August 21, 2012

Natural Health Products Directorate, Health Canada
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To Whom It May Concern:

Re: CHFA Comments on Draft Guidance Documents:
   Pathway for Licensing Natural Health Products Making Modern Health Claims
   Pathway for Licensing Natural Health Products Used as Traditional Medicines

On behalf of the Canadian Health Food Association (CHFA), we would like to thank you for the opportunity to provide comments on the draft Pathway for Licensing Natural Health Products Making Modern Health Claims and Pathway for Licensing Natural Health Products Used as Traditional Medicines guidance documents. CHFA is an industry association representing 1000 members nationwide that are involved in the manufacture and sale of natural health and organic products. As such, our interest is to ensure that Canadian consumers continue to have access to safe, effective, and high quality natural health products (NHPs), that manufacturers are empowered to make appropriate health claims, and that NHPD ask for a reasonable level of evidence based on the product’s risk category.

CHFA is pleased to have been involved in providing seed documents and recommendations dating back to 2009 and has invested significant time and resources to assist in the development of appropriate regulatory requirements for NHPs since the 53 recommendations were accepted by the Health Minister in 1998.

During the 90-day consultation period provided by Health Canada, CHFA under-took a comprehensive two-pronged approach to ensure a broad consensus of opinion. Firstly, CHFA communicated the release of the draft documents broadly to the membership on multiple occasions and sought broad perspective feedback during the initial phase as a means of determining the degree of member support for the documents. We are pleased to report that much of the feedback was complimentary to NHPD in terms of improved readability, clarity of intent, and a clear embedding of the concept of matching the amount and type of evidence to risk. While the majority of feedback CHFA received indicated broad support with
comments or suggestions in certain areas to provide clarity, we also received feedback from a limited number of members indicating they thought the documents provided sufficient clarity.

In order to coordinate specific feedback and develop a consensus position aimed at improving clarity and predictability even further, CHFA convened its long-standing working group of 25 industry experts. Following numerous meetings, discussions, and detailed review of the proposed text, CHFA is pleased to provide comprehensive feedback contained herein.

The largest amount of commentary and investment of industry time in identifying improvements was centered on Table 1 of the Pathway for Licensing Natural Health Products Making Modern Health Claims guidance document, and specific concern over embedding of (pharmaceutical) clinical trial phases. While NHPD has made great strides recently in assessing the totality of evidence for PLAs based on what appears to be more appropriate criteria than utilized in the past, there is significant concern that failure to meet any aspect of the table, including whether a clinical trial is a Phase II or III for example, coupled with an inexperienced assessment officer could result in unwarranted evidence rejection. CHFA has suggested revisions to Table 1 to better allow for the totality of evidence as an enabler to implement an appraisal tool for evidence, similar in approach to the Quality Appraisal Tool as currently used for foods.

CHFA recognizes that this key recommendation represents a natural evolution of approach to NHPs as their own entity more similar to foods than drugs. We are prepared to work collaboratively with NHPD to develop an appropriate evidence ranking system and criteria, as well as to reflect all other suggestions proposed by our working group in the pages that follow.
### 2.3 RISK-BASED APPROACH TO SAFETY AND EFFICACY

**Current PFL Text:** *Low Level of Risk:*

This level applies to those products/ingredients that, through their intended use, present a low risk to public health or the individual. This category includes 1) NHPs used for treatment, cure, risk reduction or prevention of minor diseases or conditions (including symptoms or risk factors of those conditions), which naturally resolve in a timely manner, 2) NHPs for the treatment of symptoms or risk factors of serious or major conditions or the risk reduction of these conditions, and 3) NHPs for general health maintenance, support, or promotion that refer to modification of a biochemical or physiological function of a nutritional nature or imply benefit to a minor disease or health condition.

**CHFA Comments:** The classification of risk into low, medium, and high levels has generated confusion among members as it relates to serious, major, and minor diseases/conditions. For example, we are seeking assurance that it will be possible to link the symptoms to the actual serious or major disease or condition, or the risk reduction of these conditions, in the health claim statement and still be considered low risk. Assuming products with general health claims are low risk, Annex I provides the example ‘Helps support cardiovascular health by lowering cholesterol’, while Appendix A lists ‘Helps to lower blood/plasma cholesterol levels’ as a major disease/condition. Industry members want to be assured that should they wish to link the symptom to disease/condition; the risk level of the product will not be affected. Additional CHFA comments regarding this particular example is discussed later on in this response document.

Furthermore, we are seeking assurance from NHPD that low risk products are just that, low risk, and that low risk products with only modest benefit will not be refused because of modest or theoretical risk.

