



*Voice of the Natural Products Industry*



*La voix de l'industrie des produits naturels*

# **Non-Traditional Product License Applications**

Standards of Evidence:  
Summary of Discussions held by  
stakeholders in the  
Natural Health Products Industry

## Preamble

This document has been drafted in consultation with leading industry members from across the country. It is a work in progress; we anticipate that as discussions continue, some additional work may take place.

We are pleased to present our current thinking to the NHPD as part of our efforts to become more actively involved in developing solutions for consideration and to express our views on important issues of concern. .

## Overall Considerations

1. The evidence requirements for both efficacy and safety are based on the overall risk-benefit of a product, and this risk-benefit ratio should be predictable based on defined standards. In other words, applicants need specific guidelines provided in advance to determine the exact license requirements for their products.
2. "Risk" should be defined according to both "inherent risk" (what's in the product) and "situational risk" (its recommended conditions of use), according to defined standards.
3. A decision tree should be crafted by the NHPD when reviewing PLAs following these defined predictable standards.
4. Certain very low-risk products should not require a full evaluation of evidence, only a screening of the paperwork. The amount of bureaucratic involvement should be risk-based, in other words. Random inspection of such low-risk submissions should be employed.
5. Post market notification of low risk products, such as compendial applications, should continue to be pursued by the government.
6. There should be industry consulted performance standards in place: 60 days for compendial applications (single and multi ingredient monograph products) and other low risk products and up to 180 days for higher risk products. The implementation date of performance standards for the NHPD must be made public.

## Safety Considerations

7. Safety continues to be of primary importance for the natural health products industry.
8. Evidence of safe use from human experience should continue to be required. Animal studies are acceptable as long as there is some evidence of human use and/or market history.
9. For low-risk products evidence supporting a safe dosage range (versus a specific dose) is acceptable.

10. High risk ingredients must be reclassified according to new industry consulted standards of risk (NB ingredient safety is defined as either high or low risk).
11. For low risk products, cautionary statements, supported only by theoretical information are not required to be used. In addition, for all products more generalized wording should be acceptable to advise on a caution or warning, e.g. "Do not use other than on the recommendation of a health care professional if you are on prescription medications."

## Efficacy Considerations

12. The strength of the claim is directly proportional to the strength and credibility of the evidence provided.
13. Health claims continue to be mandatory, with at least one claim per product.
14. Lower level claims need defining and must be permitted.
15. There are three levels of health claims- low, moderate and elevated- according to situational risk; the softer/more general the claim, the softer the evidence required. This is similar to the Australian model.
16. Which types of references that are permitted, needs to be clearly delineated per "level" of health claim. Applicants need to know in advance whether or not their references will support a given claim, all things being equal.
17. The evidence requirements for
  - a. low level claims can be based on secondary sources, including text references, descriptive studies, case series / reports (by naturopath or medical doctor), reputable pharmacopoeia, animal studies, observational studies, in vitro studies, Expert Opinion Reports, reputable websites, international regulatory monographs, international regulatory decisions, quality review or peer reviewed review article, or previous marketing experience. Primary sources would not be required to validate the submitted secondary sources.
  - b. Medium level claims can be based on clinical trials (uncontrolled), pilot studies, non randomized clinical trials, epidemiological cohort studies, case control series studies, populations studies (multiple time series), relevant expert committees.
  - c. High level claims should be based on randomized and controlled clinical trials, randomized and controlled multicentre study, systematic reviews (meta-analysis), NHPD monograph, relevant expert committees.
18. A minimum of one independent reference is required to support a claim.
19. A dosage range supported by safety alone is acceptable.
20. Cross paradigm combinations be permitted for claims, especially combining traditional evidence with non-traditional evidence.

