years or more.

- Does the reference describe the use of the ingredient or product with statements that imply a traditional use? For example, the claim may begin with a statement such as “Traditionally used as ...” or “In folklore used as ...” etc.

When the claim begins with such a statement, the NHPD assumes that the reference is supporting a traditional use claim and the medicinal ingredient has been used in accordance with that claim for at least 50 consecutive years.

- Does the reference specify a period that is at least 50 years ago, and can it be assumed that the ingredient was used from that period onwards for at least 50 consecutive years? For example, “The herb was used in the time of King Edward II to alleviate coughs.” Even though neither a concrete date nor time frame is given (e.g. 1284-1330 A.D), if the time being referred to is more than 50 years ago, the NHPD will assume that the reference supports a traditional use claim and that the ingredient has been used for at least 50 years.

- Does the reference provide a condition that can be diagnosed in the relevant healing paradigm? Where the condition cannot be diagnosed in the relevant healing paradigm (for example, hyperlipidemia), even if the reference indicates that it was traditionally used for that condition, it will not be accepted as a traditional use reference by the NHPD.

At least one of the two references for a traditional claim must contain information regarding recommended dose, dosage form, recommended route of administration and have some information that reflects the safe use of the product in humans.

If the recommended conditions of use, i.e. recommended use or purpose, dose (including the method of preparation), dosage form (since this is a reflection of the traditional method of preparation), or route of administration, are different from the traditional information in the references, a traditional use claim may no longer be made for the product. In such instances, the ingredient or product will be considered non-traditional, and will have to meet the evidence required for making a non-traditional use claim (see **Chapter 2.2.2**).

### **Risk Information and Traditional Products**

The NHPD recognizes that many references to traditional use do not include detailed risk information. However, as per the *Natural Health Products Regulations*, information on the safety of the NHP, when used according to the recommended conditions of use, is required. The Safety Summary Report for traditional products should incorporate the safety information available in traditional *and* scientific (non-traditional) references (see **Chapter 3**).

The NHPD recognizes that some healing paradigms may communicate risk information in language that is specific to that healing paradigm or culture. In cases where it is not evident to the consumer that the risk information is traditional in nature, include a traditional qualifier in the risk information, e.g. “Do not use in cases of external pathogenic heat (TCM)”.

When evidence is provided from various references (i.e. from references to traditional use or scientific evidence), applicants must follow the criteria listed in Table 1.

### **2.2.2 Non-Traditional Use Claims**

The evidence requirements to support a non-traditional use claim are more rigorous than what is required to support a traditional use claim. Non-traditional claims must be supported by scientific evidence (e.g. clinical trials), which may be supplemented by other forms of evidence (see **Chapter 3**).

In general, the evidence required to adequately substantiate each non-traditional claim (see **Chapter 5.4**) and its associated conditions of use will depend on the type of claim being made (see **Chapter 2.1**) and the severity of any named symptoms or conditions.

References are required to support the non-traditional claim and all of the recommended conditions of use (see **Chapter 1.1**). When the evidence is provided from various references, applicants must follow the criteria listed in Table 1.

**Table 1: Evidence from Various References**

Part of the application	Criteria
Recommended use or purpose (claim)	The references indicate the same claim as indicated in the Product Licence Application form (but may use different words to describe it). For example: Reference 1: Increases urinary flow Reference 2: Diuretic (this has the same intent as Reference 1)
Proper name	The references include the proper name of the medicinal ingredient, since common names are not always used consistently. If a particular reference supports all of the conditions of use but indicates only a common name instead of a proper name, then the reference may be used along with another acceptable reference that links the proper name with that common name.
Source	The references support the source indicated in the Product Licence Application form for each medicinal ingredient. For example: for a given herb, if the references support only the use of its roots as a source of the medicinal ingredient, then the flowers will not be acceptable as the source.
Dosage form	The dosage form is consistent with the route of administration. For example: the dosage form is a “capsule” and the route of administration supported by the references is “oral”.
Route of administration	The references support the same route of administration that is indicated in the Product Licence Application form.
Dose	The references support the same dose (or dosage range) that is indicated in the Product Licence Application form. Indicate the crude material equivalent, when applicable. For example: The recommended dose is 3-4 g crude material equivalent. Reference 1: 2-4 g crude material equivalent Reference 2: 3-5 g crude material equivalent
Tinctures and extracts	The references provide sufficient information about tinctures or extracts to calculate the crude material equivalent, when applicable. Any variations in the solvent concentration and extract ratio or potency from the cited references must be justified.
Risk information	Relevant safety information from all available sources, including traditional and scientific references, is used to determine the risk information associated with the NHP.



## 3.0 TYPES OF EVIDENCE

In general, the types of evidence to support the claims and associated conditions of use can be categorized as follows:

- references to traditional use (see **Chapter 2.2.1**);
- references to scientific evidence (see **Chapters 3.1-3.4**);
- references from expert opinion reports (see **Chapter 3.5**);
- references from reputable regulatory authority reports (see **Chapter 3.6**); and
- references to previous marketing experience (see **Chapter 3.7**).

The applicant may use any of the previous types of evidence as long as the evidence meets the requirements of the category of the claim and is sufficient to support the type of claim being made.

The NHPD recognizes different levels of evidence that reflect the strength of the evidence (see Table 2, **Chapter 5.2**). Determining the level of evidence should help the applicant to prioritize the types of evidence available. For example, if a Level I reference is available and provides information on the conditions of use and is sufficient for the type of claim being made, lower levels of evidence may not be required.

Some of the types of evidence listed above can be researched from several sources, including databases such as PubMed. Applicants may also refer to **Chapter 4.0** for general guidance on how to conduct a literature search when using a database such as PubMed.

The NHPD also maintains a list of sample references (see **Appendix 1**) that applicants may use to substantiate the safety and efficacy of medicinal ingredients. This list is not exhaustive, but is a good starting point.

The NHPD will assess the provided evidence to determine that it sufficiently supports all the conditions of use and is appropriate for the type of claim being made. Where safety issues are identified, the NHPD will evaluate the risk mitigation strategies provided by the applicant.

The following sections provide further explanations on the different types of evidence the applicant may use to generate the information required to support the proposed claim and conditions of use.

### 3.1 Clinical Studies

Evidence from clinical studies can provide valuable information about the efficacy and safety of NHPs. Although the primary objective of a clinical study may not be safety, it may still provide relevant information that can be used by the NHPD to assess the safety of the product. There are several types of clinical studies, including the following:

- systematic reviews, such as meta-analyses of randomized controlled trials or other trials;
- randomized controlled trials (preferably multicentred);

- studies without randomization and/or control groups; and
- non-experimental observational studies, such as epidemiological, cohort studies, or case-control studies.

For more information about clinical studies, refer to the *Clinical Trials for Natural Health Products* guidance document.

### **3.1.1 Systematic Reviews**

Systematic reviews, such as meta-analyses of randomized controlled trials or other clinical trials, generally provide evidence that is suitable to support all types of claims. This information must be summarized or provided in the Evidence Summary Report, when applicable. Examples of systematic reviews are the Cochrane Reviews (see <http://www.update-software.com/default.htm>), which are part of the quarterly Cochrane Database of Systematic Collaboration.

The advantage of a meta-analysis is that it employs statistical methods to combine and summarize the results of several randomized controlled trials or other clinical trials. When submitting meta-analysis as evidence to support the use of a NHP, the applicant must be aware that all the summarized trials used in the meta-analysis must explore the same recommended use or purpose. If any variations in the claims are not justified in the meta-analysis, the applicant should justify it in the Evidence Summary Report.

### **3.1.2 Randomized Controlled Trials**

Randomized controlled trials, especially multi-centered ones, provide valuable information on the effects of a NHP on humans in a controlled clinical environment. The ideal randomized controlled trial minimizes bias by distributing participants randomly and equally into the various groups (i.e. treatment or control group). Randomized controlled trials provide valuable information on the efficacy and safety of a NHP for a particular claim and generally support a claim with higher confidence compared to other types of trials.

### **3.1.3 Other Clinical Trials**

These include well-designed studies without randomization and/or control groups.

### **3.1.4 Descriptive and Observational Studies**

Epidemiology is the study of the occurrence and distribution of a disease or physiological condition in human populations and of the factors that influence this distribution. It is a type of observational and descriptive study.

The advantages of epidemiological studies include:

- animal-to-human extrapolation is not necessary;
- the conditions of exposure are “real” (i.e. occur outside the clinical trial environment); and

- there is a wide range of subjects.

Some of the disadvantages are:

- there is no control over several non-statistical variables such as exposures, lifestyles, co-exposure to other toxicants, etc.;
- there may be a memory bias in retrospective studies;
- there may be lack of actual measurements;
- there may be lengthy latency periods for some effects, especially for cancer; and
- typically there is an inability to determine cause-and-effect relationships.

Well-designed descriptive or observational studies can also be classified as comparative studies, correlational and case-control studies. Such studies may also provide valuable information. The two major types of observational studies are:

- cohort studies; and
- case-control studies.

In a cohort study, groups of individuals are defined according to the presence or absence of susceptible risk factors or disease. The groups are then assembled and followed forward (i.e. prospective cohort) or backward (i.e. retrospective cohort) in time to evaluate the outcome of interest.

In a case-control study, subjects with the disease or condition being studied (cases) are compared with a group of subjects free of that disease or condition (controls) with respect to an attribute or exposure believed to be causally related to that disease or condition.

### **3.2 Pharmacopoeias and Textbooks**

Applicants may consult pharmacopoeias and relevant textbooks, since they may provide information on some of the recommended conditions of use (e.g. recommended duration of use) that are not available from other sources.

