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Preliminary Response

Report 1 – Standards of Evidence for Non-Traditional Natural Health Products

Natural Health Products Directorate
Health Products and Food Branch

February 15, 2010



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Health Products and Food Branch

“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.”

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This document presents the Natural Health Products Directorate's preliminary response to the Natural Health Products Program Advisory Committee's report of January 26, 2010 titled "*Report 1 – Standards of Evidence for Non-Traditional Natural Health Products*".

Table of Contents

Preliminary Response	1
Appendix A: <i>Report 1 – Standards of Evidence for Non-Traditional Natural Health Products</i>	3

Preliminary Response

The Natural Health Product Directorate (NHPD) would like to acknowledge the efforts and contributions of the members of the Natural Health Products Program Advisory Committee (NHP-PAC) and its Working Group #1 on Standards of Evidence for Non-traditional Natural Health Products. On January 26, 2010, the NHP-PAC presented its *Report 1: Standards of Evidence for Non-Traditional Natural Health Products* to Ms. Michelle Boudreau, Director General, NHPD. This report included 33 recommendations (see Appendix A) ensuing from the committee deliberations, including rationales and the range of views/support for each of the recommendations.

The NHPD will complete its review and consideration of the recommendations and prioritize which ones can be implemented throughout 2010-2011 based on available resources. A detailed response for each of the 33 recommendations and action plan will be presented to the NHP-PAC at its next meeting.

The NHPD agrees that the level of the claim and the risk to the consumer should influence the standard of evidence required to support a natural health product. The NHPD will continue to apply a risk-based approach to the assessment of natural health products licence applications. Drawing from the information provided by the NHP-PAC, the NHPD will determine a method within which the level of a claim and inherent risk of a product could be matched to the type of evidence required such that the assessment could be completed in a timely manner. This would provide clear guidelines and recommendations for applicants and reviewers regarding the type of evidence required to support the safety and efficacy of a product.

The NHP-PAC recommendations focus on several key issues which include but are not limited to the following:

- Improvement of the Information Request Notice and process management
- Development of Pre-Cleared Information
- Multi Medicinal Ingredient products and their combinations
- Levels/type of evidence required to support a Product Licence Application
- Updated guidance documents and communication to stakeholders
- Adverse Reaction Reporting

The range of NHP-PAC recommendations support and in various cases validate the work currently underway at the NHPD through the Process Improvements Project initiatives and reflect other feedback received from stakeholders.

For example, the Information Request Notice process has been greatly improved such that when a reviewer sees that a product licence application could be supported by an NHPD Monograph/NHPD Abbreviated Labelling Standard, the reviewer will counter-propose a claim to the applicant. The NHPD has also

formalized a process whereby Pre-Cleared Information, such as Abbreviated Labelling Standards documents for medicinal ingredients, can be generated to positively affect the product licence applications in the assessment queue. The NHPD has also created a draft application process document to address and discuss a range of proposed performance standards and targets.

A pilot project has also been launched within the NHPD since the January 2010 NHP-PAC meeting with regards to Recommendation #20 to determine the feasibility of creating a separate assessment stream (including Therapeutic Products Directorate monographs) for product licence applications where all the medicinal ingredients attest to NHPD Pre-Cleared Information (Monographs and/or Abbreviated Labelling Standards). It is anticipated that the results of this pilot will be available for the March 2010 NHP-PAC meeting.

The NHPD acknowledges the challenges faced by applicants and reviewers in determining the standards of evidence required to support multi-medicinal ingredient products in the non-traditional stream. The NHPD is committed to developing and providing applicants and reviewers with appropriate guidelines and frameworks to clarify the types and amount of evidence required to support a claim in consideration of the NHP-PAC recommendations.

In addition, the NHPD will continue to provide applicants with timely information on new and updated Pre-Cleared Information, guidelines on safety, efficacy and quality of finished natural health products and other requirements, as it becomes available, through its Bureau of Product Review and Assessment (BPRA) e-mail list. In addition to this advance information practice, the NHPD will also focus on developing and updating guidance documents for the Health Canada website. The NHPD is committed to helping natural health products licence applicants understand the requirements to support a product licence application, and will continue to offer workshops and provide information on natural health products to stakeholders.

NHP-PAC recommendations related to adverse reaction reporting and compliance and enforcement will be brought forward to other Natural Health Products Program directorates for response (i.e., the Marketed Health Product Directorate and the Health Product Food Branch Inspectorate respectively), through existing Program committees and working groups.

An initial response to each of the 33 recommendations will be presented to the NHP-PAC at its March 2010 meeting.