**Current PFL Text:** *High Level of Risk:*

This level applies to those products/ingredients that, through their intended use, present a serious public health risk or serious individual risk. This category includes NHPs with the narrowest safety margin and effective dose range, as well as those used for treatment, cure, and prevention of serious diseases. At any level of risk, additional evidence may be necessary to substantiate safety and efficacy for:

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

**CHFA Comments:** The classification of products as ‘high level of risk’ is very similar to Factors for Listing Drugs in Schedule F, which outlines the bases for a prescription product. While we agree that extremely high risk products should be subject to additional evidentiary requirements, the above criteria are inappropriate for all risk levels of NHPs. CHFA members are interested in reducing burden for this risk category. As it stands, there appears to be little distinction between ‘high level of risk’ and Schedule F.

Furthermore, additional evidence to substantiate safety and efficacy should not be required without NHPD identifying a scientifically justified concern, not theoretical risk, particularly for the last 3 bullets above.

**CHFA Comments regarding Figure 1:** As stated above, CHFA members strongly suggest that NHPD create a greater distinction between ‘medium level of risk’, ‘high level of risk’ and Schedule F products to be represented in this flowchart.

There is further confusion among industry members as to what would constitute a ‘serious public health concern’ and ‘high public health concern’. Definitions of these terms are required to better navigate the flowchart.

Furthermore, ‘any toxicity’ should be removed or better qualified as even the most benign ingredients can demonstrate toxicity at some level. Instead, we recommend: ‘any toxicity that cannot be mitigated by a warning or risk statement’ as a means to resolve the lack of condition.
GUIDANCE FOR IMPLEMENTATION

2.4 TYPES OF HEALTH CLAIMS/APPENDIX A: EXAMPLES OF HEALTH CLAIMS BY HEALTH CONDITION

CHFA Comments regarding Claims by Health Condition and Health Effect: Once again, for serious disease/condition claims, it appears as though NHPs would loosely meet the Factors for Listing Drugs in Schedule F, particularly when reviewing the list of examples in Appendix A. As such, there is uncertainty and doubt among industry members that future claims for serious or major diseases/conditions will be approved if prescription drug-type evidence is required.

There is also little distinction between serious and major disease/condition claims in Section 2.4.1; both require intervention by a health practitioner – the definition for ‘serious disease’ explicitly states this, while the definition of ‘major disease’ implies it. The NHP industry requires clear definitions of these categories.

Further to the examples of claims provided in Appendix A, it appears that claims previously considered ‘minor’ are now reclassified as ‘major’, thus reducing the likelihood of new products obtaining approval for these claims. Examples include urinary tract infections, cholesterol, and osteoporosis. CHFA strongly recommends appropriate categorization of diseases/conditions such that suitable levels of risk can be attributed to claims.

Finally, as per the Guidance Document Schedule A and Section 3 to the Food and Drugs Act, the NHP industry is permitted to label and advertise preventative claims to the general public for diseases, disorders or abnormal physical states listed in Schedule A to the Food and Drugs Act: ‘as of June 1st, 2008, sections A.01.067 and A.01.068 of the FDR and sections 103.2 and 103.3 of the NHPR exempt NHPs and nonprescription drugs from the FDA’s section 3 general prohibition on labelling and advertising of preventative claims for Schedule A diseases’.

However, the serious diseases/conditions referenced in Appendix A discuss treatment of Schedule A diseases, disorders or abnormal physical states (for example, cancer, high blood pressure/hypertension, diabetes, depression). CHFA members are concerned about the confusion this creates and that it will lead to inconsistent decisions by assessment officers as well as reduced predictability to achieve a license.
GUIDANCE FOR IMPLEMENTATION

2.5 SAFETY EVIDENCE RECOMMENDATIONS

Current PFL Text: When necessary, safety evidence may also need to support:
- Chemistry and manufacturing information;
- Characterization of the disease implicated in the recommended use or purpose;
- Characterization of the risk factors associated with the disease implicated in the recommended use or purpose;
- Assessment of the potential for interactions;
- An independent causality assessment of adverse reactions;
- A description of the post-market surveillance program (for active surveillance data);
- Consumer research to support labelling; and/or
- A detailed benefit-to-risk assessment.

CHFA Comments: NHPD should recognize that the final 5 bullets are incredibly onerous for most products. As such, it should be clarified within this guidance document, the situation(s) in which this evidence would be required. It should also be noted that theoretical or overly precautionary ‘risks’ seldom justify NHPD’s demand for this level of costly evidence for the NHP industry.

We are also looking to NHPD for assurance that the 5th, 6th, and 7th bullets (above) related to post-marketing will be relevant to a minimal number of instances at the product licensing stage.