### **3.3 Peer-Reviewed Published Articles**

Applicants are encouraged to provide evidence from peer-reviewed sources (e.g. academic journals such as the *Journal of Toxicology*). The NHPD also considers evidence from sources that are not peer-reviewed, but this type of reference should not be the sole information submitted to support the safety and efficacy of the NHP.

### **3.4 Pre-Clinical Studies**

The primary focus of the evidence supporting safety and efficacy of an NHP must be based on experience in humans. However, data from pre-clinical (*in vitro* and animal studies) can also provide valuable information on pharmacokinetics (i.e. absorption, distribution, metabolism, and excretion of the medicinal ingredient), pharmacodynamics (i.e. mechanism of action and

relationship between concentration and effect), toxicity information, reproductive effects and the potential genotoxicity or carcinogenicity of a particular ingredient. For more information on non-human pre-clinical studies, refer to the following resources:

- OECD (Organisation for Economic Co-operation and Development) Guidelines for the Testing of Chemicals ([http://www.oecd.org/document/13/0,2340,en\\_2649\\_34377\\_2740429\\_1\\_1\\_1\\_1,00.html](http://www.oecd.org/document/13/0,2340,en_2649_34377_2740429_1_1_1_1,00.html))
- ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Guidelines (<http://www.ich.org/cache/compo/276-254-1.html>)

### **3.5 Expert Opinion Reports**

An expert opinion report may be used to provide information that is not available in the literature, (e.g. duration of use for an ingredient) or to support a new use for a previously approved ingredient. Expert opinion reports are not acceptable as the sole source of evidence to support the safety and efficacy of an NHP.

Expert opinion reports are required to meet the following criteria:

- the expert committee is comprised of a minimum of three people;
- at least one person on the expert committee has training in the field or healing paradigm related to the proposed NHP or medicinal ingredient(s);
- at least one person providing an expert opinion has scientific qualifications, including experience in research methods and training in evidence-based health care;
- all members of the expert committee must disclose any conflicts of interest;
- the report includes information for the recommended conditions of use;
- the report includes a rationale for using the expert opinion (e.g. the expert committee can provide information that is not available in the literature; and
- the qualifications and contact information of each member of the expert committee are provided.

### **3.6 Reputable Regulatory Authority Reports**

Reports concerning the safety, effectiveness, and exposure to particular ingredients or products may be generated by regulatory authorities around the world. When available, this type of information should be included with the Product Licence Application when it is relevant to the safety and efficacy evaluation of an NHP, for example:

- current regulatory status of the medicinal ingredient(s) or product (e.g. approved for sale as an over-the-counter product in [name the jurisdictions]);
- post-marketing surveillance reports;
- public advisory statements or recalls;
- adverse reaction reports; and
- ingredient or product monographs.

### **3.7 Previous Marketing Experience**

When available, information based on previous marketing experience of a finished NHP may be provided to supplement the evidence supporting the safety and efficacy of ingredients or products. For example:

- jurisdictions where application was made for marketing authorization and the results of these applications;
- when and where the ingredient or product was approved for sale;
- when and where the product was sold, and over what period of time;
- labelling information for each jurisdiction in which it was marketed;
- when, where and why the product was removed from the market, if applicable;
- the number of adverse reactions reported and a description of their nature; and
- description of product in terms of ingredients and recommended conditions of use.

As various jurisdictions have different pre-marketing requirements, the NHPD will not guarantee approval of an NHP for sale in Canada based solely on evidence from previous marketing experience.

## 4.0 LITERATURE SEARCH STRATEGIES

This section provides general guidance on conducting an appropriate literature search to compile the best possible evidence to support the proposed claim and recommended conditions of use for an NHP.

The literature search should be broad enough to cover original research articles and other documents pertinent to the recommended conditions of use. At minimum, applicants must search PubMed (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>), which is a free, Web-based, major biomedical database. Applicants are also encouraged to refer to authoritative online sources, including, but not limited to, Web sites of regulatory authorities and other reputable agencies.

The focus of the literature search should be human studies. Other types of may be included if they contribute to an understanding of the safety and efficacy of the NHP.

Applicants are recommended to use the following general guidelines:

- The literature search should concentrate on articles available in English or French. Articles in other languages will be considered if accompanied by a translation.
- Abstracts of papers may be used to screen out references that do not provide relevant information, but are not suitable for submission purposes. Abstracts submitted as the sole form of evidence will not be evaluated by the NHPD.
- Wide variation in the outcomes of studies and inconsistent or conflicting results of studies will raise serious questions about safety and efficacy. Applicants must carefully examine such results to determine whether a plausible explanation for such inconsistencies exists (e.g. differences in results may be attributed to differences in dosage, dosage form, route and frequency of administration, population tested, statistics, or other aspects of the study).
- If a search output is large (50 papers or more, for example), it may not be appropriate to include all of the articles with the application. Include only the most relevant evidence supporting the recommended conditions of use. For example:
  - If there are multiple references from the same author that provide similar information, submit only the most complete report.
  - If the claim and conditions of use are adequately supported by Level I evidence, information from other levels may not be required (see Table 2, **Chapter 5.2** for a description of the levels of evidence).
  - Maintaining records of all references consulted will facilitate the presentation of references in an appropriate format at the end of the Summary Reports (see **Chapter 9.5 and Appendix 2** for additional information on how to reference).

**NOTE: Applicants are no longer required to submit a literature search strategy as part of the Evidence Summary Report.**

## 5.0 ASSESSING THE EVIDENCE

This section provides information about the criteria the NHPD uses to determine the credibility, strength and quality of the evidence.

### 5.1 Credibility of the Evidence

Applicants may wish to use the following questions to determine the suitability of each reference for inclusion in their application:

- Is the reference generally available?
- Is it widely recognized and widely used?
- Are the authors knowledgeable in their field?
- Do the authors cite their sources?
- Has the reference been peer reviewed?
- Is it used in other jurisdictions?
- Does it present balanced data?
- Is it based on the totality of existing evidence?
- Has it been commercially published?
- Is it the most current information or edition available?

### 5.2 Strength of the Evidence

The evidence to support a claim and the remaining conditions of use may be available from a variety of references. However, depending on the type of claim (see **Chapter 2.1**), the evidence provided must be adequate (see **Chapter 5.4**) and of corresponding strength (see Table 2, **Chapter 5.2**).

Use Table 2 to determine the level (strength) of evidence from a particular type of reference.

**Table 2: Strength of Evidence Grading System<sup>1</sup>**

Levels of Evidence	Type of Evidence from Human Studies
I	Well-designed systematic reviews and meta-analyses of randomized controlled trials or other clinical trials, or at least one well-designed randomized controlled trial (preferably multicentred)
II	Well-designed clinical trials without randomization and/or control groups
III	Well-designed descriptive and observational studies, such as correlational studies, cohort studies and case-control studies
IV	Peer-reviewed published articles, conclusions of other reputable regulatory agencies or previous marketing experience, expert opinion reports, referenced textbooks, Web site (if the information is peer-reviewed and there is a hardcover version of the site, e.g. Natural Medicines Comprehensive Database)
V	References to a traditional use, pharmacopoeias

<sup>1</sup> Adapted from a model developed by the U.S. Agency for Healthcare Research and Quality.

Based on the information provided in Table 2, the strength of evidence increase from Level V, with Level I evidence being considered the strongest. Applicants are encouraged to search for evidence from all levels to support the safety and efficacy of the NHP.

A non-traditional use claim and the associated conditions of use are based on non-traditional references, which have a stronger weight of evidence than those required for a traditional use claim and the associated conditions of use.

Table 2 does not provide a level of evidence that corresponds to animal or *in vitro* studies. However, as mentioned previously, such studies may be included as supplementary evidence.

**NOTE: Web-based references such as PDR Health and Natural Medicines Comprehensive Database are considered to be a weaker level of evidence (Level IV) because they are compilations of evidence which have not been critically reviewed. As such they are not sufficient on their own to support the safety & efficacy of a traditional or non-traditional product.**

### 5.3 Quality of the Evidence

To determine and compare the quality of evidence from various studies within a particular level of evidence (see Table 2, **Chapter 5.2**), consider the following factors:

- Were the objectives of the study defined?
- Were the methods and outcome measures or endpoints clearly defined?
- Was there a clear description of the inclusion and exclusion criteria?
- Were the methods of statistical analysis adequate and well-described?
- Was there at least one control (comparison) group?
- Was the study randomized?
- Was the study double-blinded?
- Was any risk information described, such as adverse reactions or reasons for participant dropout?
- Was the medicinal ingredient in the study adequately identified (e.g. proper name) and characterized (e.g. extraction method, chromatographic fingerprint)?
- Were potential sources of bias adequately addressed?
- Was the study published in a well-recognized, reputable source?
- Was the study peer-reviewed?
- Did the authors cite (reference) their sources?

### 5.4 Adequacy of Evidence

This section provides general guidelines the applicant should use to determine how much evidence is required to support a claim. The references selected by an applicant to support the safety and efficacy of the NHP must specifically support each of the recommended conditions of



use (i.e. the recommended use or purpose (health claim), dosage form, recommended route of administration, recommended dose, recommended duration of use, if any, and risk information).

The NHPD assesses all the evidence that applicants provide. However, using the following guidelines will help to ensure that adequate evidence is provided with the initial application and enhance the efficiency of, the assessment process.