# Appendix A: Proposed Non-Traditional SOE Matrix

		Situational Risk (Claim)		
		Low-Level Claims	Med-Level Claims	High-Level Claims
		<p><b>Low-Level Claims</b></p> <p>Non-Specific                      Nutritional Support                      Generic Low-Level Claims                      Nonspecific SXS Relief                      S/F (Non-Corrective)                      Disease Prevention (minor)                      Risk Reduction (minor)</p>	<p><b>Med-Level Claims</b></p> <p>S/F (Corrective)                      Risk Reduction (major)                      Disease Prevention (major)                      Therapeutic Claims (minor)</p>	<p><b>High-Level Claims</b></p> <p>Therapeutic Claims (major)</p>
<b>Inherent Risk (Composition)</b>	<b>Low Inherent Risk</b>	<ul style="list-style-type: none"> <li>• <u>Process</u>: random review of evidence</li> <li>• <u>Efficacy</u>: does not require primary clinical data; secondary sources are sufficient</li> <li>• <u>Safety</u>: Evidence of safety in humans</li> </ul>	<ul style="list-style-type: none"> <li>• <u>Process</u>: full review of evidence (unchanged)</li> <li>• <u>Efficacy</u>: requires primary clinical data, but does not need to be controlled or randomized</li> <li>• <u>Safety</u>: Evidence of safety in humans</li> </ul>	<ul style="list-style-type: none"> <li>• <u>Process</u>: full review of evidence (unchanged)</li> <li>• <u>Efficacy</u>: requires primary clinical data that is randomized or controlled</li> <li>• <u>Safety</u>: Evidence of safety in humans</li> </ul>
	<b>High Inherent Risk</b>	<ul style="list-style-type: none"> <li>• <u>Process</u>: full review of evidence (unchanged)</li> <li>• <u>Efficacy</u>: requires primary clinical data, but does not need to be controlled or randomized</li> <li>• <u>Safety</u>: Evidence of safety in humans</li> </ul>	<ul style="list-style-type: none"> <li>• <u>Process</u>: full review of evidence (unchanged)</li> <li>• <u>Efficacy</u>: requires primary clinical data, but does not need to be controlled or randomized</li> <li>• <u>Safety</u>: Evidence of safety in humans</li> </ul>	<ul style="list-style-type: none"> <li>• <u>Process</u>: full review of evidence (unchanged)</li> <li>• <u>Efficacy</u>: requires primary clinical data that is randomized or controlled</li> <li>• <u>Safety</u>: Evidence of safety in humans</li> </ul>

# Appendix B: Types of Claims

The left column indicates the type of claim; the middle column provides the new recommended “level” for that type of claim; and the right-most column provides sample wording of that type of claim.

Claim Type	Situational Risk	Example of Wording
1. Non-Specific	Low-Level Claim	Helps maintain prostate health.
2. Nutritional Support	Low-Level Claim	Nutritional support for the prostate.
3. Generic Low-Level Claim	Low-Level Claim	Helps with prostate health / Good for the prostate / Prostate healthy
4. Structure-Function (non-corrective)	Low-Level Claim	Promotes/Supports/Maintains prostate functioning.
5. Non-specific symptom relief claim <sup>1</sup>	Low-Level Claim	Restores urinary flow [i.e., without mentioning BPH or enlarged prostate] / Eases pain during urination
6. Disease Prevention (minor diseases)	Low-Level Claim	Prevents BPH.
7. Risk Reduction (minor diseases)	Med-Level Claim	Reduces the risk of developing urinary problems associated with BPH / Reduces the risk of developing BPH.
8. Disease Prevention (major diseases)	Med-Level Claim	Prevents BPH.
9. Structure-Function (corrective)	Med-Level Claim	Restores urinary flow in persons with BPH.
10. Risk Reduction	Med-Level Claim	N/A <sup>2</sup>
11. Therapeutic (minor conditions)	Med-Level Claim	[No example – BPH would likely be considered a major disease]
12. Therapeutic claim (major disease)	High-Level Claim	Treatment of BPH.

<sup>1</sup> “Non-specific symptom relief” refers to relieving a symptom without mentioning a disease or condition. For example, if the condition was kidney stones and the symptom was painful urination, a non-specific sxs relief claim would be “Eases pain during urination” whereas a treatment version of this would be “Eliminates kidney stones” – even though they are essentially doing the same thing, other regulatory authorities (notably the TGA) do not consider them to have the same situational risk.

<sup>2</sup> BPH is typically not considered a major disease, thus no example is given here.