Industry members are very interested in obtaining a template of NHPD’s review process for the benefit-to-risk assessment. This would be beneficial to reference in case of Product License rejection and should be shared with industry to demonstrate transparency and objectivity of the review process.

Current PFL Text: For instance, risk mitigation strategies may include:
- ... Not including ingredients with a lack of evidence for safety and efficacy; and
- Limiting the amount of time that a product may be taken (including a specific duration of use).

As a general rule, risk statements do not need to reflect theoretical risk; however, certain statements may be necessary when the risks are serious and of which consumers need to be aware of in order to make an informed choice. Additionally, advisory information should be based on moderately intolerable or unexpected adverse drug reactions and not on mild transient reactions (e.g., nausea).

CHFA Comments: The second last bullet of risk mitigation strategies should be revised to: ‘Not including ingredients with a lack of evidence for safety and efficacy; and’ as an ingredient demonstrated to be safe is eligible for inclusion (i.e. efficacy does not always needs to be supported).
Furthermore, the paragraph following the bullets reintroduces NHPD’s ability to require additional risk information at their discretion; without in any way attempting to qualify on what basis the risk has been determined. The addition of risk statements must be based on evidence, rather than theoretical speculation and/or conjecture. NHPD should further understand that as part of the PLA process, one would not know about an unexpected adverse reaction in advance.

Current PFL Text:  For the low and medium categories, methodologically weak evidence should be supplemented to demonstrate consistency in results and plausibility. For the high risk category, product specific evidence is recommended. Additionally, the evidence package should include a complete critical summary reflecting the totality of evidence and should usually reflect more than one type of evidence.

CHFA Comments: These statements should be removed entirely as they do not add value. As there is no definition of ‘methodologically weak’, the statements empower NHPD to reject a study for a variety of reasons. Furthermore, the recommendation for product specific evidence in the high risk category (also in Section 2.6.1) should be removed this may lead to further product requirements instead. Implementation of the Quality Appraisal Tool, discussed in the following section, would help NHPD standardize its review process, where evidence that scores below a threshold value is indicative of being ‘methodologically weak’.
GUIDANCE FOR IMPLEMENTATION

2.6 EFFICIACY EVIDENCE RECOMMENDATIONS

Proposal to Use Quality Appraisal Tool: CHFA members strongly believe NHPD should reconsider their assessment of interventional and observational studies to be in line with the Food Directorate’s Quality Appraisal Tool in the 2009 Guidance Document for Preparing a Submission for Food Health Claims. As the NHP industry identifies itself closer to foods than pharmaceuticals, it is appropriate to adopt the Quality Appraisal Tool in an effort to provide transparency and guidance for the industry to produce the most robust, acceptable evidence as possible.

Current PFL Text: 2.6.2 Efficacy Evidence for the Medium Risk Category

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

- a well described study population;
- a record of the flow of subjects through the trial;
- power analysis to determine proper number of subjects;
- random allocation;
- blinded assessment of outcome;
- intention to treat analysis;
- should usually be assessed compared to current standard therapy; and
- in addition to validity, evidence should demonstrate reasonable causality supporting the efficacy of the product.

CHFA Comments: NHPD’s requirements for evidence, listed above, are inconsistent with current practices of submitting published clinical evidence and are not representative of the majority of published journal articles available to industry. Furthermore, the comparison of the NHPs to ‘current standard therapy’ is a very drug-oriented approach and should absolutely not be a requirement for NHPs. While the listing is robust, it is rare to find a study, let alone more than one study specific to one’s recommended conditions of use, encompassing such a high level of methodological strength and detailed reporting. There is substantial concern among industry that these criteria empower NHPD to refuse evidence for insignificant details regardless of the study’s significant outcomes.

Once again, a Quality Appraisal Tool would be a great resource in this illustration as a means to provide industry with a transparent, consistent and objective way to evaluate the available evidence. This tool would provide industry members with a standardized method for ranking/scoring evidence, where a score above a threshold value indicates a high-quality study. Use of this tool would ideally equalize the opportunity to evaluate evidence for both industry and government.
GUIDANCE FOR IMPLEMENTATION

TABLE 1. ACCEPTABILITY AS MINIMUM SAFETY AND EFFICACY EVIDENCE BY RISK CATEGORY

CHFA proposes the following changes to Table 1:

