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Canada's Natural Health Products: A Regulatory Overview

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Abstract

Since its inception in 2004, Canadian regulation of natural health products (NHPs) has been evolving. Implementation of the novel Natural Health Products law by Health Canada, the national regulatory agency, has been responsive to both consumer desires for novel products for health care, but also potential concerns over quality and safety. The agency has developed numerous webpages explaining its approach to this new regulatory category, which has included regulations and guidance documents and refinement of both. Due to its many layers, the information is not very transparent. In addition, the information has been changing and is constantly under revision. For this reason, a review of the legislation, regulation and policies was embarked upon which led to the preparation of an overview of up to date information that we hope will be useful to those who plan to pursue the Canadian NHP system.

Keywords: Natural Health Products; Regulations, Canada

Introduction

Canada's regulatory approach to natural ingredients, such as botanicals, probiotics, and other complex products, is somewhat unique. This ingredient class has defied global regulatory harmonization, although certain regions have commonalities in their approach. Canadian law allows such ingredients to be sold not only as foods, cosmetics, and drugs, but also in a novel category: "Natural Health Products" (NHPs). Very recently New Zealand has adopted a similar approach in proposed legislation [1]. While Health Canada's website displays both historical and current material on NHPs, there is no overarching summary that describes the full range of possibilities NHP products encompassed by the law.

By regulation Canada defines NHPs as "a plant or a plant material, an alga, a bacterium, a fungus or a non-human animal material, extracts or isolates, vitamins and its synthetic duplicate. Also homeopathic medicines, traditional medicines, minerals, probiotics and other products, like amino acids and essential fatty acids, that are manufactured, sold or represented for use in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms. NHPs intended use is to restore or correct organic functions or modify organic functions in humans, in a manner that maintains or promotes health." Excluded are products sold as food, fortified foods, and prescription products, drugs administered by puncturing the skin, and substances that are regulated under the Tobacco Act or the Controlled Drugs and Substances Act. NHPs are sold as over-the-counter (OTC) products and must, therefore, be safe for consumers to use without a prescription [2]. NHP formulations must generally follow the same that are used for "traditional" medicine. Therefore, the majority of licensed NHPs are administered orally, although some are topically or sublingually applied.

As a regulatory category NHPs represent a compromise resulting from years of assessment and discussions with Canadian consumers, academics, health care practitioners and industry stakeholders. Although NHPs are not "drugs," they are, however, allowed greater latitude than either foods or nutritional ("dietary") supplements to make claims of efficacy and therapeutic benefit. Such claims border on those generally reserved for non-prescription drugs in most countries. NHPs are also required to comply with category-specific manufacturing quality and safety standards.

Over a decade of changes

The Canadian Natural Health Product Regulations came into effect as of January 1, 2004, which were under the jurisdiction of the newly established Natural Health Products Directorate within Health Canada. In 2004, a large number of NHPs were already being marketed in Canada, creating an instant back-log for the regulatory agency. Over the ensuing decade, out of necessity and stakeholder demand, Canadian regulation of NHPs has advanced significantly. From 2004 to December 2010, over 43,000 products were authorized for sale in Canada, 27,914 PLs were approved and 1,120 SLs were issued [3]. However, by March 2013 this number had significantly expanded, represented by 60,750 NHP product licenses [4]. As of February 1, 2016, based on the Licensed Natural Health Product Database (LNHPD), Canada has issued more than 99,000 NHP product licenses.

Updates in the code were incorporated in 2008 by reference into the Natural Health Product Regulations SOR/2003-196 [5]. In 2015 Health Canada underwent a reorganization, during which two regulatory categories and "disinfectant drugs" were combined into a new entity: the Natural and Non-prescription Health Products Directorate (NNHPD).

Product Classification

NHPs are permitted a wide variety of potential claims that verge on what would be considered "OTC" drug claims in most regulatory jurisdictions. These include health claims, structure-function claims, and claims of therapeutic benefit and disease prevention.

Products can bear claims based on their use as traditional medicines, or they can carry "modern health claims" [6]. Each has its own pathway for licensing, as described in guidance documents [7]. Well-characterized products can utilize a monograph system, which has been undergoing updates, as described further below. The agency's current policies for novel health claims, use of risk information and combination of NHPs, have also been further delineated at the agency's website.

Review requirements are based on assessment of levels "risk" and "uncertainty" to ensure the deliverance of safe consumer products. Sponsors wanting to sell their NHPs on the Canadian domestic market must submit individual product dossiers, demonstrating conformance to both product quality standards, as well as appropriate and sufficient evidence in support for the intended "recommendations for use."