Appendix A: Report 1 – Standards of Evidence for Non-Traditional Natural Health Products

A complete copy of *Report 1 – Standards of Evidence for Non-Traditional Natural Health Products* is available on the following pages.

– Report 1 –

**Standards of Evidence for
Non-Traditional Natural Health Products**



Report of the Natural Health Products Program Advisory Committee
to the Natural Health Products Program

January 26, 2010

Table of Contents

Foreword.....	1
Recommendations	2
Reference List.....	23
Appendix A – Draft List of References Proposed as Pre-Cleared Information.....	24
Appendix B – Recommendation on Fungal Enzyme (Addendum, March 22, 2010)	34

This Report is available on the Health Canada Website at: www.healthcanada.gc.ca

Foreword

The Natural Health Products Program Advisory Committee (NHP-PAC) is an expert advisory committee formed to provide Health Canada's Natural Health Products Program with timely advice and recommendations on issues under federal responsibility for assuring the safety, quality and efficacy of natural health products for sale in Canada. Collectively, the Committee members provide regulatory and related expertise and advice pertaining to risk/benefit assessments of natural health products, to assist the Natural Health Products Program with making appropriate risk management decisions. The decision-making responsibility remains with the Natural Health Products Program.

Report 1: Standards of Evidence for Non-Traditional Natural Health Products was presented to Ms. Michelle Boudreau, Director General, Natural Health Products Directorate (NHPD) on January 26, 2010 (Meeting #3, Agenda Item #4) by the NHP-PAC in follow-up to a commitment made by the Committee at its September 14-15, 2009 meeting to submit a report containing recommendations on issues of interest related to the Standards of Evidence for Non-Traditional Natural Health Products, as identified by the NHPD.

An initial draft report was presented to the Committee for deliberation at its December 2009 meeting (Agenda Item #2) by the Committee's Working Group #1 on Standards of Evidence for Non-Traditional Natural Health Products. Working group members included: Mr. R. Rosenes, Co-chair (Canadian Treatment Action Council), Ms S. O'Reilly, Co-chair (Canadian Association of Naturopathic Doctors; Dr. P. Saunders, Alternate), Ms. S. Aberdour (SISU Inc.), Ms. R. Campbell (Natural Factor's Nutritional Products Inc.), Mr. C. Carter (Canadian Health Food Association), Ms. B. J. Johnston (Natures Formulae Health Products Inc.), Dr. P. Jones (University of Manitoba), Ms. M. Jutras (Canadian Council of Herbalists Association), Mr. D. Skinner (Consumer Health Products Canada; Mr. A. Kingsley, Alternate), Ms. L. Stephenson (Best Medicines Coalition), Mr. B. Wagner, (NHP Consulting Inc.), and Ms. B. Wells (Canadian Chain Drug Store Association).

The following report includes the recommendations ensuing from the Committee's deliberations, with rationales and the range of views provided for each of the recommendations. The overall recommendation of the Committee is that the Natural Health Products Program should immediately implement its supported recommendations to expedite the application review process. Note – An addendum to recommendation # 29 (fungal enzymes) was made on March 22, 2010 (Meeting #4).

Recommendations

#	Recommendation	Recommended by	Rationale for Recommendation
1	<p>The <i>Evidence for the Safety and Efficacy of Finished Natural Health Products</i> Guidance Document (the Guidance Document) should be amended to provide more clarity on the definition of risk. Risk should be defined according to both “manufacturing risk” (what is in the product) and “situational risk” (its recommended conditions of use), according to defined standards.</p>	All	<p>The risk level of a natural health product is tied to the level of evidence and can be described as manufacturing risk (Good Manufacturing Practices) and situational risk (ingredient, consumer). The evidence requirements for both efficacy and safety are based on the overall risk-benefit of a product. Risk-benefit ratio should be predictable based on defined standards.</p>
2A	<p>The Guidance Document should be amended to provide guidance and clarity about the minimum amount and robustness of evidence required to seek Health Canada approval and communicate evidence requirement changes to stakeholders. Other recommendations in this report provide further specificity to this recommendation.</p>	All	<p>The evidence requirements for both efficacy and safety are based on the overall risk-benefit of a product. This risk-benefit ratio should be predictable based on defined standards; applicants need specific guidelines provided in advance to determine the exact licence requirements for their products. Guidance (predictive value) on the type of evidence required for the level of health claim is needed for product licence applicants, e.g., how much and what kind of evidence is needed for non-traditional products.</p>
2B	<p>All updates are promptly incorporated into the guidance document and disseminated to stakeholders.</p>		