<table>
<thead>
<tr>
<th>Evidence Type</th>
<th>Risk Category</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>High</td>
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<td></td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Low</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>NHPD Published Pre-cleared information</td>
<td>yes</td>
</tr>
<tr>
<td>Phase II or phase IV High quality clinical trials (randomized, controlled, well-</td>
<td>yes ^1</td>
</tr>
<tr>
<td>designed)</td>
<td>yes ^1 ^2</td>
</tr>
<tr>
<td></td>
<td>yes</td>
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<tr>
<td>Meta-analysis (controlled and well-designed)</td>
<td>no</td>
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<tr>
<td></td>
<td>yes ^3</td>
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<tr>
<td></td>
<td>yes</td>
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<tr>
<td>Two prospective observational studies</td>
<td>yes ^4 ^5 ^6 ^7</td>
</tr>
<tr>
<td></td>
<td>yes ^4 ^5 ^6</td>
</tr>
<tr>
<td></td>
<td>yes ^8</td>
</tr>
<tr>
<td>Evidence from a regulatory agency demonstrating the evaluation of safety and</td>
<td>no</td>
</tr>
<tr>
<td>or efficacy</td>
<td>yes ^3</td>
</tr>
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<td></td>
<td>yes</td>
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<tr>
<td>Systematic review other than meta-analysis</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>yes ^3</td>
</tr>
<tr>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>Published, peer-reviewed, detailed narrative reviews which cite detailed</td>
<td>no</td>
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<tr>
<td>primary evidence</td>
<td>yes</td>
</tr>
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<td></td>
<td>yes</td>
</tr>
<tr>
<td>Two phase II One good quality clinical trials (Only one reference is required</td>
<td>no</td>
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<tr>
<td>for safety)</td>
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</tr>
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<td></td>
<td>yes ^10</td>
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<td>Two retrospective observational studies or combinations of one prospective</td>
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<tr>
<td>study and one retrospective study. (Only one reference is required for safety)</td>
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</tr>
<tr>
<td></td>
<td>yes ^11</td>
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<tr>
<td>Two other types of epidemiological studies (Only one reference is required for</td>
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<tr>
<td>safety)</td>
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</tr>
<tr>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>Published compilations referring to</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>yes</td>
</tr>
</tbody>
</table>

*1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11: Additional criteria or notes for each type of evidence.
| **traditional use** ♦ (safety **only** and efficacy) | | |
| Reputable textbook | no ♦ | no ♦ **yes** | yes *12 |
| Demonstration of food use (Safety-**only**) | no ♦ **yes** | no ♦ **yes** | yes |
| Efficacy (if claim approved by qualified regulatory authority) | yes | yes | |
| **Previous Market History** | | |
| Efficacy | | |
| Safety only (with qualified regulatory authority) | Average of 1000 units/bottles per year sold over 10 years | Average of 1000 units/bottles per year sold over 30 years |
| **Expert opinion** | 3 expert opinions, each with 3+ years of use |
| Minimum efficacy requirements for antioxidant claims only | High | Medium | Low |
| At least one from the evidence types listed above | n/a | n/a | yes |
| Reputable textbook with human *in vivo* data | n/a | n/a | yes |
| *In vivo* animal evidence using a validated model | n/a | n/a | yes |
| Industry accepted standard or other *in vitro* data | n/a | n/a | yes |

**CHFA Comments:** CHFA members agree that more types of evidence should be considered, particularly for the high and medium risk categories. The revised table reflects the suggested Quality Appraisal Tool, used by the Food Directorate, as CHFA members believe it is far more appropriate in evaluating evidence versus the clinical trial phases, which are more suited for pharmaceuticals. As this Table is thought to be fundamental in the future assessments of PLAs, the following comments were collected from CHFA members:

- **Phase III or phase IV High quality clinical trials (randomized, controlled, well-designed):** Change in wording to reflect Quality Appraisal Tool

- **Meta-analysis (controlled and well-designed):** This should be acceptable for the high risk category

- **Two prospective observational studies:** Industry is requesting clarification and guidance from NHPD with respect to sample sizes, NHPD’s process of analysis, as well as in which cases cohort studies would be acceptable
Evidence from a regulatory agency demonstrating the evaluation of safety and/or efficacy: If the product is approved in a country with a comparable regulatory framework to Canada, the product should also be licensed in Canada as a means to facilitate trade.

Systematic review other than meta-analysis: A systematic review, if recent, should be acceptable for the medium risk category.

Published, peer-reviewed, detailed narrative reviews which cite detailed primary evidence: This should be acceptable for the medium risk category.

