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Notice to Non-Traditional Product Licence Applicants
Evidence Criteria-Evidence Assessment Template

November 2009

Background
The Natural Health Products Directorate (NHPD) has received just over 18 000 Non-Traditional Product Licence Applications (PLA) since 2004. As such, Non-Traditional applications represent nearly half of the total number of applications received by NHPD. These applications are considered to be the most complex for both applicants and the NHPD.

To address some of the challenges associated with the review of these applications, the NHPD developed and implemented a Process Improvement Project. The main component of this project was determining Non-Traditional Evidence Criteria. The Evidence Criteria were developed based on a number of critical evidence deficiencies the NHPD had frequently encountered since it began assessing PLA's in January 2004. Many of these criteria were communicated to industry in the fall of 2006 via Communiqués and at the NHPD Winter 2007 Information Sessions.

Applicants should note that the NHPD thoroughly assesses all PLA's to ensure that the evidence provided is appropriate for the product and that Non-traditional PLA's are not being subjected to new evidence requirements. The NHPD is simply modifying its assessment process to ensure that PLA's with critically deficient evidence are identified at the earliest stage of the review process.

Information and tools related to these Evidence Criteria are available at the end of this Notice and can be used by applicants to ensure that the evidence portions of their non-traditional PLA's are not critically deficient and meet a minimum level of quality.

Update and Progress to date
NHPD now performs an initial assessment of all Non-Traditional PLA's against these Evidence Criteria. PLA's which do not contain any of the evidence deficiencies will remain in queue for full assessment of their safety, efficacy and quality. For those containing critical deficiencies, applicants are issued an Evidence Information Request Notice (E-IRN) outlining the deficiencies. Upon receipt of the E-IRN, applicants have a thirty day period within which to respond to the deficiencies or to withdraw their application.

Since January 2009, the NHPD has been focusing its efforts on the initial assessment of all Non-Traditional applications in order to provide applicants with feedback on critically deficient applications much earlier in the process. The NHPD has issued over 5400 E-IRNs for Non-Traditional PLA's and is currently performing the initial assessment on Non-Traditional applications received in July 2009. Due to the large volume of E-IRNs which NHPD was able to issue this year, flexibility was provided in some cases regarding the amount of time provided to respond to the notices. Feedback received from applicants indicated that the flexibility allowed by NHPD was adequate.

Of the 5400 E-IRNs issued, the NHPD has received over 3600 E-IRN responses to date. Approximately 900 applications were refused as a response was not received within the 30 day allotted timeframe or the extension period agreed upon between the NHPD and applicant. In addition, 1000 requests from applicants to withdraw their application were received. It is important to note that over 2100 Non-Traditional applications did not contain any of the critical deficiencies and as a result are now pending full assessment.

Next Steps

At the beginning of October 2009, the NHPD began reviewing the 3600 E-IRN responses that have been received, with a focus on those applications originally submitted prior to April 1, 2008. The E-IRN response will be evaluated against the same Evidence Criteria used in the initial assessment. As part of the E-IRN response review, the NHPD will be considering all additional evidence, justification(s)/rationale(s), and original information provided. If all of the critical evidence deficiencies have been adequately addressed, the application will then undergo a full assessment. As described in the E-IRN, applications will be refused if the E-IRN response does not adequately address the critical evidence deficiencies identified in the E-IRN.

The primary purpose of this Notice is to inform applicants that NHPD will commence sending refusal notices for E-IRN responses deemed inadequate within the next week.

The NHPD will continue to communicate progress on this Non-Traditional Process Improvement Project to applicants. Should you have any questions or concerns, please do not hesitate to contact your Submission Coordinator.

The Natural Health Products Directorate
Health Canada

www.healthcanada.gc.ca/nhp

Attachment(s)

- Evidence Criteria
- Evidence Assessment Template

Evidence Criteria

Prior to submitting their non-traditional PLAs, applicants are strongly encouraged to cross check their supporting evidence against the Evidence Criteria below to ensure that it is not critically deficient and meets a minimum level of quality.

1) Evidence has not been provided for the medicinal ingredient(s) [XXX and YYY].

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

2) The product and/or medicinal ingredient on the PLA form is not comparable to the product and/or medicinal ingredient included in the evidence.

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

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

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

Examples of evidence that are not considered adequate to support the safety and efficacy of products include:

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

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

As per Chapter 1.3 of the Evidence for Safety and Efficacy of Finished Natural Health Products guidance document, applicants must submit evidence from relevant sources to support the safety and efficacy of the NHP according to its recommended conditions of use. That evidence must come from human use; animal or in vitro experimental evidence may be considered as additional, supporting information but cannot be the basis for approval. While animal and in vitro studies can provide plausible explanations of how a medicinal ingredient will work, they are not sufficient evidence on their own to support effectiveness in humans.

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

Example of evidence deficiency: The recommended daily dose of Medicinal Ingredient X in the PLA provides 300 mg however the evidence provided supports a daily dose of 60mg. The evidence may support efficacy but would not support safety.

Example of evidence deficiency: The recommended daily dose of Medicinal Ingredient Y in the PLA provides 50 mg however the evidence provided supports a daily dose of 150 mg. The evidence may support safety but would not support efficacy.

6) **No dosing information at all is provided/contained within the evidence submitted.**

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

7) **The claim(s) supported by the safety and efficacy evidence has/have no direct relevance to the claim(s) for the product OR the evidence does not support at least one of the claims.**

Example of relevance:

The evidence endpoint is the effect of treatment on LDL cholesterol whereas the claim indicated on the PLA is for “Cardiovascular health”. This is acceptable.