#	Recommendation	Recommended by	Rationale for Recommendation
3	<p>The increasing role of consumers consulting their health care professional should be acknowledged and encouraged. As well, Health Canada should inform health care professionals, where possible, when their patient files an adverse event report with Health Canada to support follow-up with patients and also to support comprehensiveness and accuracy of adverse reactions information received. This relates to the awareness/information provided to health care Professionals.</p> <p>The adverse reaction categories are: causal, not causal, not able to determine. Suggestion that those Health Canada reviewers and policy analysts who understand the therapeutic aspects of the products be involved in the adverse reaction data analysis from the NHPD to:</p> <ul style="list-style-type: none"> ▪ link the approval/review context and understanding of consumer behaviour; ▪ provide a mechanism to share knowledge/educate on natural health products ▪ increase awareness and information on adverse reaction reporting, with information targeting specific stakeholder groups to address specific needs. 	All	<p>This should lead to greater post-market surveillance, therefore greater safety for the consumer (supports rapid response). This is not a recommendation to change the Standards of Evidence.</p> <p>Supports unique nature of health care professional responsibility and follow-up with clients – Adverse event may be an expected outcome of treatment (aggravation of symptoms/conditions is a desired response)</p>

#	Recommendation	Recommended by	Rationale for Recommendation
	It is proposed that this recommendation be brought forward to the Marketed Health Products Directorate (MHPD) for implementation.		
4	The NHPD should provide clear feedback in Information Request Notices (IRNs) that are issued when a reference submitted by an applicant is not accepted (e.g., an Expert Opinion Report, previous market experience, textbook – see comment Recommendation #10). Where possible, the NHPD should outline which section of the reference was problematic as well as offer potential solutions (e.g., Pre-Cleared Information). The NHPD should ensure that the rationales used in Information Request Notices are up-to-date.	All	When an applicant receives an Information Request Notice noting the insufficiency of a particular evidence source, it is unknown whether all or some of the content in the reference is unacceptable. Industry requires predictability for what portions of the reference (e.g., pharmacopeia or paradigm specific texts) are acceptable for the evidentiary support of the different types of health claim. This amendment will enable timely, efficient clarification for applicants about what is meant in the Information Request Notice. This is not a recommendation to change the Standards of Evidence guidance document.
5	The evidence levels (I to IV) in Table 2 (strength of evidence grading table) in the Guidance Document should be reviewed and clarified to enhance guidance for and consensus between industry and reviewers (when and how the various levels are used). Other recommendations in this report provide further specificity to this recommendation.	All	A full review of the Standards of Evidence levels and fuller clarification/definition to clarify and define the levels for applicants. There is a variation between the understanding of applicants regarding what falls into the guideline and what is applied by reviewers. This recommendation is linked to #4 & 6.

#	Recommendation	Recommended by	Rationale for Recommendation
6	<p>Evidence of previous market experience can be considered evidence for safe use in humans at a given dose if the product was consumed within an identified minimum number of years and/or minimum number of units sold and provided additional evidence supports the safe use in the market place (i.e., evidence of a low AR rate). The NHPD should undertake further investigation including seeking expert opinion from epidemiologists, to identify the required minimum number of units sold and minimum number of years on the market, with consideration given to AR reporting sources (e.g., country collecting), to be accepted as supporting evidence. The Guidance Document should be amended to clearly identify the requirements (parameters, specificity) related to using previous market experience as evidence. This guidance should be accompanied/supported by a form including the questions applicants need to answer when submitting this type of supporting evidence (e.g., number of years on market, source country of adverse event report...).</p> <p>Noted regarding use of adverse reaction reports that adverse event reporting is poor in most countries and it would therefore be important to identify countries with recognized quality</p>	All	<p>Guidance (predictive value) on the type of evidence required for the level of health claim is needed for industry (product licence applicants), e.g., how much and what kind of evidence is needed for non-traditional products.</p> <p>There is a need to clarify for applicants the conditions under which market experience is accepted as supporting evidence, this includes specifying aspects such as the minimum number of years the product has been on the market, the number of units sold and adverse event reports. There is a need to specify:</p> <ul style="list-style-type: none"> • the international jurisdictions recognized by Health Canada as reliable sources of evidence for history of safe use – which meet requirements for (identified) minimum numbers of years on the market and reporting of adverse reactions (some countries do not track adverse events) • minimum number of years and units sold according to the country where the product is manufactured, in consideration of the varying level of product safety in different jurisdictions. • minimum number of years of use by health care professionals (e.g., 5 to 10 years of