Two-phase II One good quality clinical trials (Only one reference is required for safety): Change in wording to reflect Quality Appraisal Tool. Furthermore, in Guidance Document Schedule A and Section 3 to the Food and Drugs Act, it states under Section 4.1 Primary clinical evidence required to support a preventative claim, “In most cases, a minimum of two, independently conducted, randomized, controlled clinical trials of good quality (as determined by a validated assessment tool, such as the Jadad scale) are required to substantiate the proposed Schedule A disease preventative claim. However, a single robust multicentre study may be acceptable provided it is well designed, well conducted, appropriately analysed and provides statistically significant and clinically relevant results. Prospective observational studies may also be acceptable under certain circumstances (e.g., diseases with long latency for which there are no validated surrogates). In such cases, more than one prospective observational study, along with other levels of evidence that are strongly supportive, would be required.” If TPD recognizes a single robust study in place of two clinical trials for pharmaceuticals, NHPD should provide a similar allowance without the requirement for the clinical trial to be multi-centered.

Two retrospective observational studies or combinations of one prospective study and one retrospective study (Only one reference is required for safety): CHFA members believe this should be acceptable evidence for the medium risk category, particularly as we are proposing to rank/score evidence based on the Quality Appraisal Tool.

Two other types of epidemiological studies (Only one reference is required for safety): This should be acceptable for the medium risk category.

Published compilations referring to traditional use (safety only and efficacy): This should not be qualified strictly for safety. Also, this evidence should be acceptable for the medium risk category.
**Reputable textbook:** CHFA members agree that the referenced textbook should be high quality and well-recognized. Furthermore, it should be available as evidence for both the low and medium risk categories.

**Demonstration of food use [Safety only]Efficacy (if claim approved by qualified regulatory authority):** Approval for a claim by another authority should be recognized across all risk categories.

**Previous Market History & Expert opinion:** There is strong consensus that both market history and expert opinions should be considered as types of evidence. Following consultation with industry leaders and naturopathic doctors, CHFA further believes that there should not be a distinction between the risk categories for these types of evidence. Please note that ‘qualified regulatory authority’ suggests a proper adverse reaction reporting program be in place.

**Industry accepted standard or other in vitro data:** As antioxidant claims are low risk, industry standards should be accepted, as should *in vitro* data.
Current PFL Text:  Route of Administration
- ... Evidence for other routes of administration may be considered when specific knowledge of the ingredient mechanism of action is known, (e.g., sublingual use may help support oral use, if evidence of the specific mechanism of action is provided).

CHFA Comments: We collectively feel NHPD should allow manufacturers to site safety information from one route of administration to support another. For example, safety information related to oral use can be used to support a topical application, provided there are no clear scientific concerns. In this scenario, CHFA members believe the most additional evidence they may need to submit to NHPD is a skin irritation study. This is further discussed in CHFA’s comment for Appendix F.

Current PFL Text:  Duration of Use
- A duration of use statement based on the conditions in the evidence should be provided unless the ingredients are without a known risk to a wide ranging target population and are not likely to pose a risk over long-term supplementation.
- An unlimited duration of use without sufficient advisory information should be supported by at least 6 months of use without identified adverse effects.
- The duration of use should be limited in cases where there is some concern that the long-term use of an ingredient/product may pose a risk to health (e.g., novel ingredients, common ingredients with very high doses, claims that include treatment of symptoms or conditions that do not resolve quickly and if they persist may mask a more serious underlying medical condition).
- Preclinical evidence may be required when ingredients similar to that in the product have been identified with risks that require longer observational periods than 6 months to ensure long-term safety.

CHFA Comments: CHFA members strongly believe that the duration of use for a product should only be specified if the totality of evidence establishes that extended use is problematic. Furthermore, NHPD should not cite hypothetical or theoretical risk to limit exposure as relevant scientific evidence should be referenced instead. As such, CHFA recommends removal of the first two bullets above.

We also recommend that the third bullet should read “The duration of use should be limited in cases where there is some concern that the long-term use of an ingredient/product may pose a significant risk to health”. An example was provided where NHPD enforced a limited duration of use of a protein powder to 6 months as they deemed food evidence did not support the safety of protein supplementation. When presented with a clinical trial supporting the safe use of whey protein the
limited duration remained enforced as some subjects experienced mild gastrointestinal disturbances during the clinical trial. We feel that mild gastrointestinal disturbances in a small percentage of the study population is not a significant risk to health, especially when the product contains the statement “May cause mild gastrointestinal disturbances”, and similarly expect NHPD to evaluate such scenarios appropriately in the future.