Products are assigned to one of three product classes. Class I products must conform to a NNHPD monograph. Class II products includes both traditional and non-traditional products that can be supported by both a NNHPD monograph, along with additional requirements. Class III products are more complex, with "safety" and "efficacy" profiles of "higher uncertainty." Class III products includes novel and innovative NHPs that, in addition to monographs, must also demonstrate product-specific safety and efficacy data, as further described below in Table 1.

More importantly, the product class impacts the licensing and review process, including review timelines, as described in the following sections, based on a risk-based approach. For example: the lower the "risk", the shorter the agency product license review timeline.

Product Class	Product Description	Comments
Class I	"Products that can be indexed against an individual monograph"* Well established safety and efficacy profile comply with all parameters of an individual NNHPD monograph. "Compendial" or "Homeopathy Monographs" may be selected.	High level of certainty of safety and efficacy. Shortest review time.
Class II	"Safety and efficacy profiles of medium certainty" "Traditional" and "Non-Traditional" products supported entirely by a combination of NNHPD monographs as well as Homeopathic products ("Homeopathic with Non-Specific Claim" and "Category IV Monographs/Labelling Standards") Any fruits or vegetables listed in the Canadian Nutrient File; products self-identified to be identical to licensed products and TCM; products identical to a TCM pharmacopoeia.	Medium level of certain of safety and efficacy. Mid-range review times. Require support for safety and efficacy.
Class III	"Safety and efficacy profiles of higher uncertainty" "Traditional", "Non-Traditional" and "Homeopathic with a Specific Claim" products. May include, but not limited to: innovative products with partially or completely novel safety and efficacy profiles; applications partially referencing monograph information but still requiring some assessment, and applications containing a mixture of monograph ingredients and additional supporting evidence (i.e., a dosage form or route of administration not indicated on the monograph(s) Also products with previously unlicensed claims for serious conditions, never before seen ingredients or combinations, and products with significant safety concern.	Lowest level of certainty safety and efficacy. Longest review times. Products require support for safety and efficacy.

Table 1: Canadian NHP Product Classifications.
*"Compendium of Monographs" [http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/index_e.html]- "The Approach to NHPs" [http://www.hc-sc.gc.ca/dhp-mps/prodnatur/nhp-new-nouvelle-psn-eng.php]. **TCM: Traditional Chinese Medicines.

Impact of "risk" level on claims support

Oversight is considered paramount to afford Canadian consumers informed and appropriate healthcare choices. In a 2012 survey, 77% of Canadians agreed that NHPs can be used to "maintain or promote" health, with 71% of Canadians having used a NHP [8]. Thus NHPs must be safe and effective under their "recommended conditions of use."

To determine the level of evidence required to support specific claims, a risk-based system has been developed. Products are assigned to one of three levels of risk: "low", "medium", or "high", based on individual ingredients, proposed claims ("recommendations for use"), as well as the product as a whole (Table 2).

Low Level of Risk: Wide margins of safety, which are to be used in minor diseases or conditions, or for health maintenance or support.

Medium (significant) Level of Risk: Used for treatment, cure, or prevention of major diseases or health conditions which are not naturally resolved within a timely manner, or which can have undesirable effects that may persist or worsen, if proper care is not pursued in a timely manner.

High Level (serious) of Risk: Narrow safety margins and effective dose range; used for treatment, cure, and prevention of serious diseases that require supervision by a health care practitioner, or are debilitating or potentially life threatening without effective treatment.

Risk assignment is made based on a number of factors that include, but are not limited to the probability and frequency of adverse effects, severity and seriousness of the disease or condition for which the product is indicated for use, and the potential health impact associated with a lower than expected performance of the product. The agency may require that the product have clinical and nonclinical studies. Such studies may include the product's potential for interactions with drugs or other therapies used for a particular condition.

At the low-risk end of the spectrum, Health Canada continues to capitalize on previous decisions to create and update monographs, thereby expanding Class I and II products. These efforts promote the expeditious review of products with "high certainty" of safety, while freeing up agency resources for the review of Class III products, with novel claims and ingredients and more "uncertain" safety considerations.