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	reporting, e.g., that collect comprehensive reports from industry, consumers and health care professionals. In addition, health care professionals should receive reports.		use without adverse event) in consideration that long term use of a product by a health care professional occurs only where the product is considered to be without risk to the patient.
7	The NHPD should <u>formalize</u> the mechanism whereby information on review decisions (e.g., review report) is accessible to applicants, related to their applications, in order to facilitate feedback as appropriate. This is not related to refusals for which there is an appeal process in place (Reconsideration Process).	All	This will lead to improved quality of applications.
8	There should be industry-consulted performance standards in place. The following performance targets were suggested: 180 days for non-traditional, non-compendial applications, 60-120 days for amendments (single and multi ingredient products; depending on the nature of the amendments), and 60 days for compendial applications. The implementation date of performance standards for the NHPD must be made public.	All	The idea of random assessments raises liability issues for the NHPD, and to avoid such issues assessments should be focused on streamlining the process within a fixed amount of time.

#	Recommendation	Recommended by	Rationale for Recommendation
9	The NHPD should accept animal evidence to support safety and efficacy where the animal model used is validated as an appropriate representation for humans, where there is also a long evidence of human use and/or market history. Animal evidence should not be accepted as the sole evidence supporting safety and efficacy of a natural health product. It should be clarified in Table 2 of the Guidance Document when/under what conditions animal studies can be used as evidence. The term 'long' needs to be defined.	All	Recognizes validated models and, where this validation does not exist, recognizes that animal models may not appropriately translate to humans, and that the bioactive substance being tested may behave differently. See Source Document 42 - description of physiologically based kinetic modeling approach used to "amplify" information from animal data in ways that render these outputs meaningful in the human context.
10	Cautionary statements, supported only by theoretical information, are not required to be used.	All	There needs to be evidence that an actual risk is likely to occur if there is to be a fair representation of the benefits and risks of a product. Otherwise needlessly warning consumers will reduce the benefit available to them by unnecessarily alarming them; thereby, creating an impression that they should avoid using the product.
11	Observational data should continue to be permitted as Level III evidence in Table 2 (strength of the evidence grading system) in the Guidance Document to support safety, provided the study is well designed (i.e., correlation studies, cohort studies, and case-control studies).	All	Observational data doesn't test hypotheses and are therefore not specific and relatively weak sources of data as the outcome of these studies could be due to a number of other factors.

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12	Qualitative studies should be considered as Level III evidence for efficacy where they are well-designed, validated surveys (e.g., correlation, cohort or case-control studies). The Guidance Document should be amended to clarify this.	All	<p>Health Canada has stated it is open to preliminary meetings with sponsors to review their study methodology to determine whether or not it is sufficient.</p> <p>Cresswell (1994) defines qualitative study as an inquiry process to understand a problem using a complex holistic view/picture based on words, reporting of information, and conducted in a natural setting (e.g. anthropology, sociology). Therefore it is really inquiry, theory testing, data collection, and statistical analysis to determine if the theory is correct. As such correlation, cohort, case-controlled, analysis of use patterns and/or treatment patterns, analysis of expert opinion can be included as qualitative studies. From another source, valid qualitative studies do not require statistical analysis (Strauss and Corbin 1990). They accept the dynamic and complex nature of the human social experience and seek to understand it. One medical source says it is used extensively in primary care and patient care and includes detailed case studies.</p>

#	Recommendation	Recommended by	Rationale for Recommendation
13	As with clinical trials designed for risk reduction claims of Schedule A diseases, the Guidance Document should be amended to allow surrogate markers for clinical trials for supporting efficacy, provided data justifying the validity of the surrogate marker is provided.	All	<p>Surrogate markers are discussed in section 4.3 of the HPFB draft guidance document for <i>Schedule A and Section 3 to the Food and Drugs Act</i>, which states:</p> <p>“Risk reduction claims that are based on evidence generated by randomized, controlled, clinical trials with clinical outcomes that can be expressed either as a decreased incidence of the disease or a reduction of a factor, or a surrogate thereof, of the many that contribute to the development of a disease. Surrogate endpoints are risk biomarkers that can be used to predict disease risk provided that the relationship between the biomarker and the disease has been conclusively established.</p> <p>Substantiation of risk reduction claims involves the same scientific rigour as that applied to prevention claims and is based on the same types of study design and strength of evidence. The acceptability of utilizing a biomarker in lieu of clinical measurements of the incidence of disease or other clinical endpoints should be discussed with the appropriate Directorate prior to the initiation of studies involving the use surrogate markers. Data justifying the validity of the surrogate marker must be provided at that time.”</p>