“Common ingredients with very high doses” is also an issue for members as NHPD commonly regards a product as ‘high dose’ based simply on a gravimetric quantity with no reference value. CHFA cannot emphasize enough the necessity to decrease ambiguity and subjectivity from reviewers by referencing relevant scientific literature,

Finally, the last/fourth bullet is puzzling as one would assume that clinical evidence has been presented to support the safety and efficacy of the ingredient; and that clinical evidence is of more value than preclinical evidence. CHFA recommends removal of this bullet as well.
APPENDICES
APPENDIX C: LINKING EVIDENCE TO INGREDIENT FORM

General CHFA Comments: NHPD must be sensitive to the fact that limited reporting in scientific literature is a complicating factor in matching identity, source material, chemical form, physical form, and dosage form of all ingredients in a product to the ingredients described in respective publications. Ideally, all details outlined in Table 4 would be disclosed in the literature, but these details are often lacking. This is particularly an issue when trying to support the safety and efficacy of medicinal ingredients, especially when it comes to herbal extract ingredients standardized to contain certain constituents.

CHFA members further insist that safety information to support a source material should not be required for an isolate product. As isolates are traditionally 95% pure, we cannot find justification in Health Canada’s ask for safety information related to the source matter, unless there is a known concern regarding the source. For example, quercetin is commonly isolated from Sophora japonica flower yet this is not an approved source on the new quercetin monograph.

By extension, safety information to support a source material of extracts should not be necessary if the extract itself can be supported, and the remaining components of the finished products can be shown to be innocuous. This is further discussed in CHFA’s comments on Appendix D.
APPENDICES
APPENDIX D: LINKING EVIDENCE TO USE OF EXTRACTS

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

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

CHFA Comments: Extract solvent systems and ratios are of concern to CHFA members. The request for this information to be included is inconsistent with past practices and a majority of monographs. Most studies do not specify a solvent system but rather indicate the quantity crude equivalent (QCE). It should be noted that the majority of products currently on the market were licensed based on unspecified solvents. CHFA members are pleased to have these products available to consumers and do not wish to have future extract applications rejected due to unspecified solvents.

Furthermore, NHPD is urged to understand that it is simply not possible to provide extract ratios for ingredients that are produced by the blending of extracts to make a standardized amount as the ratios are often variable. For example, green tea extracts of high and low polyphenol amounts are combined to produce a 60% standardized total. Currently, applicants are fabricating extract ratios on ePLAs for these types of ingredients. While there is value in extract ratios (via QCE) to support safety of unspecified extracts, it is meaningless for standardized extracts.

CHFA members strongly agree that evidence of QCE should be sufficient. Furthermore, comparison to the raw herb should also be accepted as ultimately, the solvent is insignificant if the ingredient can be equated to the raw herb.

Current PFL Text: The following examples illustrate when an evidence based justification is required:
- To use a non-hydroethanolic extract in support of the safety of crude material, an evidence-based justification is needed to demonstrate that the extract method used yields a full-spectrum extract;
- To use the Quantity Crude Equivalent (QCE) of an extract to support of the safety of other extracts, evidence-based justification is needed to demonstrate that the methods of preparation are sufficiently comparable, thus ensuring that the
The constituents in the two extracts will be comparable. The minimum requirement is that the solvent system should be similar;

- To use crude material to support an extract or vice versa, justification is required that the extract will be a full-spectrum extract (i.e., the extraction of the botanical material is as complete as possible) and is comparable in terms of its safety in humans; and

- To use crude material in support of an extract for efficacy, then justification is required that all known active (and co-active) constituents of the crude material are present in the extract.

**CHFA Comments:** CHFA members have suggested removing the first bullet and simply indicating that extracts do not support the safety of crude material as one can argue that no extract, regardless of solvent is inherently “full spectrum”. Members also note that as a scientific definition for “full-spectrum extract” is missing.

Similarly, the third and fourth bullets appear to be inconsistent with current and past practices as quantity crude material has always been used as a means to support the safety and efficacy of extracts, as published in most NHPD monographs. These bullets negate the use of QCE and should therefore be removed.
APPENDICES
APPENDIX F: EVIDENCE SCREENING CRITERIA FOR MODERN HEALTH CLAIMS

Current PFL Text: Examples where the medicinal ingredient(s) in the evidence does not adequately represent the medicinal ingredient(s) listed on the PLA form, may include differences in:
- Extract/isolate vs. crude material (e.g., Green tea leaf extract standardized to 15% EGCG vs. Green tea leaf); and,

CHFA Comments: Please see previous comments regarding extract ratios and standardized extracts in Appendix D.

Current PFL Text: Examples of evidence that is not considered adequate as sole support for the safety and efficacy of products include:
- Compilations of evidence that have not been critically reviewed (e.g., Natural Medicines Comprehensive Database, Physicians’ Desk Reference (PDR) Health, general information websites);

CHFA Comments: If industry is not permitted to reference ‘evidence that have not been critically reviewed’, NHPD should similarly refrain from considering these sources of information when reviewing a PLA. The playing field should be level for both industry and government.