#### **5.4.1 Adequate Evidence**

The NHPD considers evidence to be adequate when it:

- specifically supports the claim and all remaining recommended conditions of use;
- is from relevant levels in Table 2 (see **Chapter 5.2**);
- reflects the concept of self-care (see **Chapter 1.2**);
- reflects the totality of evidence (see **Chapter 1.3**);
- is from reputable and well-recognized sources;
- is mostly of high quality (see **Chapter 5.3**); and
- supports the safety of the product when used according to the recommended conditions of use.

#### **5.4.2 Inadequate Evidence**

The NHPD considers the evidence inadequate when it:

- does not specifically support the claim and all remaining recommended conditions of use;
- does not support the use of the NHP for self-care (see **Chapter 1.2**);
- does not reflect the totality of evidence (see **Chapter 1.3**);
- is mostly unreferenced or from low-quality sources;
- does not support the safety of the product when used according to the recommended conditions of use.

If the evidence provided is inadequate, the applicant will be given one opportunity to provide additional information *via* an Information Request Notice (IRN). If the information provided in response to the IRN is also inadequate, the application may be refused.

## 6.0 NON-MEDICINAL INGREDIENTS

A non-medicinal ingredient is defined as any substance added to a NHP formulation to confer suitable consistency or form to the medicinal ingredients. In a manner consistent with existing regulations for conventional pharmaceuticals, non-medicinal ingredients should not exhibit any pharmacological effects of their own, should not exceed the minimum concentration required for the formulation, and should be safe in the amounts used. The presence of a non-medicinal ingredient must not adversely affect the bioavailability, pharmacological activity or safety of the medicinal ingredients. As well, non-medicinal ingredients must not interfere with assays and tests for the medicinal ingredients and, when present, antimicrobial preservative effectiveness. Non-medicinal ingredients should be the least toxic available that are appropriate to the formulation.

The NHPD has developed a List of Acceptable Non-medicinal Ingredients ([http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/nmi\\_list1\\_e.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/nmi_list1_e.html)) that are generally regarded to be of minimal toxicological concern. A list of acceptable non-medicinal ingredient purposes can be found in the *Product Licensing Guidance Document*.

Non-medicinal ingredients can include, but are not limited to, diluents, binders, lubricants, disintegrators, colouring agents, fragrances and flavours that are necessary for the formulation of the dosage form. Non-medicinal ingredient purposes such as surfactants, which are only applicable to topical products, are also indicated. Antimicrobial preservatives and antioxidants will be considered as non-medicinal ingredients but should not be used as alternatives to Good Manufacturing Practices.

As per section 5 of the Regulations, the common name and purpose of all non-medicinal ingredients must be provided in the Product Licence Application. Individual components of non-medicinal ingredient mixtures must be individually listed in the Product Licence Application form, except when:

- the mixture has a common name on the List of Acceptable Non-Medicinal Ingredients; or
- the mixture is a proprietary blend of flavours or aromatics that may be qualitatively described, e.g. “artificial fruit flavour blend A106”.

If there is a particular safety concern with a non-medicinal ingredient, the NHPD may request additional information, such as its quantity. The NHPD suggests that applicants keep updated information on specifications, alternative formulations and each ingredient's components (e.g. supplier's name and address, percent weight per weight, certified limits when applicable, Chemical Abstract Service numbers or other reference numbers such as FEMA No., and purpose in formulation).

## 6.1 Acceptable Non-Medicinal Ingredients

### 6.1.1 Ingredients on the Acceptable List and Within Limitations (if applicable)

As previously mentioned, the NHPD's List of Acceptable Non-medicinal Ingredients includes non-medicinal ingredients that are generally regarded to be of minimal toxicological concern. Where appropriate, certain limitations regarding quantity, dosage form and route of administration are listed. Respecting any specified limitations, non-medicinal ingredients found on the acceptable list require no further assessment.

### 6.1.2 Ingredients on the Acceptable List but Outside the Limitations OR Not on the Acceptable List

Non-medicinal ingredients found on the acceptable list but used outside of any specified limitations, or non-medicinal ingredients not found on the acceptable list, may be used in NHPs provided that they meet the NHPD's definition of a non-medicinal ingredient (see above). The NHPD will assess these non-medicinal ingredients for safety and therefore may require additional information. The assessment will proceed more efficiently if the supporting information is provided in the initial application. As per sections 15 and 16 of the Regulations, the applicant may be asked to provide the following information for any non-medicinal ingredient, including components of mixtures:

- its proper name, common name, source, purpose and quantity;
- previous evaluation results from specified jurisdictions and their agencies to provide information on the conditions of use, restrictions, as well as approval and withdrawal history, if applicable;
- reference to relevant sources, such as the *United States Pharmacopeia*, that can be cited to justify the use of the non-medicinal ingredient outside the specified limitations;
- rationale for its use within the NHPD's definition of a non-medicinal ingredient (see above);
- references to toxicological information.

A list of suggested references related to non-medicinal ingredients is found in **Appendix 3**.

## 6.2 Unacceptable Non-Medicinal Ingredients

Unacceptable non-medicinal ingredients include ingredients that may cause harm in the amounts used, exhibit pharmacological activity, alter the pharmacological activity or safety of the medicinal ingredients, or have potential adverse effects on health.

Unacceptable non-medicinal ingredients include, but are not limited to:

- ingredients that have adverse effects (e.g. carcinogens; neurotoxins; ingredients with a high risk of transmitting transmissible spongiform encephalopathy);
- ingredients that exhibit pharmacological activity (e.g. safeners);
- ingredients that are regulated as drugs in Canada or other jurisdictions;
- agricultural chemicals; and

- other ingredients not fitting the definition of a non-medicinal ingredient in the Product Licensing guidance document.

Certain ingredients may have both non-medicinal and medicinal properties, depending on dosage. They will be subject to full assessment as medicinal ingredients if they are outside the specified limitations of the List of Acceptable Non-medicinal Ingredients. For example, if peppermint oil is used as a flavouring agent within the specified limitation of concentration, the NHPD will consider it to be a non-medicinal ingredient. However, if the concentration of peppermint oil is sufficient to exhibit pharmacological activity, it should be assessed as a medicinal ingredient and must be declared as such on the Product Licence Application and label.

Herbs not having a recognized non-medicinal purpose are generally unacceptable as non-medicinal ingredients. They should be assessed as medicinal ingredients. One such example is a product containing echinacea leaf powder as filler in an echinacea root capsule. While this would not cause any concern for safety, the leaf powder is not without pharmacological effects, and thus does not meet the definition of a non-medicinal ingredient. Echinacea leaf powder contains constituents that may have a stimulatory effect on the immune system and thus might actually improve the efficacy of the product for treating symptoms of a cold.

The reason for this approach is that all NHPs in substantive amounts can have pharmacological effects. For most of these products, no research has been done to determine a minimum dose below which there is no significant pharmacological effect. No arbitrary concentration of such substances (e.g. 10%) below which the medicinal ingredient can be treated as non-medicinal is scientifically defensible.

In the above examples, the herb can be removed from the non-medicinal ingredients list and be indicated as a medicinal ingredient in the Product Licence Application form along with all required supporting information, including an acceptable combination rationale (see **Chapter 8.1**). In such cases, product reformulation is not necessary.

The use of spent herbs (the material remaining after extraction) as fillers must be justified by the applicant based on whether or not any medicinal activity remains in the material.

### **6.3 Incidental Ingredients**

Incidental ingredients are ingredients that may have been present in the raw material, but in the final dosage form they remain at quantities too insignificant to contribute to a non-medicinal ingredient purpose. Incidental ingredients are not required to be listed on the Product Licence Application form and label.

## **7.0 SPECIAL TOPICS: INGREDIENTS SUBJECT TO ADDITIONAL REQUIREMENTS**

This section focuses on additional information applicants should provide for specific ingredients to ensure the NHP is safe for use in humans.

### **7.1 Ingredients Derived from Animal Tissue**

Any ingredient derived from animal tissue must be declared as such on the Product Licence Application and the Animal Tissue Form must be completed. For more details, refer to the relevant section in the NHPD's *Product Licensing Guidance Document*.

Animal tissue-derived ingredients may be subject to specific requirements for quality (see the NHPD's *Quality of Finished Natural Health Products* guidance document). For example, specified risk materials (SRM) are prohibited for manufacturing and/or in the processing of NHPs. SRM are defined in the *Food and Drug Regulations* as the skull, brain, trigeminal ganglia (nerves attached to the brain), eyes, tonsils, spinal cord and dorsal root ganglia (nerves attached to the spinal cord) of cattle aged 30 months or older AND the distal ileum (part of small intestine) of cattle of all ages.

Gelatin may be used in formulating or encapsulating NHPs, and may be made from a variety of animal materials. In order to further enhance the continued safety and quality of those products which contain gelatin made from the bones of the following animals: cattle, sheep, goat, deer, and elk, which are susceptible to Transmissible Spongiform Encephalopathy (TSE) diseases such as Bovine Spongiform Encephalopathy (BSE or Mad Cow Disease), refer to the NHPD *Revised Policy for Gelatin in Natural Health Products* ([http://www.hc-sc.gc.ca/dhp-mps/prodnatur/bulletins/gelatin\\_gelatine\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/prodnatur/bulletins/gelatin_gelatine_e.html)).

### **7.2 Additional Requirements for Probiotics**

A probiotic is defined in the *Natural Health Products Regulations* as a monoculture or mixed culture of live microorganisms that benefit the microbiota indigenous to humans. Unlike other NHPs, conventional toxicology and safety evaluation is not sufficient to evaluate the safety of probiotic microorganisms. A probiotic is supposed to survive or/and grow in order to benefit humans, which makes the use of these tests ineffective for probiotics. Therefore, a multi-disciplinary approach is necessary to examine the pathological, genetic, toxicological, immunological, gastro-enterological, and microbiological aspects of the safety of probiotic strains. These requirements are mainly based on FAO/WHO's *Guidelines for the evaluation of probiotics in food - Report of a joint FAO/WHO working group on drafting guidelines for the evaluation of probiotics in food* (2002). They apply to all strains currently not listed on the Therapeutic Products Directorate's Labelling Standard for Intestinal Flora Modifiers.