#	Recommendation	Recommended by	Rationale for Recommendation
14	<p>Level IV studies are, generally speaking, secondary sources (with the exception of Expert Opinion Reports which are more primary) in that they do not put forward original (i.e., primary) data. The NHPD must embrace secondary data that is reputable (especially Pre-Cleared References) that may not always require validation of the primary data directly from the applicant. The NHPD should develop a short list of reputable journals which can be used as Pre-Cleared Information, and where journal data is not contradictory and the claim type and level is appropriate (e.g., not a treatment claim), accept two independent journal sources with the same conclusion (but not using the same referenced primary data) as supporting evidence for efficacy of a product. Information Request Notices should clearly state the reason(s) a journal reference was not accepted – see Recommendation #4. The applicant may be requested to provide the primary data to the NHPD, where the secondary data is not accepted.</p>	All	<p>At present, the NHPD accepts Level IV evidence if it references/discusses primary sources - and if the secondary sources do not summarize those primary sources in heavy detail, the NHPD will ask for the primary studies in turn. Scientific articles are often costly to purchase, or they may not be available in English or French (yet the review article discusses their details in English or French), and we must find ways of trusting the data. This especially holds true where the risk of failed efficacy is low.</p> <p>The reference to secondary sources generally refers to review articles rather than primary data published in a credible peer-reviewed journal. In order to develop a short list of acceptable secondary sources two criteria should be used. First, the peer review process should have the confidence of the regulator. Second, the review article should accurately represent the primary research within the context of the claim in the applicant's submission.</p>

#	Recommendation	Recommended by	Rationale for Recommendation
15	<p>Expert Opinion Reports may only be considered as Level IV evidence supporting the efficacy of a natural health product if the report meets all of the criteria listed in section 3.5 of the Guidance Document.</p> <ul style="list-style-type: none"> ▪ In lieu of an Expert Opinion Report developed by three authors, the Guidance Document should be amended to accept a meta-analysis of a significant number of expert opinion reports compiled by single authors. The meta-analysis must provide credentials of the experts analyzed in order to ensure the credibility of the meta-analysis. <p>Such reports could be used to provide validation of an animal model, evidence for dosing issues or for demonstrating rationale in cross-paradigm combinations.</p>	All	<p>Health Canada has stated they are open to preliminary meetings with sponsors to review their study methodology to determine whether or not it is sufficient.</p> <p>Three independent sources (authors), representing agreement between three experts provides a reasonable amount of supporting evidence. Range of dose should be considered.</p>
16	<p>Safety must be demonstrated (crude equivalent if extract) based on dose ranges from traditional medicine, clinical trials or previous marketing experience, <i>idea of excipient being the same</i>. See recommendation #10. Where previous marketing history is the only human data, animal toxicity studies must be provided as well.</p>	All	<p>Where non-standardized extracts are involved, safety need only be supported on the basis of calculating crude equivalents (<i>i.e.</i>, based on extract/tincture ratios), and the specific preparation method would not have to match that of a reference for such non-standardized extracts, provided the crude equivalent is</p>

#	Recommendation	Recommended by	Rationale for Recommendation
	<p>A crude equivalent extract can be physically altered such as drying, grinding or extracting using a traditional excipient but not chemically altered. From crude plant material a wide spectrum extract is produced. This wide spectrum extract can be a liquid or dried to a relatively low concentration (usually 5:1 or lower). Any higher concentration that has been fractionated or altered with a different excipient is not considered an equivalent.</p>		<p>supported. NHPD monographs are typically written in this way, in that all non-standardized extracts are generally considered equivalent to one another (so long as they are comparable based on crude equivalent).</p>
17	<p>For multi-ingredient non-traditional products, where the individual ingredients attest to NHPD Monographs, the <i>Compendium of Monographs</i> guidance should be amended to allow monograph combination products to be evaluated under the 60-day disposition, provided no safety concern exists for the combination and a rationale supports the logical combination of the products (i.e., they all support the same organ system, all treat the same symptom or prevent the same illness etc).</p>	All	<p>The review process was also discussed in terms of possible flexibility reflecting the industry's need to balance market access with the ability to generate quality data supporting efficacy over time.</p>
18	<p>For the combination of ingredients that are individually supported in terms of safety and efficacy by Level V traditional evidence <u>from the same paradigm</u>, or from both traditional & non-</p>	All	<p>Novel combination of (traditional-use) ingredients make a product novel, thus it would be a non-traditional application and adequate evidence should be supplied to</p>