Current PFL Text: 8. The route of administration supported by the safety and efficacy evidence must be the same as the route of administration indicated in the recommended conditions of use section of the PLA.
Example of missing evidence:
- The evidence provided supports the safety and efficacy of product X/medicinal ingredient(s) when taken as an intravenous solution/injection but the PLA indicates that the route of administration for the product is oral. Furthermore, as per Schedule 2 of the Natural Health Products Regulations, products administered by injection are prohibited.

CHFA Comments: NHPD should provide literature to support the increased safety risk in the example above instead of relying on theoretical risk to limit the possible routes of administration of the proposed product. A product considered safe to administer by injection should be safe as an oral dosage, and by extension, an oral dosage should be considered safe to be applied topically, unless there is specific evidence to the contrary.
The recurring theme among members’ comments is that if the NHP industry is restricted to providing relevant scientific literature to support a product, NHPD should also be limited to referencing relevant scientific literature in their review. There is no place for theoretical risk.

Additionally, CHFA members feel there would be greater benefit to industry if Appendix F appeared as table checklist.
ANNEXES
ANNEX I: GENERAL HEALTH CLAIMS

Current PFL Text: 3.0. Scope:
The following list outlines that which falls out of the scope of the application of this annex:

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

CHFA Comments: The above 5 bullets are not necessary and should be eliminated from the document. Instead, the document should refer to Figure 1: Risk-Based Approach for Determining Safety and Efficacy Evidence for NHPs Making Modern Health Claims as this flowchart is sufficient in defining the scope. CHFA members agree that these bullets are ambiguous and should instead be reflected in a guidance document specific to quality and product testing. Specifically, the second and forth bullets are heavily related to quality control, while the third bullet is already captured by Figure 1, and the last bullet relates directly to the inspectorate. CHFA believes it is inappropriate to include quality testing guidance in this document as it should be reserved for a separate publication.

Current PFL Text: Evidence requirements
Applicants wishing to apply for a “source of” claim are required to test for the presence of the constituent or ingredient (i.e., identification testing) and may be asked to provide evidence for quantification such as an assay at the finished product or raw material stage; however, this will not be a requirement upon submission. Any constituents on which a claim is based must be bioavailable. Applicants should have the results of the aforementioned tests maintained such that they could be provided to Health Canada in a timely manner upon request.
**CHFA Comments:** CHFA members found the above text confusing as NHPD’s expectations are not clearly defined. We feel strongly that showing relevance of an ingredient in the body, through various means, should suffice in NHPD’s review of the product’s claims. The expectation to determine bioavailability is of great concern to the NHP industry and we wish to emphasize that an ingredient’s known effect (as per scientific literature, for example) should supersede the requirement to provide pharmacokinetic information.

In our discussions, a comparable scenario was drawn between steak and whey protein. Surely NHPD is not suggesting that bioavailability data is required to show that steak is a source of protein, and should similarly not expect this data for whey.

**Current PFL Text:**  
*Claims for the Maintenance of Good Health*

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

**CHFA Comments:** There is a strong consensus that the claim “for the maintenance of good health” should not be limited to essential nutrients. For example, dietary fiber promotes laxation and therefore also contributes to the maintenance of good health.

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

- Helps support cardiovascular health by lowering cholesterol
- Helps support digestion by adding to the body's natural microflora

**CHFA Comments:** The example "Helps support cardiovascular health by lowering cholesterol" as a general claim is contradictory to page 19 of Table 2 Examples of health claims by health conditions (Appendix A), where lowering cholesterol is classified as a major disease/condition. This contradiction, as well as others found throughout the text, only promotes confusion for industry members.

Furthermore, CHFA members fear that specifying a mechanism of action will not benefit consumers, but rather require further evidence instead. In many cases, the mechanism of action is not known. To now require this type of evidence expands upon that which is currently requested.

**General CHFA Comments:** CHFA members would like to see NHPD offer increased flexibility for softer claims. The qualifier 'may' is particularly helpful for new ingredients, or old ingredients with new claims,
mainly due to limited or preliminary data. As such, NHPD should permit the qualifier 'may' for softer general health claims.
ANNEXES

ANNEX II: COMBINATION INGREDIENTS

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

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

**CHFA Comments:** There was a consensus between CHFA’s working group members that the above three bullets must be qualified by NHPD so as to remove the potential for theoretical risk. Industry members cannot postulate on possible risk and require strengthened wording to ensure NHPD will adhere to relevant evidence published in literature. For example, “there is no scientifically demonstrated increased risk…”

Furthermore, with reference to the first bullet regarding increased risk, industry members ask that NHPD confirm our recent understanding attributed to NHPD that precautionary statements for ingredients below 10% of the demonstrated minimum effective dosage do not need to be included on the product label.