Certain probiotic bacteria have been associated with human illnesses and/or have a high risk of developing antibiotic resistance and are not suited for use as probiotics. Products containing the following strains or species will be rejected as NHPs without further consideration:

- *Bacillus cereus*;
- *Bacillus clausii* CNCM MA23/3V & CNCM MA66/4M;
- *Enterococcus spp.*;
- *Bifidobacterium dentium*;
- *Lactobacillus plantarum* CNCM MA40/5B-p;
- *Parascardovia denticolens*;
- *Pediococcus acidilactici* CNCM MA28/6B; and
- *Scardovia inopinata*.

## 7.2.1 Safety Considerations

### Antibiotic Resistance Profile

As with any bacteria, antibiotic resistance exists among some probiotic bacteria. The resistance may be related to chromosomal, transposon or plasmid genes. Bacteria containing transmissible resistance genes, especially to antibiotics important in human medicine, should not be used as probiotics. Information submitted should include the pattern of resistance to antibiotics, the mechanism of resistance, and the resistance transfer mechanism.

Questions to be answered by the applicant include the following:

- Is it intrinsic or acquired?
- If acquired, is it due to gene mutation in a gene intrinsic to the bacterium?
- If not, is it due to gene transfer?

The antibiotics tested should include Ceftiofur, ceftriaxone, ciprofloxacin, amikacin, amoxicillin-clavulanic acid, gentamicin, Kanamycin, nalidixic acid, streptomycin, trimethoprim-sulfamethoxazole, ampicillin, ceftiofur, cephalothin, chloramphenicol, sulfamethoxazole and tetracycline.

Bacterial strains owe their antibiotics resistance to the production of enzymes that chemically modify structures of the antibiotics such as the aminoglycoside units. These strains can develop antibiotic resistance by mutating in the presence of the drug, resulting in the resistant strain having a selective advantage and possibly replacing the parent strain.

### Production of Antibiotics

Certain bacterial strains may produce antibiotics, especially those with structural similarities to antibiotics important in human medicine. Exposure to these bacteria encourages development of resistance to these important antibiotics. Such strains should not be used as probiotics.

### Pathogenic Potential

Organisms that are not commonly used or do not have a long history of use need to be tested for pathogenic potential. This includes the genetics of the taxonomic unit and the growth and biochemical characteristics under a variety of relevant environmental conditions.

If the strain is from a taxonomic group known to contain some strains capable of toxin production, it should be demonstrated that the strain to be used in the product is free of virulent factors and toxin production. Evidence should be sought at a genotypic rather than at a phenotypic level.

If the strain under evaluation belongs to a species with known hemolytic potential, determination of hemolytic activity is required.

### **Metabolic Activities**

Certain strains produce metabolites which may cause problems in human physiology. For example, consumption of *Lactobacillus* tablets has been associated with D-lactic acidosis in patients with short bowel syndrome. Probiotic strains tested positive for D-lactate production or not tested should be contraindicated for consumers with short bowel syndrome. As a second example, certain *Lactobacillus* species possess bile salt deconjugase activity that may cause bile salt deconjugation. The location of such activity in the intestine is important so the applicant must ensure that deconjugation in the small intestine is not increased and no changes occur in the large intestine.

### **7.2.2 Efficacy Considerations**

As with other NHPs, pre-clinical experiments using animal models are encouraged before proceeding to human clinical trials. Probiotic strains need to meet and maintain certain criteria to be efficacious. These criteria include minimum daily dose, acid and bile stability, intestinal mucosal adhesion properties, and viability throughout product shelf life.

#### **Minimum Daily Dose (MDD)**

The minimum daily doses vary with different probiotic strains and should be determined to recommend the proper dosage range. For example, to yield fecal recovery, the MDD is  $10^{10}$  Colony Forming Units (CFU)/day for *L. rhamnosus* GG. For *L. johnsonii* LJ1,  $10^9$  CFU/day is required for immune effects.

#### **Acid and Bile Stability**

Probiotic strains must be able to tolerate the acidic and protease-rich conditions of the stomach and the digestive conditions in the small intestine so that they can reach the target site in the large intestine. These qualities are affected by environmental factors and long-term sub-culturing.

#### **Adhesion Characterization**

The ability to adhere to the intestinal mucosa is one of the more important selection criteria for probiotics because adhesion to the intestinal mucosa is considered a prerequisite for

colonization/growth. Adhesion to intestinal biopsy samples, if possible, should be considered as a final *in vitro* adhesion test.

### **Impact of Diet on Probiotic Bacteria**

Another critical factor in successful therapy is the co-administration of a diet containing key growth factors for probiotic bacteria. For example, lactobacilli require a diet high in milk or lactose content, and products based on these bacteria should have labelling instructions for the special diet requirements.



## 8.0 COMBINATION OF MEDICINAL INGREDIENTS

In multiple ingredient NHPs, the NHPD allows any combination of the substances listed in Schedule 1 of the Regulations, provided that there is no concern regarding safety and there is a sound rationale for the combination. The NHPD is compiling a list, to be published on the NHPD Web site, of ingredients that present an unacceptable risk when combined with other ingredients (e.g. any ingredient containing ephedrine in combination with any ingredient containing caffeine). Applications for such combinations will not be approved.

If a product is associated with a particular healing paradigm, the combination must be logically explainable within that paradigm. When ingredients and their claims originate from different healing paradigms, a rationale must be provided for why that cross-paradigm combination is logical.

### 8.1 Rationale for the Combination

For each medicinal ingredient in the formulation, a clear and logical rationale is required to support the following:

- the claim being made for the combination;
- the dosage of each individual medicinal ingredient found in the multiple ingredient product;
- its safety and efficacy in combination with the other medicinal ingredient(s) under the recommended conditions of use;
- the benefits outweighing the risks of the combination; and
- the logic of a cross-paradigm combination (if applicable).

The combination rationale is *not* required under certain circumstances, for example:

- the product is identified as a “traditional formulation” (see **Chapter 8.4.1**); or
- all the medicinal ingredients are vitamins and minerals; or
- adequate evidence is provided to support the safety and efficacy of the *finished product*.

When the level of evidence supporting a claim is higher for one ingredient than for another (see **Chapter 5.2**), the claim wording must not imply that the higher level of evidence applies to all of the ingredients.

### 8.2 Doses of Components in Multiple Ingredient Products

- Each component must contribute positively to the claimed intended effects or, as in many Traditional Chinese Medicine formulations, be intended to specifically counteract expected adverse reactions of other ingredients.
- Component doses may be additive (for the same symptom) or complementary (for different symptoms of the same health condition).
- There must be a sufficient dose of at least one component, or a sufficient dose provided by the additive effects of a combination of components, to justify the proposed claim; additional medicinal ingredients may then also be present in quantities justified in the rationale.

- A multiple ingredient product containing only miniscule doses of components that do not add up to provide a therapeutic dose would not have any claim that could be supported by evidence and thus would not be acceptable to the NHPD.

### 8.3 Safety

- All medicinal ingredients must be safe for over-the-counter purposes under the recommended conditions of use.
- Risk information may be more complex for a multiple ingredient product depending on ingredient quantities and interactions.
- Products that contain ingredients specifically included to cause an unpleasant reaction in order to prevent the product's abuse will require strong justification to be acceptable to Health Canada.
- Factors that may prevent a formulation from being approved include the following:
  - interactions between components that significantly diminish the benefits versus the risks, such as:
    - › pharmacokinetic (absorption, distribution, metabolism, and excretion);
    - › pharmacodynamic (mechanism of action and relationship between concentration and effect); or
    - › physicochemical (chemical reactions between components due to their physical properties, such as tannin-protein precipitations).
    - › additive adverse reactions; or
    - › significant differences between the duration of action of the components, unless it can be demonstrated that such a combination is beneficial despite or because of the differences in duration of action.

Significant differences between the recommended duration of use of the components, for example a medicinal ingredient only suitable for short-term use in a multiple ingredient product recommended for long-term use.

## 8.4 Classification of Multiple Ingredient Products

### 8.4.1 Traditional Formulations

Certain medicinal ingredients have been traditionally used together in specific formulations. Such formulations are considered to be “traditional”. For instance, most Traditional Chinese Medicine remedies are formulations of many herbs. The components of a particular combination may be well-established and the rationale for the formulation is logical according to that healing paradigm.

For traditional formulations that meet the criteria set out in **Chapter 2.2.1** for the traditional pharmacopoeial assessment stream, a combination rationale is *not* required since the composition of components in its entirety is specified within and supported by the referenced pharmacopoeia.

For traditional formulations that are *not* suitable for assessment in the pharmacopoeial stream, two independent references are required to support the combination of traditional ingredients and associated claim(s).

## **8.4.2 Non-traditional Formulations**

A formulation is considered to be non-traditional when it does not meet the criteria of a traditional formulation as defined in **Chapter 8.4.1**. Note that a combination of a non-traditional medicinal ingredient with traditional medicinal ingredients is a non-traditional combination. Similarly, cross-paradigm formulations may combine individual components with traditional claims within their original cultural context. For example, an ingredient with a Traditional Chinese Medicine claim may be combined with another ingredient having an Ayurvedic claim. Since the new proposed formulation is neither from Traditional Chinese nor Ayurvedic medicine, the claim for the multiple ingredient product must clearly indicate that the medicinal ingredients have been used individually in traditional medicine but must not indicate that the formulation itself is “traditional”.