#	Recommendation	Recommended by	Rationale for Recommendation
	<p>traditional evidence sources, the Guidance Document should be amended to permit their novel combination, in absence of any known safety concern, under the non-traditional review stream if accompanied by a rationale for their combination and at least one additional piece of evidence (Level I-IV) which adequately supports safety and efficacy of that combination in humans. An example of the claim wording would be: “these ingredients are traditionally used to promote sleep”</p>		<p>support its safety and efficacy in humans as well as a rationale for the combination of the ingredients. Section 2.2.1 of the Guidance Document states that “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...” If traditional and scientific evidence are available to support a proposed claim, then both the scientific and traditional evidence must be independently sufficient to support the safety and efficacy of the product. Traditional evidence cannot be used to “top up” a deficiency in scientific evidence. The claim should maintain the language to communicate to consumers that the evidence is of traditional nature so as to not confuse traditional and non-traditional evidentiary support, i.e., “the ingredients are traditionally used for...” It is important for consumers to know the source of the evidence used. This change would allow claims (labels) that would not otherwise be permitted (if not permitted to use evidence from both sources).</p>

#	Recommendation	Recommended by	Rationale for Recommendation
19	<p>For the combination of ingredients that are individually supported in terms of safety and efficacy by Level V traditional evidence <u>from different traditional paradigms</u>, the Guidance Document should be amended to permit their novel combination, in absence of any known safety concern, under the non-traditional review stream if accompanied by a rationale for their combination and at least one additional piece of evidence (Level I-IV) which adequately supports safety and efficacy of that combination in humans, e.g., licorice – where the two evidence sources for dose, can be from two different paradigms for dose, and another paradigm can be used for efficacy. An example of the claim wording would be: “these ingredients are traditionally used to promote sleep.” The Guidance Document should be amended to reflect this.</p>	All	<p>Novel combination of traditional-use ingredients make a product novel, thus it would be a non-traditional application and adequate evidence should be supplied to support its safety and efficacy in humans as well as a rationale for the combination of the ingredients. Section 2.2.1 of the Guidance Document states that “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...” If traditional and scientific evidence are available to support a proposed claim, then both the scientific and traditional evidence must be independently sufficient to support the safety and efficacy of the product. Traditional evidence cannot be used to “top up” a deficiency in scientific evidence. The claim should maintain the language to communicate to consumers that the evidence is of traditional nature so as not to confuse traditional and non-traditional evidentiary support, i.e., “the ingredients are traditionally used for...” It is important for consumers to know the source of the evidence used. This change would allow claims (labels)</p>

#	Recommendation	Recommended by	Rationale for Recommendation
			that would not otherwise be permitted (if not permitted to use evidence from both sources).
20	Products supported by “Pre-Cleared Information,” in the NHPD risk-based assessment process, should not require a full evaluation of evidence, only a screening of the paperwork. Validation of these products should be undertaken through random inspections.	All	To speed up application process.
21	The Guidance Document should be revised to include a decision tree that focuses on application type. The NHPD should review the draft decision tree and advise the Committee of any further required input. It is the expectation of the Committee that there will be further input required from it.	All	The focus should move away from describing the conditions (level of evidence required for type of claim) towards a focus on describing application types (licensing requirements and stream).
22	Health Canada should only approve health claims on products when the data supports the proposed dose or dosing range.	All	<p>The current standards of evidence do not restrict product sponsors from being able to market products with low doses, provided they have some support for their use for a health outcome at that low dose.</p> <p>This standard already applies to traditional products.</p>

#	Recommendation	Recommended by	Rationale for Recommendation
23	The NHPD should continue to review existing Aromatherapy/essential oil textbooks and seek advice from experts in the field to determine the allowable claims for topical use and ingested products, which are supported under the current standards of evidence.	All	Advice needed to help fill gap for essential oils related to lack of data supporting the safety and dosage.
24	<p>The NHPD should continue to pursue development of further sources of Pre-Cleared Information (PCI) and therefore add more products and/or ingredients to the Class I licence application review:</p> <ul style="list-style-type: none"> a) Validate List of References (Appendix A) provided by the Task Group through consultation with experts including health care professionals, and adopt as Pre-Cleared Information those appropriately validated references. b) Revise Guidance Document to include the Pre-Cleared Information references with identification of the specific aspects the reference supports (i.e., evidence for safety, efficacy and/or non- medicinal ingredient of the product) under the current standards of evidence. c) Consult with the natural health products industry and health care practitioners to nominate foreign monographs to be reviewed 	All	<p>Task Group on References: S. O'Reilly (lead), P. Saunders, M. Jutras, S. Aberdour, (B. Wagner, A. Kingsley, observers)</p> <p>Pre-Cleared Information sources provide predictability and establish awareness of acceptable reference sources for stakeholders, in particular product licence applicants. The proposed list of references in Appendix A represents references (e.g., pharmacopeia and paradigm specific texts) identified in consultation with health care professionals as references that are commonly used by health care professionals in Canada.</p> <p>To address the need to provide additional data to support the efficacy, it is suggested that the industry collaborate with credible researchers internally, government agencies, and through research-based associations.</p>