Evidence type	Considerations
High Risk Category	
NNHPD published monographs.	N/A
Phase 3 or Phase 4 clinical trials (randomized, controlled, well-designed).	For treatment, cure, and prevention claims or for health support claims when they imply treatment, cure, prevention, and risk reduction claims if the study is not multi-centered, at least two studies are required.
Meta-analysis (controlled and well-designed).	Conclusions should be based primarily on Phase 3 trials, not Phase 2 trials; primary evidence may be requested.
Prospective observational studies or combinations of one prospective study and one retrospective study.	Evidence only meets minimum requirements for prevention and risk reduction claims. Two pieces of evidence of equivalent ranking or higher are required to support efficacy.
Evidence of a positive decision from another regulatory agency.	Documentation in the form of an authorization letter or positive decision must be submitted that includes details on what was approved. A description of the regulatory requirements from the other regulatory agency should be provided.
Medium Risk Category	
All acceptable minimum evidence requirements for the high risk category.	N/A
Systematic review other than meta-analysis.	Conclusions should be based primarily on Phase 3 trials, not Phase 2 trials; primary evidence may be requested.
Published, peer-reviewed, detailed narrative reviews which cite detailed primary evidence.	Detail should include: defining characteristics of the ingredient; primary endpoints/ outcomes with statistical and clinical significance; the studied sub-population's age, gender, and health state; the dosing regimen and dosage form; the route of administration; the directions of use; any restrictions to study entry of participants based on interactions/risk; any identified adverse reactions
Phase 2 clinical trials.	Two pieces of evidence of equivalent ranking or higher are required to support efficacy.
	When the evidence provided to support the claim is methodologically weak, it should be supplemented to demonstrate consistency in results and plausibility.
Phase 2 clinical trials.	Two pieces of evidence of equivalent ranking or higher are required to support efficacy. When the evidence provided to support the claim is methodologically weak, it should be supplemented to demonstrate consistency in results and plausibility.
Epidemiological studies.	Evidence only meets minimum requirements for prevention and risk reduction claims. Two pieces of evidence of equivalent ranking or higher are required to support efficacy.
Published compilations referring to traditional use.	Evidence can be used to support safety only.
Low Risk Category	
All acceptable minimum evidence requirements for the high and medium risk categories.	N/A
Phase 2 clinical trials.	One piece of evidence of equivalent ranking or higher is required to support efficacy. When the evidence provided to support the claim is methodologically weak, it should be supplemented to demonstrate consistency in results and plausibility.
Epidemiological studies.	Evidence only meets minimum requirements for prevention and risk reduction claims. One pieces of evidence of equivalent ranking or higher are required to support efficacy.
Pilot and open label studies.	Two pieces of evidence of equivalent ranking are required to support efficacy. The two different studies may be of equivalent or higher ranking. When the evidence provided to support the claim is methodologically weak, it should be supplemented to demonstrate consistency in results and plausibility.
Reputable textbooks.	Textbook should reflect human in vivo data if the ingredient is an essential nutrient.
Demonstration of food use.	Evidence can be used to support safety only.

Table 2: Risk-Based Evidence for NHP Claims Support.
Note: A risk-based approach is applied in the classification of NHP, and also to the issuance of Products and Site Licenses. Product benefits are weighed against known and potential risks and supportive good quality evidence is required to support specific claims [From: http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/modern-eng.php

Marketing Requirements

To market a NHP product sponsors must obtain appropriate licenses. Health Canada awards NHPs a Product License (PL) and, as of September 1, 2014, it also provides a Natural Product Number (NPN), which is analogous to the Drug Identification Number (DIN) for drugs. If the product is homeopathic, it can bear a NPN, a Homeopathic Medicine Number (HMN), or a "DIN HM". Domestic sites that manufacture, package, label or import NHPs are required to have a Site License (SL). Licensing requirements do not apply to retailers or to healthcare practitioners who compound products on an individual basis for their patients [9].

Sponsors must submit a Product License Application (PLA) which contains detailed information regarding the product's composition, chemical attributes, source and preparation, including dose, formulation, and pharmacological action of any "medicinal" (active) ingredients. All "medicinal" (active) and "non-medicinal" (inactive or excipient) ingredients in the NHP must be listed in the Natural Health Products Ingredients Database (NHPID), along with their respective purpose. Furthermore, a Finished Product Specifications (FPS) form must be completed that describes product testing, to include: identity and quantity of each active ingredient; purity; potency (as applicable); and respective tolerance limits for each test.

The PLA must also include "recommended conditions for use," dosage form, route of administration, duration of use, and risk information that includes cautions, warnings, contraindications and known adverse reactions. To support this information, a critical summary reflecting the totality of evidence should be presented in a systematic review. For each reference used, a critical analysis should be provided which addresses study design, quality, quantity and validity of each evidence type that supports and refutes the claim, demonstration of statistically significant outcomes, clinically meaningful differences, relevance to the target population, and overall consistency of the results across all studies of acceptable quality.