## **8.5 Products Packaged and Sold in Combination**

Products comprising individual preparations packaged and sold as one dosage unit (e.g. three different capsules in a cellophane wrapper to be taken together to “relieve menopausal symptoms”) are assessed in the same manner and have the same evidence requirements as other multiple ingredient products. The claims must be commensurate with the supporting evidence. The combination may be considered additive or complementary, based on the evidence and rationale.

However, this approach does not apply to certain products which are actually several different approved products, each with its own Natural Product Number (NPN), homeopathic medicine number (DIN-HM), or Drug Identification Number (DIN), packaged together for convenience or for marketing purposes (e.g. three different vitamin products with different NPNs, which may also be sold separately), which are defined as Kits. Also, this approach does not apply to a drug (natural health product, biologic, or pharmaceutical) packaged together with a medical device, which is defined as a Therapeutic Combination Product. Health Canada is developing a separate policy to cover kits and therapeutic combination products.

## **8.6 Relative Amounts of Constituents in Formulations**

### **8.6.1 Complementary Combinations**

Two or more medicinal ingredients with different types of pharmacological actions may be present at their respective therapeutic doses to treat different symptoms of a single condition. For example, vitamin C might be combined with echinacea for a sore throat and seneca snakeroot as an expectorant to treat the symptoms of a chest cold.

Two or more medicinal ingredients may be present in one product at full therapeutic doses for treating the same symptoms, provided that there is sufficient evidence supporting the individual

ingredients' safety and efficacy, and that the benefits outweigh the risks for their use in combination. For example, echinacea root that treats the pain of a sore throat might be combined with slippery elm that coats and soothes a sore throat.

### 8.6.2 Additive Combinations

When two or more medicinal ingredients in a single product have the same pharmacological action and may therefore present a risk for over-medicating the consumer if each is included at the full therapeutic dose (e.g. borage oil + evening primrose oil that both contain gamma-linolenic acid to help relieve the symptoms of eczema, or hops + passion flower + chamomile as a sleep aid), the Additive Combinations Evaluation form (**Appendix 5A**) can be used to calculate the appropriate quantity of each medicinal ingredient so that it falls within a reasonable percentage range (80-20%) to ensure the safety and efficacy of the multiple ingredient product for that particular use or purpose.

Multiple medicinal ingredients with the same effect are assumed to be additive unless there is evidence of:

- synergy (the activity of the combination is greater than the sum of the activities of the components); or
- antagonism (the activity of the combination is less than the sum of the activities of the components).

In general there is no arbitrary minimum limit for the acceptable range of doses (i.e. no <10% rule), but when there are established minimum effective doses, as is the case for some vitamins and minerals, they must be followed.

For all additive medicinal ingredients in the multiple ingredient product at the recommended daily dose, the sum of the percentages of the individual medicinal ingredient minimum daily reference doses must be equal to or greater than 80%, and the sum of the percentages of the individual medicinal ingredient maximum daily reference doses must be equal to or less than 120% as per the sample Additive Combinations Evaluation Form, **Appendix 5B**.

## 8.7 Monographs and Multiple Ingredient Products

Single-ingredient monographs in the NHPD *Compendium of Monographs* may be referenced as evidence to support the safety and efficacy of one or more individual medicinal ingredients in multiple ingredient products. All of the other requirements for multiple ingredient products (e.g. the rationale for the combination) apply to such products. Multiple ingredient products that are not themselves monographed (e.g. in a Product Category Monograph) do not fall within the 60-day disposition clause of the Regulations because the combination rationale and Summary Reports will require evaluation.

The *Food and Drug Regulations* permit considerable flexibility in how vitamins and minerals may be combined, a practice that continues under the *Natural Health Products Regulations*. In addition to some single ingredient monographs for vitamins and minerals, a monograph for multi-vitamin/mineral products and monographs for a number of other types of multiple ingredient products are being added to the *Compendium of Monographs*.

## 9.0 SAFETY AND EFFICACY SUBMISSION REQUIREMENTS

As per section 1.5(g) of the Regulations, the Product Licence Application must contain information that supports the safety and efficacy of the NHP when it is used in accordance with the recommended conditions of use.

Following the template found in **Appendix 4**, present the required information in either paragraph or point form. For all cited information, indicate references within the body of the text using an author-date format (see **Appendix 2** for additional information on formatting references).

The required information consists of the following elements:

- Evidence Summary Report;
- Safety Summary Report;
- Combination Rationale (if applicable);
- Non-medicinal Ingredient Information (if applicable);
- copies of references to support safety and efficacy; and
- a list of all references submitted.

The intent of the Summary Reports is to help the applicant provide the safety and efficacy information in a format that will facilitate the assessment process. The NHPD uses these reports in the evaluation of the evidence provided to support the safety and efficacy of an NHP.

Applicants are encouraged to devote sufficient time to prepare a clear and concise package. Inaccurate or incomplete reports will delay the assessment process and may result in the refusal of the application.

The NHPD will ensure that all information provided in the Summary Reports will be protected.

### 9.1 Evidence Summary Report

The Evidence Summary Report consists of the following 3 sections:

#### 9.1.1 Recommended Use or Purpose (health claim)

In this section, provide the following:

- the proposed health claim as indicated in the Product Licence Application form;
- the type of claim (treatment, risk-reduction, structure-function or non-specific); and
- references (author-date style) that support the claim.

For example:

Claim 1: “helps to build healthy cartilage”

- structure-function claim
- references that support this claim: Gunter et al. 2006; Ahmed et al. 2005; Merrill 2003.

Claim 2: “helps to relieve the pain of osteoarthritis”

- therapeutic claim
- references that support this claim: Gunter et al., 2006; Smith et al., 1993.

### 9.1.2 Critical Overview

The critical overview should be organized based on the claims of the product.

In this section, provide the following:

- a critical analysis and summary of the totality of evidence (see Chapter 1.3) from all relevant sources of evidence (see Chapter 3) pertaining to the use of the NHP according to the recommended conditions of use;
- pharmacokinetic and pharmacodynamic information where available (human data preferred, animal or in vitro where necessary), to support its safety and/or efficacy; and
- in-text references (author-date style) for the above.

### Selecting the Evidence for the Submission

From the literature search results (see **Chapter 4**), select for the submission the highest quality evidence available (see **Chapter 3**) that is **relevant** to support the safety and efficacy of the NHP according to the recommended conditions of use indicated in the Product Licence Application form. For example:

- If the claim is “supports heart health”, ensure that the evidence specifically supports efficacy of the NHP when used for supporting heart health.
- If the recommended dose is 1500 mg/day, provide evidence that specifically supports the efficacy of a dose of 1500 mg/day.
- If the ingredient is an extract, make sure sufficient information is provided to allow comparison between the proposed daily dose and that in the references.
- If the sub-population is “children”, ensure that the evidence provided adequately supports efficacy in children.
- If the dosage form is a “tablet” and the route of administration is “oral”, do not provide evidence for routes and forms that are not relevant, such as intravenous.
- If the NHP is intended for long-term use, do not provide evidence that can only support short-term use.
- If only short-term studies are available, provide the duration of use supported by these studies on the PLA form.

## Summarizing the Evidence in the Submission

In paragraph or point form, critically summarize the relevant evidence by briefly describing the following:

- the type of evidence;
- method (trial design);
- participants or subjects (number, inclusion criteria and if available exclusion criteria);
- daily dose and frequency;
- treatment characteristics (e.g. dosage form, formulation, methods of preparation, route of administration, etc.);
- duration of treatment;
- endpoints or measures of efficacy;
- effects or results (noting statistical significance, non-significance and trends);
- conclusions on the totality of the evidence; and
- in-text references (author-date style) for all evidence summarized.

Note: for meta-analysis and systematic reviews, no further analysis is required.

### 9.1.3 Dosage and Other Conditions of Use

In this section, provide information to support the recommended conditions of use indicated in the Product Licence Application form:

- dose (amount, frequency and directions of use, including reference to the Additive Combinations Evaluation Form if appropriate, see **Chapter 8.1**);
- dosage form;
- route of administration; and
- duration of use (if any).

Include references (author-date style) to support **each** of the recommended conditions of use, for example, take one capsule 3x/day (total daily dose: 600 mg) (Carson 2006; Berthold et al., 2005) with meals (Agarwal et al., 2006). Use for a minimum of 6 weeks (Agarwal et al. 2006).

## 9.2 Safety Summary Report

A Safety Summary Report is not required for applications attesting to a monograph from the NHPD *Compendium of Monographs* or a TPD Category IV Monograph or Labelling Standard. Please ensure to attest to the monograph on the PLA form.

For all other types of product licence applications, the Safety Summary Report should consist of the following 2 sections.

### 9.2.1 Safety Overview

In this section, provide a summary of all relevant safety information related to the NHP, including the following:

- known adverse reactions associated with its use (including adverse reaction reports, if available);
- preclinical or clinical toxicology (see Section 3.4 and only submit if applicable);
- previous marketing experience (see Section 3.7);
- interactions (e.g. with other medicinal products, foods, standardized laboratory tests);
- in-text references (author-date style) for the above.

### 9.2.2 Risk Information and Risk Mitigation

In this section, provide the following:

- risk information, including cautions, warnings, and contraindications associated with the use of the NHP for self-care;
- strategies to mitigate any risk(s) associated with the use of the NHP for self-care; and
- in-text references (author-date style) for the above.