#	Recommendation	Recommended by	Rationale for Recommendation
	<p>and possibly adopted into the <i>Compendium of Monographs</i>. Links to #14.</p>		
25	<p>Where two references for the same indication support two different safe and effective doses, the product should be permitted with a dose that falls within that dosage range. The Guidance Document should be amended to clarify this.</p>	All	<p>The regulations specify there must be a dosage. Dose is linked to the discussion on risk: risk-based approach and use of Pre-Cleared Information, classes of licences (risk categories). Dosage range to meet gaps.</p>
26	<p>Health claims continue to be mandatory with at least one claim per product and a minimum of one independent reference required to support a claim. The strength of the claim is directly proportional to the strength and credibility of the evidence provided.</p>	All	<p>Matches claim to the evidence (the claim determines the evidence required); supports innovation. The preponderance of evidence supports the claim.</p>
27	<p>The Guidance Document should be amended to clarify that where a product licence application lacks the evidence to support the proposed health claim but (i) the submitted evidence does support another health claim with minor adjustments or (ii) a new monograph in the <i>Compendium of Monographs</i> or an Abbreviated Labelling Standard is available, the NHPD should contact the applicant to provide advice.</p>	All	<p>Speeds up application process.</p>

#	Recommendation	Recommended by	Rationale for Recommendation
	A process should be implemented to provide an opportunity for applicants to clarify to the NHPD the intent of the evidence used to support the claim (submission meeting).		
28	Appendix 5A of the Guidance Document should be amended to explain that the template for additive combinations may not be appropriate for some combinations of natural ingredients. The NHPD should seek advice from experts in the field in order to determine if a logic model template for the additive effects of herbs with other ingredients could be developed. The NHPD should refer to health care professional models of blends.	All	The additive combination template does work when for herbal products; it is a different challenge than when the combination contains vitamins or minerals or other type of ingredients. There should be a distinction made between the two.
29	<p>The NHPD should accept all fungal enzyme product applications regardless of source on the understanding that the NHPD is currently compiling material on this topic, which will be brought back to the Committee for further discussion.</p> <p>See Appendix B – Recommendation on Fungal Enzyme (Addendum, March 22, 2010).</p>	All	Safe history of use of fungal enzymes on the market.

#	Recommendation	Recommended by	Rationale for Recommendation
30	<p>Recommendation for medicinal ingredients and non-medicinal ingredients in Non-Traditional natural health products:</p> <p>For medicinal ingredients, the claim is based on a therapeutically dosed ingredient or ingredients according to an additive table. There may be other medicinal ingredients that are a part of the formula. They must be safe, as demonstrated by at least one reference and in consideration of the totality of evidence, and there must be evidence to support the rationale for their inclusion as medicinal ingredients in the formula. Medicinal ingredients should appear on the label quantitatively.</p> <p>If the formula cannot satisfy the conditions above, providing the ingredients are safe, the group felt that one of two approaches could be taken:</p> <ul style="list-style-type: none"> a) list those ingredients as non-medicinal ingredients without requiring further evaluation. b) allow those ingredients to be used as non-medicinal ingredients only if the ingredient meets NHPD current non-medicinal ingredients definition for their non-medicinal use. 	All	<p>It facilitates a more informed choice and prevents misleading claims. There are many ingredients which would not meet a dose requirement -- on their own or via an additive effect -- but which the manufacturer still has sound reason to believe is not an innocuous/non-medicinal ingredient, albeit cannot demonstrate this from a dosing perspective. This is of paramount importance to preserving innovation -- if companies cannot experiment with safe ingredients for creating novel formulations, we lose innovation. Even as such, it is still expected that at least one medicinal ingredient supports at least one health claim, as the bare minimum. Because the NHPD currently licences multi-ingredient products not requiring every medicinal ingredient to have a supported claim (albeit a rationale is required to justify its presence still), labelling such "rationalized" ingredients as medicinal ingredients might be misleading to consumers. Consumers must know which ingredients form the basis for the product claims, in order to make truly informed decisions.</p> <p>Permitting medicinal ingredients at non medicinal levels without an adequate rationale</p>

#	Recommendation	Recommended by	Rationale for Recommendation
	Guidance documents should be amended to provide clarity for both applicants and reviewers.		<p>or supporting evidence runs the risk of misleading the consumer into believing that the ingredients are providing significant benefit, when there is a reasonable chance that they are having little or no real effect. For example, ingredients known to have a therapeutic dose range in the 100's of milligrams, are unlikely to be providing significant effect when used in doses such as 5 or 25mg, even if they are combined with ingredients with which they may have a synergistic effect. Although the philosophy of "synergy" in complementary and alternative medicines and herbal medicine is an important one, there must be reasonable limits placed on how low a dose of an ingredient can be allowed under this philosophy. Synergy alone cannot be used to justify the use of medicinal ingredients at non-medicinal ingredient doses, particularly when there is very large gap between established therapeutic dose ranges and those being proposed in a combination natural health product.</p>