**Current PFL Text:** A sub-therapeutic ingredient should be listed as non-medicinal when it is added to confer suitable consistency or form to the medicinal ingredients as per the definition of a non-medicinal ingredient.

**CHFA Comments:** We believe this text should be revised to delimit the purpose of a non-medicinal ingredient beyond consistency and form. Instead, a sub-therapeutic ingredient should be able to confer any purpose per definition of a non-medicinal ingredient in Section 1.5 (i.e., flavour, colour). We recommend: ‘A sub-therapeutic ingredient should be listed as non-medicinal when it is added to confer suitable consistency or form any purpose to the medicinal ingredients as per the definition of a non-medicinal ingredient’

Further to the definition of a non-medicinal ingredient (NMI) in the proposed guidance document, NHPD should consider that these ingredient can, and often do, have pharmacological effects and may interfere with the tests or assays for the medicinal ingredients. For example, calcium carbonate is pharmacologically active but continues to be used as a NMI. Similarly, manufactures must sometimes quantify the amount of NMI via the input method as finished product testing is not appropriate. As such,
NHPD is recommended to update their definition of a NMI in consideration of these challenges, as well as to include the purposes of flavour and colour.

**Current PFL Text:**  *Risk information: risk information should not be contradictory or the same or similar for two or more ingredients.*

**CHFA Comments:** This statement is difficult to understand. CHFA suggests that the text be revised to: “Risk information: risk information should not be contradictory or the same or similar for two or more ingredients”. Alternatively, a far more generic and preferred statement is “Combination ingredients should not pose unacceptable risk that cannot be mitigated”.

**General CHFA Comments:** Further comments received for Annex II included the lack of reference to cross-paradigm combinations, which was previously included in Section 8.0 of the Evidence for Safety and Efficacy of Finished Natural Health Products Guidance Document (December 2006, Version 2). CHFA members request that NHPD re-adopt the allowance for cross-paradigm combination products that can be logically rationalized.

NHPD should also clarify how combination products fit into the evidence requirements laid out in Table 1 to decrease ambiguity for future applicants.
PATHWAY FOR LICENSING NATURAL HEALTH PRODUCTS USED AS TRADITIONAL MEDICINES

General CHFA Comments: In contrast to the proposed Pathway for Licensing Natural Health Products Making Modern Health Claims guidance document, the Pathway for Licensing Natural Health Products used as Traditional Medicines received much less input from industry members. A number of key overlapping concepts suggested in the Modern Health Claims guidance document are applicable here, including the proposed ranking structure for evidence (Quality Appraisal Tool, see page 8), general health claims (see page 18) and linking evidence to use of extracts (see page 16). Furthermore, the following comments were collected from our working group:

The first CHFA recommendation put forth, specific to traditional medicines, is the suggestion to reduce the timeframe for demonstrating a long history of use in the traditional healing paradigm from 50 years to 30 years. Industry members support this reduction as NHPD has previously indicated the possibility for this amendment.

Additionally, NHPD should be sensitive to the fact that many references dating back 50 years do not include use, dosage form, route of administration, dose, and duration of use of the medicinal ingredient or product. As such, it is unrealistic to require all of this above information as it limits the industry to citing Pharmacopeia. These criteria should not eliminate a product from the review process.

Lastly, while NHPD has stated that traditional use claims may appear on non-traditional products, it is also stated that medicinal ingredients supporting traditional claims must meet the criteria of the Pathway for Licensing Natural Health Products used as Traditional Medicines guidance document. This is a concern because these criteria require that all medicinal products are found within a single system of traditional medicine. Industry members hope that different traditional paradigms can be combined in one non-traditional product so as to encourage product innovation.
In conclusion, these guidance documents, as well as the revised quality guidance document, are critical to the future of the NHP sector and the support of the regulatory framework. CHFA and its members are pleased to have had the opportunity to provide feedback during the 90-day consultation period. It is apparent from the many positive comments that CHFA received during our extensive review with members, including several consultants that work very closely with NHPD, that NHPD staff should be commended for the progress achieved in providing appropriate guidance to industry.

We trust that our comments and recommendations will be given due consideration and be seen as supporting and building on the progress that NHPD to improve clarity and remove ambiguity from the guidance documents. Furthermore, we would appreciate some early feedback as to NHPD’s next steps moving forward in light of comments received from all stakeholders. We reiterate our commitment to work collaboratively with NHPD, and we continue to offer CHFA regulatory forums and newsletter communications as a means of communicating transparently to members and non-members alike.

Sincerely,

Helen Sherrard
President
Canadian Health Food Association