"Advisory" language can be submitted to mitigate safety issues, such as warning statements or contraindications for harmful outcomes considered "mild" to "moderate." "Serious" or "severe" outcomes that occur only in a very limited and specific population, and which can be clearly contraindicated on the product label, are the exception to this rule. All other risks should be mitigated by appropriate "recommended conditions of use."

Premarket review and approval

The NNHPD conducts the pre-market review of the NHP PLA. Key review elements are safety, quality, and efficacy. Submission of a signed PLA is regarded as an attestation acknowledging the license holder's responsibility to meet the requirements and conform to quality and Good Manufacturing Practices (GMPs).

Both the timing and process steps of the PLA review process reflect the product Class, as shown in Table 3. Review time for PLAs can take up to 180 days, particularly for PLAs of products with unique claims or ingredients (i.e., a therapeutic or preventive claim for a Class III product). PLAs for products that conform to a NNHPD monograph (Class I) may only take 10 days for a decision.

Application Type (Review Time*)		Screening Process: Administrative Processing for Application Completeness	Screening Process: Type of Notice Issued	Screening Process: Screening	Full Assessment	Regulatory Decision Issued
Class I (10 Business Days*)	Compendial	10 Business Days	NA	NA	NA	Product License or Rejection Letter or Refusal Letter
	Homeopathy Monograph					
	Class I Post-Licensing Change					
Class II (30 Calendar Days*)	Non-traditional	10 Calendar Days	Application Acknowledgement Letter or Rejection Letter	20 Calendar Days	NA	Product License or Refusal Letter
	Traditional					
	Category IV/Labelling Standard					
	Homeopathic Medicines Non-Specific Claim					
	Class II Post-Licensing Change					
Class III (180 Calendar Days*)	Non-Traditional	10 Calendar days	Application Acknowledgement Letter or Rejection Letter	20 Calendar Days	180 Calendar Days	Product License or Refusal Letter
	Traditional					
	Homeopathic Medicines with Specific Claim					

	Class III Post-Licensing Change					

Table 3: Product License Review Standards and Management for NHPs (Health Canada NNHPD).
NA: Not applicable. *These service standards apply to PLAs submitted using NNHPD "ePLA" form. Submissions using a different format will be assessed within 180 calendar days following Screening. **180 calendar days from successful completion of the screening process.

Upon submission, the PLA is initially screened by the regulatory agency, which results in one of the following actions: Notice of Acceptance, Notice of Rejection with Administrative Deficiencies (listing the deficiencies in the PLA), or Refusal (unacceptable for review). Deficiencies identified during the regulatory review process can result in the issuance of an Information Request Notice (IRN). If the IRN response is deemed deficient or if the applicant does not satisfy all Class III requirements, an Application Refusal Letter may then be issued. Upon the receipt of a Refusal Letter, any resubmission will be as a new application.

Product benefits are weighed against known and potential risks, based on information amassed from authorized NHPs and the information the sponsor is required to provide in the PLA. Upon satisfactory review of the PLA, the agency grants the NPN, which allows the product to be marketed in Canada, and the "recommended conditions for use" become the "Terms of Market Authorization" (TMA) under the approved product license.

Use of a risk-based approach is also applied to the issuance of SLs. Sites conducting "high risk" activities or handling "higher risk" products will be required to submit more documentation regarding their activities, than sites dealing with "lower risk" activities or high risk products. Health Canada recognizes self-assessments, independent or third-party on-site audits to demonstrate compliance with GMPs standards.

Health Canada's approach to the regulation of NHPs is both unique and evolving. Although ingredients used in NHPs are in many ways similar or identical to those allowed for "dietary supplements"- a distinct category of "foods" sold in the United States - further comparison between the Canadian and United States regulatory systems requires a level of discussion that is beyond the scope of this manuscript.

To summarize the NPHs of Canada are neither foods nor drugs, but a special stand-alone regulatory category. As such they have greater latitude than either foods or nutritional ("dietary") supplements to make claims of efficacy and therapeutic benefit. However, such claims are limited to those generally reserved for non-prescription drugs in most countries, all the while conforming to category-specific manufacturing quality and safety standards.

Canadian guidance and licensing requirements for marketing NHPs continue to respond to increasing demands by consumers for new, diverse, and exotic products, and the increasing need to identify natural products able to "treat, cure or mitigate" common diseases not yet controlled adequately by conventional medicine. Canadian regulators strive to meet the goals set out in the legal mandate "to give Canadians access to a wide range of natural health products that are safe, effective and of high quality," encouraging freedom of choice and providing market opportunities.

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