#	Recommendation	Recommended by	Rationale for Recommendation
31	<p>For multi-ingredient non-traditional products, where the individual ingredients may have a synergistic or additive effect, the Guidance Document should be amended to permit their combination in a formulation that is supported in terms of safety and efficacy by evidence Level I-IV. Health care professional models for blends should be used by the NHPD for evidence on combinations/blends.</p>	<p>For – 11 Abstain – 1</p>	<p>This Recommendation is linked to Recommendation #28. To be useful and informative for applicants, the additive table needs to be revised to clarify the requirements (reasons) for additives. This addresses one of the most difficult aspects/concepts for applications. Neither applicants nor reviewers know what is expected (there is no tradition for the combination, but there is for the components). It is possible to capture the tradition of the component and thereby rationale for the blend, but there is currently no vehicle to do this. As long as the formulation is supported by evidence: a third category. There is a history of use for blends available through health care professional models which can provide evidence for combinations, including theory behind the blend. Key to innovation.</p>
32	<p>Disclaimers (clarify wording) on products not meeting the standard of evidence required to support a health claim should not be granted market access. It is up to the discretion of the NHPD reviewers, acting as agents of the Minister of Health, to determine if qualified wording is necessary, given the evidence provided, that the product is likely to produce the intended effect,</p>	<p>For – 7 Against – 4 Abstain - 1</p>	<p>Disclaimers (clarify term) place an unfair burden on the consumers to judge the health merit of the product for sale.</p>

#	Recommendation	Recommended by	Rationale for Recommendation
	however qualified wording should be avoided in general as the concept of probability is inherent within the product review process.		
33	Qualified wording on products meeting the standard of evidence required to support a health claim should be granted market access. It is up to the discretion of the NHPD (clarify parameters) reviewers to determine if qualified wording is necessary, given the evidence provided, that the product is likely to produce the intended effect. An “appeal” process should be implemented to provide an opportunity for applicant to clarify the intent of the qualifier used (submission meeting)	For – 5 Against – 6 Abstain -1	As long as a health claim is clear and there is supporting evidence (safe, effective), the claim should be permitted. This supports innovation and life cycle using potentially interim claims with changes made once more robust data is available. Qualified wording can help to inform the consumer.

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Appendix B – Recommendation on Fungal Enzyme (Addendum, March 22, 2010)

Applications for the licensing of fungal enzymes currently fall into three categories:

1. applications that include adequate evidence supporting a claim and a safe dosing range;
2. applications for licenses which are transferred to Natural Product Number (NPN) status from the Drug Identification Number (DIN) registration system; and,
3. applications that do not have adequate evidence supporting a claim or a safe dosing range and did not have a previous DIN license.

For the **first category**, a license can be granted under the full application of the regulations.

For the **second category**, these products have been granted a market continuance under a transitional provision that recognizes that there had been a DIN granted but the pre-existing conditions of DIN licensure may or may not have met the standards of evidence under the natural health products regulatory system. The policy is deemed transitional and allows such products to continue to be sold whether or not the original evidence used to make the licensing decision would meet current standards.

Such a system gives rise to **two sub-classes**. The first is a transitional DIN that has adequate evidence to meet the current standards and the second is where the evidence is insufficient to meet the current standards. The former can be granted a license under the full application of the regulations. The latter sub-class gives rise to a concern that such products do not meet the standards but should be given the opportunity to update their evidence, or to revise their claim so that a license can be granted under the full application of the regulations.

For the **third category**, a license cannot be granted under the full application of the regulations.

Recommendation for Transitional provisions

Where a product is granted transitional DIN registration **and** there is insufficient available evidence to confirm its licensure under the full application of the regulations, NHPD should issue a notice of consultation to conduct a review of the

ingredients in question. During this consultation ingredients under review may continue with their assigned license subject to the final determination of the review.

Exception for equitable access

During the class review of evidence, other products may apply for licenses for formulations equivalent to an already licensed product under the transitional provisions. If deemed to be equivalent then a transitional license may be granted and the product may continue with their assigned license subject to the final determination of the review.

Note: If a product formulation is not equivalent to that outlined under the exception conditions it would, by definition, be in the “third category” and a license cannot be granted under the full application of the regulations.