# Appendix C: Low-Level Evidence Resources

Evidence Description	NHPD Current	Proposed New Level
Descriptive studies	Level III	LOW LEVEL
Case series / case report (performed by either a Naturopath or Medical Doctor)	Level III (only if it is well designed)	LOW LEVEL (specifically allowing for case series conducted by licensed Naturopathic Doctors)
Reputable pharmacopoeia <sup>3</sup>	Level V (only suitable for Traditional claims)	LOW LEVEL (only when reference has non-traditional indication)
Regulatory monograph (other country) <sup>4</sup>	Level IV (but not accepted on its own merit)	LOW LEVEL (when indication is non-traditional)
Evidence-based text reference <sup>5</sup>	Level IV (but not accepted on its own merit); must provide primary sources in addition to this	LOW LEVEL (must be peer-reviewed and fully referenced)
Reputable websites <sup>6</sup>	Level IV (but not accepted on its own merit), only if it is also published	LOW LEVEL

<sup>3</sup> In other words, a reference recognized by the WHO as being a country's official pharmacopoeia, such as the *European Pharmacopoeia* or the *Indian Pharmacopoeia*. The indication would not be restricted to traditional medicine – these would be non-traditional recommendations by and large.

<sup>4</sup> Such as the European Union "Community Monographs", the TGA monographs, or those from the Commission E.

<sup>5</sup> Such as ESCOP or Hoffman or various *Materia Medica* published in the last hundred years. The NHPD and TGA have an excellent list as a starting point.

<sup>6</sup> Such as *A Modern Herbal* (Grieve), Natural Medicines Comprehensive Database (NMCD), Natural Standard, or Physicians' Desk Reference (PDR), all of which have paper editions published with periodic revisions.

Relevant expert committees	Level IV (though this needs greater definition and clarity)	LOW LEVEL (permitted for scientific claims)
Approval from Reputable Country (Other Marketing Experience)	Level IV (though this needs greater definition and clarity)	LOW LEVEL (i.e., EU, TGA and FDA)
Review Article (peer-reviewed) <sup>7</sup>	Level IV (must be based on human evidence and primary sources should also be provided)	LOW LEVEL (primary sources not required)
Previous Marketing Experience	Level IV (though in reality this does not stand for efficacy, only for safety evidence)	(not permitted for efficacy)
ANY MED-LEVEL EVIDENCE	Permitted in lieu of LOW LEVEL evidence	
ANY HIGH-LEVEL EVIDENCE	Permitted in lieu of LOW LEVEL evidence	

---

<sup>7</sup> While the NHPD does accept this right now (as "Level IV"), the primary sources are usually requested to validate the secondary sources. In other words, what is proposed is that a reputable review article (e.g., from *Alternative Medicine Review*) would be sufficient on its own, in that the NHPD would not need to see the full text of the clinical trials mentioned in that AMR review article. This proposal would mean that primary data would not need to be made available if the secondary sources are provided.

# Appendix D: Med-Level Evidence Resources

Evidence Description	NHPD Current	Proposed New Level
Clinical trial (uncontrolled); pilot studies	Level II (must be well designed)	MEDIUM LEVEL
Clinical trials (non-randomized)	Level II (must be well designed)	MEDIUM LEVEL
Epidemiological cohort study	Level III	MEDIUM LEVEL
Case-control series studies	Level III	MEDIUM LEVEL
Population studies (multiple time series)	Level III	MEDIUM LEVEL
Relevant expert committees	Level IV (though this needs greater definition and clarity)	MEDIUM LEVEL (permitted for scientific claims) <sup>8</sup>
ANY HIGH-LEVEL EVIDENCE	Permitted in lieu of HIGH-LEVEL evidence	

<sup>8</sup> Though it would be generally understood that the weightier the claim, the greater the consensus and/or strength of the expert committee would be needed.

## Appendix E: High-Level Evidence Resources

Evidence Description	NHPD Current	Proposed New Level
RCT (randomized <u>and</u> controlled)	Level I	HIGH LEVEL: same as before
Multicentre study (randomised, controlled)	Level I	HIGH LEVEL: same as before
Systematic review (meta-analysis)	Level I	HIGH LEVEL: same as before
NHPD Monograph <sup>9</sup>	Level I	HIGH LEVEL: same as before
Relevant expert committees	Level IV (though this needs greater definition and clarity)	HIGH LEVEL (permitted for scientific claims) <sup>10</sup>

<sup>9</sup> It is suggested that an NHPD monograph would be on the same level as RCT's, cited as evidence for a Non-Compendial submission, given that dose and source information are matching.

<sup>10</sup> Though it would be generally understood that the weightier the claim, the greater the consensus and/or strength of the expert committee would be needed.