### Developing Risk Mitigation Strategies

In general, risk mitigation strategies should reflect the nature of the risk associated with the use of the NHP for self-care (see **Chapter 1.2**), and may include the use of specific risk information on product labels.

Consider the following factors when identifying the nature of the risk:

- severity of the adverse effect;
- probability or frequency of the adverse effect;
- severity of the disease or condition for which the NHP is indicated for use;
- potentially sensitive sub-populations.

### Safety Factors

Use the following “safety factor” questions as a guide to help determine the nature and level of risk. If the answer to any of these questions is “yes”, identify the nature of the risk and suggest strategies for risk mitigation.

- Are individualized instructions and/or direct practitioner supervision, adjunctive therapy with scheduled drugs or routine laboratory monitoring required to ensure the safety or effectiveness of the medicinal ingredient or product?
- Is the medicinal ingredient or product used in treatment of a disease that is not appropriate for self-care, e.g. a serious disease easily misdiagnosed by the public?
- Does use of the medicinal ingredient or product mask other ailments or their development?



- Does the medicinal ingredient or product have known adverse effects at the recommended or therapeutic dosage level?
- Is there a narrow margin of safety between the therapeutic and toxic doses, especially in populations such as seniors, children and pregnant or nursing women?
- Does the medicinal ingredient or product have a demonstrated potential for addiction, abuse or severe dependency that is likely to lead to harmful non-medicinal use?
- Does the medicinal ingredient or product have a therapeutic effect based on recently established pharmacological concepts, the consequences of which have not yet been fully established?
- Have experimental data shown that the medicinal ingredient or product induces toxicity in animals? If so, has it been in use long enough to establish the pattern or frequency of long-term toxic effects in humans?
- Does the medicinal ingredient or product have known adverse interactions with other NHPs, drugs, or foods?
- Is the medicinal ingredient or product known to affect results of standard laboratory or other diagnostic tests?
- Does the medicinal ingredient or product contribute to, or is it likely to contribute to, the development of resistant strains of micro-organisms in humans?
- Does the medicinal ingredient or product possess a high level of risk relative to expected benefits?

### **Risk Information for Pregnancy and Breastfeeding**

A statement to the effect of “Do not use if pregnant or breastfeeding” is required to be indicated in the Product Licence Application form and on the label of all NHPs for which there is insufficient evidence based on generally available and acceptable scientific literature to establish their safe and efficacious use by pregnant or breastfeeding women.

### **9.3 Combination Rationale**

For multiple ingredient products, provide a rationale that explains why combining those medicinal ingredients at their respective quantities is likely to be safe and effective under the recommended conditions of use (see **Chapter 8.1**).

### **9.4 Non-Medical Ingredient Information**

For any non-medicinal ingredient **not found** on the NHPD List of Acceptable Non-medicinal Ingredients (see **Chapter 6**), NHPD may require the following information to evaluate its safety:

- its proper name, common name, source, purpose and quantity;
- previous evaluation results from specified jurisdictions and their agencies to provide information on the conditions of use, restrictions, as well as approval and withdrawal history, if applicable;
- reference to credible sources, such as the *United States Pharmacopeia*, that can be cited to justify its use outside the specified limitations;

- rationale for its use within the NHPD’s definition of a non-medicinal ingredient (**Chapter 6**); and
- references to toxicological information.

## **9.5 References**

In this section, provide the following:

- reference list that details all references that are submitted in full text with the application; and
- copy (in full text) of references that are relevant to support the safety and efficacy of the NHP according to its recommended conditions of use.

It is recommended that each full-text article submitted with the application be directly cited in the Summary Reports. This will ensure a more timely review. Do not submit articles that are not directly relevant to support the safety and efficacy of the NHP according to its recommended conditions of use.

Refer to **Appendix 2** for more information on formatting references.

## GLOSSARY

**Adaptogen.** A substance which increases the body's general, non-specific resistance to a wide spectrum of physical, chemical and biological factors. An adaptogen by definition must:

- be innocuous;
- have a wide range of therapeutic activity;
- manifest its action only against a corresponding challenge (physical, chemical or biological) to the system; and
- have a normalizing action irrespective of the direction of foregoing pathological changes.

**Adverse Reaction.** A noxious and unintended response to a NHP that occurs at any dose used to test for the diagnosis, treatment or prevention of a disease or for modifying an organic function.

**Animal.** A member of the biological kingdom *Animalia*, consisting of complex multicellular eukaryotes with cells that have a membrane but no wall, have muscle and nervous tissue in most members, are heterotrophs that mostly ingest food into a specialized cavity where it is digested, and reproduce sexually by means of motile sperm and larger, non-motile eggs. Some animals reproduce through asexual reproduction.

**Antagonism.** Interference in the physiological action of an ingredient by another resulting effect lower than expected.

**Clinical Trial.** An investigation in respect to a NHP that involves human subjects and is intended to discover or verify its clinical, pharmacological or pharmacodynamic effects, to identify any adverse events that are related to its use, to study its absorption, distribution, metabolism and excretion, or to ascertain its safety or efficacy.

**Common Name.** For any medicinal or non-medicinal ingredient contained in a NHP, the name by which it is commonly known and is designated in a scientific or technical reference.

**Conditions of Use.** (see Recommended Conditions of Use).

**Constituent.** A component part, i.e. a single chemical isolated from a whole herb.

**DIN (drug identification number).** A numerical code assigned to each drug product marketed under or in accordance with the *Food and Drugs Act* and the *Food and Drug Regulations*.

**Dosage Form.** The final physical form of the NHP which may be used by the consumer without requiring any further manufacturing.

**Effectiveness.** A measure of the accuracy or success of a diagnostic or therapeutic technique when carried out in an average clinical environment. The extent to which a treatment achieves its intended purpose.

**Efficacy.** The extent to which a specific intervention, procedure, regimen or service produces a beneficial result under ideal conditions.

**Extract.** A substance prepared by treating a plant or a plant material, an alga, a bacterium, a fungus, or non-human animal material with solvents or pressure to remove any constituents.

**Filling.** Transferring and enclosing a bulk product into its final container.

**Finished product.** A product that has undergone all stages of production, including packaging in its final container and labelling.

**Formulating.** Preparing components and combining raw materials into a finished dosage form.

**Health Claim.** A statement about the expected benefits to the consumer of taking a NHP.

**Homeopathic Medicine.** To be considered a homeopathic medicine, a product must meet two criteria. It must be:

- Manufactured from, or contain as medicinal ingredients, only substances referenced in a homeopathic monograph in one of the following homeopathic pharmacopoeias, as they are amended from time to time:
  - *Homeopathic Pharmacopeia of the United States* (HPUS)
  - *Homöopathische Arzneibuch* (HAB) or German Homeopathic Pharmacopoeia
  - *Pharmacopée française* or French Pharmacopoeia (PhF)
  - *European Pharmacopoeia* (Ph.Eur.)
  - *Encyclopedia of Homeopathic Pharmacopoeia* (EHP)
- Prepared in accordance with the methods outlined in one of the homeopathic pharmacopoeias listed above, as they are amended from time to time.

**Ingredient.** A single substance that is a component part of any combination or mixture. For example, vitamin C is a common ingredient in a multivitamin product. (see also Product)

**Interaction.** In pharmacology, the phenomenon that the combined effects of two substances differ from the sum of their separate effects (as in synergism and antagonism).

**Isolate.** A purified constituent of a defined molecular structure obtained from a plant or a plant material, an alga, a bacterium, a fungus or a non-human animal material.

**Label (noun).** Includes any legend, word or mark attached to, included in, belonging to or accompanying any food, drug, cosmetic, device or package. NHPs are included.

**Label (verb).** To affix the inner or outer label of the NHP.

**Mineral:** A naturally occurring, solid, inorganic substance with a definite and predictable chemical composition and physical properties.

**Natural Health Product (NHP).** A substance set out in Schedule 1 or a combination of substances in which all the medicinal ingredients are substances set out in Schedule 1, a homeopathic medicine or a traditional medicine that is manufactured, sold or represented for use in:

- 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.

However, a NHP does not include a substance set out in Schedule 2, any combination of substances that includes a substance set out in Schedule 2 or a homeopathic medicine or a traditional medicine that is or includes a substance set out in Schedule 2. Furthermore, a substance or combination of substances or a traditional medicine is not considered to be a NHP if its sale, under the *Food and Drug Regulations*, is required to be pursuant to a prescription when it is sold other than in accordance with section C.01.043 of those regulations. Note that homeopathic medicines may be made from Schedule D substances, Schedule F substances, or *tabacum* and *nicotinum* because they are subject to the *Food and Drugs Act* so they are substances exempted from the *Tobacco Act*.

**Probiotic.** A monoculture or mixed-culture of live micro-organisms that benefit the microbiota indigenous to humans.

**Product Licence Applicant.** An individual with legal ownership of and responsibility for the NHP. The product licence applicant may be located in or outside of Canada. Applicants who are located outside of Canada must identify a Canadian representative.

**Proper Name.** In respect of an ingredient of a NHP, one of the following:

- if the ingredient is a vitamin, the name for that vitamin set out in item 3 of Schedule 1;
- if the ingredient is a plant or a plant material, an alga, a bacterium, a fungus, a non-human animal material or a probiotic, the Latin nomenclature of its genus and, if any, its specific epithet; and
- if the ingredient is other than one described in paragraphs (a) or (b), the chemical name of the ingredient.

**Qualification.** To make competent or eligible for an office, position, or task by having the proper or necessary skills, knowledge, credentials, accomplishments or qualities.