Examples of evidence deficiency:

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

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

8) The route of administration supported by the safety and efficacy evidence differs from the route of administration indicated in the recommended conditions of use section of the PLA.

Example of evidence deficiency: 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.

Evidence Assessment Template

The Evidence Assessment Template is a tool that was developed to help applicants organize their evidence and ensure that the evidence they intend to submit as part of a non-traditional Product Licence Application (PLA) is complete and adequately supports the safety and efficacy of the natural health product for which they are seeking a licence.

Applicants should use this template in conjunction with the Evidence Criteria.

Instructions on how to use the Evidence Assessment Template:

1. List the recommended use(s) or purpose(s) of the product under the "recommended use(s) or purpose(s)" section at the very top of the template.

2. Under the column "Recommended Daily Dose of the MI", indicate the recommended daily dose for each medicinal ingredient, which corresponds to the quantity of the medicinal ingredient multiplied by the recommended daily amount (e.g. 300 mg, 3 times daily corresponds to a daily dose of 900 mg). If the medicinal ingredient is an extract, include the source material and indicate the daily quantity crude equivalent (QDE).

3. Under the column "Evidence", indicate the name of the author and the year (for an article) or the title of the book for each piece of evidence to be submitted, next to the medicinal ingredient it is related to.

4. While reading the evidence to be submitted, determine if it supports the safety and/or the efficacy of each medicinal ingredient in terms of daily dose, source information, and recommended use(s) or purposes(s). It is recommended that you use the Evidence Criteria as a guide to help you determine if the evidence you intend to submit is appropriate and complete.

5. Under the column "What does the Evidence Support", indicate if the evidence submitted supports the safety, the efficacy or both for each medicinal ingredient. In addition, note which of the recommended uses or purposes are supported by the piece of evidence.

6. Complete the summary for the product by answering the two (2) questions at the bottom of the Evidence Assessment Template. **Note**: answering "no" to one of the two questions means that the evidence you intend to submit is deficient.

Evidence Assessment Template

Recommended Use(s) or Purpose(s):

1) _____
2) _____
3) _____
4) _____

** Not limited to four. Additional uses or purposes may be added as needed.*

Medicinal Ingredients (MI)	**Recommended Daily Dose of the MI**	**Evidence** ** include author's name, date, reference title*	**What does the evidence support?**			
			Safety		**Efficacy**	
			Yes	**No**	**Yes**	**No**

Summary	**Yes**	**No**
Is the **safety** of all the medicinal ingredients supported by the evidence?		
Is the **efficacy** of the product supported by the evidence?		

Note: If the answer to the above questions is "no", the submission still contains critical evidence deficiencies.

EXAMPLE #1

Evidence Assessment Template

Recommended Use or Purpose:

1- Source of omega-3 fatty acids for the maintenance of good health
2- Helps support cognitive health and/or brain function
3- Helps maintain/support cardiovascular health
4- Helps to reduce serum triglycerides/triacylglycerols

Medicinal Ingredients (MI)	Recommended Daily Dose of the MI	Evidence ** include author's name, date, reference title*	What dose the evidence support			
			Safety		Efficacy	
			Yes	No	Yes	No
Fish oil	1000 mg/day 350 mg EPA 200 mg DHA EPA+DHA = 550 mg, ratio EPA:DHA = 1.75:1	NHPD Fish oil monograph, 2008	X		X (1,2,3)	
		DEF, 2004	X		X (3)	
Seal oil	1000 mg/day 60 mg EPA 90 mg DHA 40 mg DPA EPA+DHA = 150 mg	NHPD Seal oil monograph. 2008	X		X (1)	
		GHI, 1999	X			X

Summary	Yes	No
Is the **safety** of all the medicinal ingredients supported by the evidence?	X	
Is the **efficacy** of the product supported by the evidence?		X

Comments: The efficacy of the product related to recommended use #4 is not supported by the evidence. Hence, the evidence is deficient.

Two (2) options are available to the applicant:

- Remove recommended use #4 from the PLA
- Provide additional evidence which supports the efficacy of recommended use #4

EXAMPLE #2

Evidence Assessment Template

Recommended Use or Purpose:

1- Helps to maintain immune function
2- Provides temporary relief of the symptoms of upper respiratory tract infections

Medicinal Ingredients (MI)	Recommended Daily Dose of the MI	**Evidence** ** include author's name, date, reference title*	**What dose the evidence support**			
			Safety		**Efficacy**	
			Yes	**No**	**Yes**	**No**
Goldenseal	240 mg/day QCE = 1.68g Root	NHPD Goldenseal monograph, 2008	X			X
Echinacea	300 mg/day QCE = 1.2g Root	NHPD Echinacea purpurea monograph, 2008	X		X (2)	
Ginger	150 mg/day QCE = 1.5g Root	NHPD Ginger monograph, 2008	X			X
Siberian ginseng (Eleuthero)	300 mg/day QCE = 6g Root	NHPD Eleuthero monograph, 2008	X			X
Zinc	30 mg/day	NHPD Zinc monograph, 2008	X		X (1)	
Andrographis	112.5 mg, 33.75 mg (30%) andrographolide Stem and leaves	JKL et al. 2002	X			X

Summary	**Yes**	**No**
Is the **safety** of all the medicinal ingredients supported by the evidence?	X	
Is the **efficacy** of the product supported by the evidence?	X	

Comments: the evidence provided is not deficient as the safety of each MI is supported by the evidence as are the two recommended uses.