**Quantity.** The amount of medicinal ingredient(s) per dosage unit.

**Recommended Conditions of Use.** As defined in section 1(1) of the *Natural Health Products Regulations*, recommended conditions of use for a natural health product means:

- its recommended use or purpose;

- its dosage form;
- its recommended route of administration;
- its recommended dose;
- its recommended duration of use, if any; and
- its risk information, including any cautions, warnings, contraindications or known adverse reactions associated with its use.

**Risk-reduction Claim.** A claim which describes the relationship between using a product and reducing the risk of developing a chronic disease or abnormal physiological state by significantly altering a major risk factor or factors recognized to be involved in its development.

**Safener.** An ingredient used in some herbal NHPs that mitigates or alters the effects of the primary medicinal ingredient to prevent adverse reactions. Because safeners are biologically active, they are subject to the same data requirements as for a medicinal ingredient.

**Safety.** The ability for a NHP to produce a beneficial health outcome, outweighing the risk associated with using it, in humans, according to the recommended conditions of use.

**Self-care.** Self-care involves the activities individuals undertake for the prevention, treatment and symptomatic relief of diseases, injuries or chronic conditions that individuals can recognize and manage on their own behalf, either independently or in cooperation with a health care practitioner.

**Standards of Evidence.** Clearly defined criteria used by regulators to evaluate the safety, quality and effectiveness of a claim regarding a health product or food. The criteria define the amount and type of data required to support the safety of a product and all health claims that are associated with it. Although Standards of Evidence may differ from one type of product to another, they are consistent within a similar category of products.

**Structure-Function Claim.** A claim which describes the effect of a product on a structure or physiological function in the human body, or a product's support of an anatomical, physiological, or mental function. This category includes claims of maintaining or promoting health.

**Synergy.** The interaction of two or more components leads to their combined effect which is greater than the sum of their individual effects.

**Traditional Medicine.** The sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness. Traditional medicine has a long history (at least 50 consecutive years) of use.

**Therapeutic Claim.** A claim which relates to the diagnosis, treatment, mitigation or prevention of a disease, disorder, or abnormal physical state or its symptoms in humans.

**Vitamin.** An organic substance needed in small amounts to maintain normal health.

## APPENDIX 1: EXAMPLES OF USEFUL REFERENCES

The following resources may be useful in the literature search for safety and efficacy evidence.

### References to Traditional Use

Bensky D, Barolet R (1990). *Chinese Herbal Medicine: Formulas and Strategies*. Seattle (WA): Eastland Press.

Bensky D, Gamble A (1993). *Chinese Herbal Medicine: Materia Medica 2<sup>nd</sup> Ed*. Seattle (WA): Eastland Press.

Hsu H-Y, Chen Y-P, Shen S-J, Hsu C-S, Chen C-C, Chen, Chang H-C (1986). *Oriental materia medica: a concise guide*. Long Beach (CA): Oriental Healing Arts Institute.

Marles RJ, Clavelle C, Monteleone L, Tays N, Burns D (2000). *Aboriginal plant use in Canada's northwest boreal forest*. Vancouver (BC): UBC Press.

Moerman DE (1999). *Native American Ethnobotany*. Portland (OR): Timber Press Inc.

Williamson EM (2002). *Major Herbs of Ayurveda*. London (UK): Churchill Livingstone.

### Pharmacopoeias, Dispensatories

*The Ayurvedic Pharmacopoeia of India, Volume II, Part I*. (1999). New Delhi: The Controller of Publications.

*The Ayurvedic Pharmacopoeia of India, Volume I, Part I*. Reprint (2001). New Delhi: The Controller of Publications.

*The Ayurvedic Pharmacopoeia of India, Volume III, Part I* (2001). New Delhi: The Controller of Publications.

*The Ayurvedic Pharmacopoeia of India, Volume IV, Part I* (2004). New Delhi: The Controller of Publications

Bradley, P.R, editor. *British Herbal Compendium Vol. 1* (1992).. Bournemouth (UK): British Herbal Medicine Association.

*British Herbal Pharmacopoeia* (1996). Great Britain (UK): British Herbal Medicine Association.

Felter HW, Lloyd JU (1983). *King's American Dispensatory* (Volumes 1 and 2). Sandy, OR: Eclectic Medical Publications.

*The Homeopathic Pharmacopoeia of the United States* (2000). Washington DC: Homeopathic Pharmacopoeia Convention of the United States.

*The Japanese Pharmacopoeia*, 14th edition, English version (2001). Tokyo: Society of Japanese Pharmacopoeia.

*Pharmacopoeia of the People's Republic of China*, English edition (2000). Beijing: The State Pharmacopoeia Commission of P.R. China.

*United States Pharmacopeia and National Formulary (USP 29 - NF 24)* (2006). Rockville, MD: United States Pharmacopoeial Convention.

Upton R, editor. *American Herbal Pharmacopoeia and Therapeutic Compendium*. Santa Cruz (CA) (Monograph series).

Willoughby MJ, Mills SY, compilers. *The British Herbal Pharmacopoeia* (1996). Exeter, UK: A publication of the British Herbal Medicine Association.

### **Monographs**

Blumenthal M *et al*, editors. *Herbal Medicine: Expanded Commission E Monographs* (2000). Boston (MA): Integrative Medicine Communications.

Blumenthal M *et al*, editors. *The Complete German Commission E Monographs* (1998). Boston (MA): Integrative Medicine Communications.

Blumenthal M and Riggins CW (1997). *Popular Herbs in the U.S. Market: Therapeutic Monographs*. Austin (TX): American Botanical Council.

*Monographs on the Medicinal Uses of Plant Drugs* (1999). Exeter (UK): A publication of the European Scientific Cooperative on Phytotherapy.

*WHO Monographs on Selected Medicinal Plants* (Volumes 1 and 2) (1999). Geneva (Switzerland): World Health Organization.

*Compendium of Monographs* (2006). Ottawa (ON): Natural Health Products Directorate, Health Canada. Available at: [http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/index\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/index_e.html)

### **Reference Texts**

Barnes J, Anderson LA, Phillison JD (2002). *Herbal Medicines* (2nd edition). London (UK): Pharmaceutical Press.

Bisset NG, editor (1989). *Herbal Drugs and Phytopharmaceuticals*. Ann Arbor (MI): CRC Press.



Boon H, Smith M (2003). *A Complete Natural Medicine Guide to the 50 Most Common Herbs: A Botanical Pharmacy*. Toronto (ON): Robert Rose Inc.

Brinker F (2001). *Herb Contraindications & Drug Interactions* (3rd edition). Sandy (OR): Eclectic Medical Publications.

Chandler F, editor (2000). *Herbs: Everyday Reference for Health Professionals*. Ottawa (ON): Canadian Pharmacists Association and the Canadian Medical Association.

Huang, KC (1999). *The Pharmacology of Chinese Herbs*. (2nd edition). Boca Raton (FL): CRC Press.

Leung AY, Foster S (1996). *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics*. (2nd edition). New York (NY): John Wiley & Sons, Inc.

McGuffin M *et al*, editors (1997). *Botanical Safety Handbook*. Boca Raton (FL): CRC Press.

McGuffin M, Kartesz JF, Leung A Y, Tucker AO, editors (2000). *Herbs of Commerce* (2nd edition). US: American Herbal Products Association.

*Research guidelines for evaluating the safety and efficacy of herbal medicines* (1993). World Health Organization Regional Office for the Western Pacific. Available at: [http://www.wpro.who.int/publications/pub\\_9290611103.htm](http://www.wpro.who.int/publications/pub_9290611103.htm)

### **Journals with a Focus on Peer-Reviewed Research Articles**

*Fitoterapia: The Journal for the Study of Medicinal Plants*. Elsevier Science Publishers, ISSN: 0367-326X.

*Journal of Ethnopharmacology*. Elsevier Science Inc., Journal Information Center, 655 Avenue of the Americas, New York, NY 10010.

*Pharmaceutical Biology* (formerly *International Journal of Pharmacognosy*). Swets & Zeitlinger Publishers, P.O. Box 825, 2160 SZ Lisse, The Netherlands.

*Phytomedicine*. VCH Publishers Inc., 303 NW 12th Avenue, Deerfield Beach FL 33442-1705.

*Phytotherapy Research*. Heyden & Son Ltd., Spectrum House, Hillview Gardens, London NW4 2JQ, United Kingdom.

*Planta Medica*. Georg Thieme Verlag, Stuttgart, Germany.

## **APPENDIX 2: FORMATTING REFERENCES**

The Harvard system is an example of an author-date referencing format that is commonly used in scientific works.

### **In-text References**

In-text references to another work are immediately followed by the author's surname and year of publication in brackets, with no punctuation in between, e.g.:

Similar dose-response trends were reported in a previous study (Smith 2006).

Where the author's name is naturally integrated into a sentence, only the year is bracketed, e.g.:

- Smith (2006) previously reported similar dose-response trends.

When there are two authors for a particular work, both surnames appear before the date, e.g.:

Some of the suggested mechanisms of action have been investigated in vitro (Costa-Meyers and Meyers 2004).

When there are three or more authors, the first author's surname and "et al." appear before the date, e.g.:

- In a recent review, Bennett et al. (2005) noted that...
- The treatment group showed significant clinical improvement (Newall et al. 2005).

When more than one work is referenced in one statement, the references are separated by a semicolon, e.g.:

- Other risk factors for this condition include family history and increasing age (James 2006; Lee et al. 1999).

When two or more works are cited from the same author and published in the same year, they are distinguished by a lower-case letter added to the date, e.g.:

- Clinical studies conducted by Bowen and de Vries (2005a, 2005b) have shown...
- Bowen and de Vries (2005a) have shown...; this was later confirmed (2005b) in a similar study.

### **Reference List**

In the Reference List, provide the complete details of the references that are cited in the Summary Reports (as in-text references) and/or submitted in full text with the application.

A full-text copy of all works cited (in-text references) in the Summary Reports is required to be submitted with the application. However, if necessary and relevant to support the safety and efficacy of the NHP according to its recommended conditions of use, full-text copies of additional articles that are not directly cited in the Summary Reports may also be submitted. Do not include in the Reference List any works that have not been directly cited in the Summary Reports and/or submitted in full text with the application.

### **Formatting the Reference List**

The Reference List is organized alphabetically by the first author's surname. The year of publication immediately follows the author name(s) of the author(s). If no author is named, list the title of the work only.

Refer to the following examples for formatting references for specific types of publications:

#### **Periodical (Journal) Articles:**

[Surname, Initial(s) (Date)]. [Article title]. [Periodical title, volume (issue, if any): pp.#].

#### **Examples:**

##### **Single author:**

Habtemariam S (2002). Hamamelitannin from *Hamamelis virginiana* inhibits the tumour necrosis factor-alpha (TNF)-induced endothelial cell death *in vitro*. *Toxicol* 40:83-88.

##### **Up to six authors:**

Dauer A, Metzner P, Shimmer O (1998). Proanthocyanidins from the bark of *Hamamelis virginiana* exhibit antimutagenic properties against nitroaromatic compounds. *Planta Med* 64(4):324-327.

##### **More than six authors:** List the first six authors, followed by "et al.":

Hughes-Formella BJ, Bohnsack K, Rippke F, Benner G, Rudolph M, Taush I et al. (1998). Anti-inflammatory effect of Hamamelis lotion in a UVB erythema test. *Dermatology* 96(3):316-322.

#### **Books:**

[Surname, Initial(s) (Date)]. [*Book title, edition* (if not the first)]. [Place of publication: publisher, pp. #].

**Examples:****Single author:**

Chevallier A. (1996). *The Encyclopaedia of Medicinal Plants*. New York: Dorling Kindersley, pp. 9-11.

**Up to six authors:** (as for periodicals, list all authors).

**More than six authors:** (as for periodicals, list the first six authors, followed by “et al.”).

**Edited Book:**

Blumenthal M, Goldberg A, Brinkmann J, editors (2000). *Herbal Medicine: Expanded Commission E Monographs*. Boston (MA): Integrative Medicine Communications, pp. 17-22.

**No author named:**

*Style manual for authors, editors and printers* (1988). Canberra: Australian Government Publishing Service, pp. 56-60.

**Electronic Sources:**

The details required for electronic sources (CD-ROMs, diskettes, web sites, etc.) are similar to those required for printed references, with the addition of a **retrieval statement**, which includes:

- the type of medium;
- the name, or Web site address; and
- the date the information was accessed.

**Example:**

RTECS (Registry of Toxic Effects of Chemical Substances) (2001). Canadian Centre for Occupational Health and Safety [Internet]. [Hamilton, cited November 6, 2002]. Available at: <http://ccinfoweb.ccohs.ca/rtecs/Action.lasso?-database=rtecs&-layout=Display&-response=detail.html&-op=eq&RTECS+NUMBER=MG8325000&-search>

### **APPENDIX 3: NON-MEDICINAL INGREDIENTS REFERENCE LIST**

*Committee on Food Chemicals Codex* (1996). Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Food Chemical Codex . (4th edition). Washington (DC): National Academy Press.

Kibbe AH. *Handbook of Pharmaceutical Excipients (3rd edition)* (2000). Washington DC (US): American Pharmaceutical Association.

*European Pharmacopoeia*. Published under the direction of the European Directorate for the Quality of Medicines, European Pharmacopoeia Commission Council of Europe (partial agreement) in accordance with the Convention on the elaboration of a European pharmacopoeia.

Minister of Public Works and Government Services (2001). *Canadian Food and Drug Regulations*. Ottawa (Canada): Government of Canada. [http://www.hc-sc.gc.ca/food-aliment/friia-raaii/food\\_drugs-aliments\\_droques/act-loi/e\\_index.html](http://www.hc-sc.gc.ca/food-aliment/friia-raaii/food_drugs-aliments_droques/act-loi/e_index.html)

Minister of Public Works and Government Services (2003). *Natural Health Products Regulations of the Canadian Food and Drugs Act*. Ottawa (Canada): Government of Canada. Available at: [http://www.hc-sc.gc.ca/food-aliment/friia-raaii/food\\_drugs-aliments\\_droques/act-loi/e\\_index.html](http://www.hc-sc.gc.ca/food-aliment/friia-raaii/food_drugs-aliments_droques/act-loi/e_index.html)

*Pharmacopée Française*. Commission Nationale de la Pharmacopée Française, Agence française de sécurité sanitaire des produits de santé, Direction des laboratoires et des contrôles, Unité pharmacopée.

*The British Pharmacopoeia*. Published under the direction of the General Council of Medical Education and Registration of the United Kingdom, pursuant to the Acts XXI & XXII Victoria, cap. XC, 1858 and XXV and XXVI Victoria, cap. XCI, 1862.

*The International Pharmacopoeia*. Marketing and Dissemination. World Health Organization, Geneva (Switzerland): World Health Organization.

United States Pharmacopoeial Convention (2001). *The United States Pharmacopoeia*. The National Formulary. Rockville (MD): United States Pharmacopoeial Convention.

## **APPENDIX 4: SAFETY & EFFICACY SUBMISSION REQUIREMENTS TEMPLATE**

### **1. Evidence Summary Report**

1.1 Recommended use or purpose (health claim):

1.2 Critical Overview:

1.3 Dosage and other Conditions of Use:

### **2. Safety Summary Report**

2.1 Safety Overview:

2.2 Risk Information and Risk Mitigation:

### **3. Combination Rationale (if applicable)**

### **4. Non-Medicinal Ingredient Information (if applicable)**

### **5. References**

## APPENDIX 5A: TEMPLATE FOR ADDITIVE COMBINATIONS EVALUATION FORM

Product Name:						
Additive Indication:						
Recommended Dose:						
Medicinal Ingredient, Source, Single Ingredient Daily Reference Dose Range	Minimum Daily Reference Dose (mg/day)	Maximum Daily Reference Dose (mg/day)	Weight per Dosage Unit (mg)	Recommended Product Daily Dose (mg/day)	% Minimum Daily Reference Dose	% Maximum Daily Reference Dose
Sum of Percentages:						

**Note:** references are required to support each medicinal ingredient’s conditions of use, and the conditions of use for the combination product when available.

The calculations are performed as follows:

$$\% \text{ Minimum Daily Reference Dose} = 100\% \times [(\text{Recommended Product Daily Dose}) / (\text{Minimum Daily Reference Dose})]$$

$$\% \text{ Maximum Daily Reference Dose} = 100\% \times [(\text{Recommended Product Daily Dose}) / (\text{Maximum Daily Reference Dose})]$$

## APPENDIX 5B: SAMPLE ADDITIVE COMBINATIONS EVALUATION FORM

Product Name:	"Gelican"					
Additive Indication:	Traditionally used as a sedative to help you get to sleep <sup>1,2</sup>					
Recommended Dose:	2 tablets at bedtime <sup>1,2</sup>					
Medicinal Ingredient, Source, Single Ingredient Daily Reference Dose Range	Minimum Daily Reference Dose (mg/day)	Maximum Daily Reference Dose (mg/day)	Weight per Dosage Unit (mg)	Recommended Product Daily Dose (mg/day)	% Minimum Daily Reference Dose	% Maximum Daily Reference Dose
<i>Passiflora incarnata</i> dried flowers 250-1000 mg 3x/day <sup>3,4</sup>	750	3000	300	2 x 300 = 600	600/750= 80%	600/3000 = 20%
<i>Humulus lupulus</i> dried strobiles 500-1000 mg/day <sup>5,6</sup>	500	1000	150	2 x 150 = 300	300/500= 60%	300/1000 = 30%
<i>Matricaria recutita</i> dried flowers 2000-8000 mg 3x/day <sup>7,8</sup>	6000	24000	500	2 x 500 = 1000	1000/6000 = 17%	1000/24000 = 4%
Sum of Percentages:					157%	54%

<sup>1-8</sup> Literature references providing conditions of use including single and daily doses, etc.

At the recommended dose:

- the Percent Minimum Daily Reference Dose sums to 157%, which is greater than 80% and supports efficacy
- the Percent Maximum Daily Reference Dose sums to 54%, which is less than 120% and supports safety.

The safety and efficacy of the overall combination is within the acceptable 80% to 120% range.



## APPENDIX 6: CHECKLIST FOR TRADITIONAL PHARMACOPOEIAL ASSESSMENT STREAM

Application to a Traditional Chinese Medicine (TCM) submissions citing *Pharmacopoeia of the People's Republic of China* (PPRC) or *State Drug Standard* (SDS)

Information	Identical to PPRC or SDS (Yes or No)*
All medicinal ingredients	
Quantity of medicinal ingredients as per crude material equivalent, when applicable	
Recommended use or purpose	
Recommended dose	
Recommended route of administration	
Recommended duration of use (if any)	
Dosage form	
Directions of use	
Risk information (cautions, warnings, contraindications, known adverse reactions)	
Methods of preparation (traditional)	
Copy of the relevant pages from the PPRC or SDS (in English or French) provided.	
Copy of literature search for current scientific risk information search provided.	
Product makes no Schedule A claim.	

\* Only those products for which all responses are “yes” will be assessed in the pharmacopoeial stream.