

Botanical Regulation: Comparison of the United States and Canada

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Introduction

Botanicals are defined as ingredients or finished products “of or relating to plants” or “a substance obtained from a plant.” Botanicals have been used by humans since the beginning of civilization. Archaeological excavation documents the medicinal use of plants by humans dating back as far as 60,000 years [1]. Today about 80% of the world still uses plants and plant-based products to treat medical conditions [2].

Botanicals can be regulated as foods, food and dietary ingredients, drugs, devices, cosmetics, flavorings, color additives, fragrances and more. When used in healthcare, botanicals have defied regulatory harmonization. Even within the North American continent the regulatory approach to botanicals differs by country. This article will discuss the Canadian and US perspectives on botanical regulation: how they are similar, and where they diverge.

United States Regulation

Unlike many regulatory systems the US has no “herbal” or “traditional” medicine category. Four overarching principles help to define US regulation [3]:

- Route of administration;
- Form or formulation;
- Safety;
- Intended use, i.e., what the product is intended to do.

For example, a topically applied botanical product can never be a food or dietary supplement; however, depending on its safety and intended use, it might be a drug, cosmetic or device. Plants used in vaccines or as substrates for monoclonal antibodies are “biologics”, which are regulated under the US Public Health Service Act. [4,5]. Foods, drugs, cosmetics and devices are regulated under the Federal Food, Drug and Cosmetic Act (FDCA). Regardless of an ingredient’s current market channel, if its labeling shows that it is intended to affect the structure or function of the body and/or “treat”, “prevent” or “mitigate” a medical condition, the US regulates it as a “drug”.

Botanical ingredients are often marketed as foods. A botanical can be a conventional food (e.g., vegetables, spices), a dietary supplement, or a “food for special dietary use”. Because botanicals are explicitly named in the Dietary Supplement Health and Education Act (DSHEA) as ingredients that can be used in finished dietary supplements, it was commonly thought that botanicals could not be drugs. A dietary supplement is “a product (other than tobacco) that is intended to supplement the diet....” DSHEA also specifies the formulations for dietary supplements, which differ from those of conventional foods.

In policy guidance, FDA provides a regulatory definition for “botanicals” as “products that include plant materials, algae,

macroscopic fungi, and combinations thereof”. However, it also describes what products do not fall under this definition: highly purified ingredients derived from plants, such as Taxol[®]; products of fermentation; or homeopathic drugs. These exceptions are addressed under different regulatory approaches in the US [6].

Canadian Regulation

Canadian law does not explicitly define “botanicals”. Similar to the US, Canada allows botanical ingredients and finished products to be marketed in a variety of domestic channels. Botanicals can be marketed in Canada as foods, food additives, cosmetics, and devices. Botanical ingredients, such as acacia gum, agar, carrageenan, and pectin are included on Health Canada’s “List of Permitted Emulsifying, Gelling, Stabilizing or Thickening Agents (Lists of Permitted Food Additives)”. When used in cosmetics, Canadian regulation requires that botanical ingredients be listed according to genus and species, or the complete International Nomenclature of Cosmetic Ingredients (INCI) name.

Unique to Canada is a category called Natural Health Products (NHPs). By regulation NHPs are defined as products that may contain: “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” [7]. NHPs include homeopathic medicines, or herbal or medicines of traditional medicine practices that are intended for use in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms. The intended use of NHPs is to “restore or correct organic functions or modify organic functions in humans, in a manner that maintains or promotes health” [7].

NHPs are regulated by the Nonprescription Natural Health Products Directorate (NNHPD). As such they are not foods, fortified foods, prescription products, or drugs administered by puncturing the skin, or any substance that is regulated under the Tobacco or the Controlled Drugs and Substances Acts of Canada. NHPs are sold “direct to consumer” (DTC), and therefore, they are restricted to oral, topical, or sublingual routes of administration [8].

Canada regulates NHPs based on their intended use that includes: the health condition (serious, major, minor); health effect (diagnoses, treatment, cure, risk reduction, prevention, general health maintenance, support or promotion, anti-oxidant); or general health claims (relate to modifying organic functions in a manner that maintains or promotes health (i.e., nutrient structure-function and quality of life claims). Health Canada has not yet provided explicit guidance regarding the development pathway of botanicals as prescription drugs.

Labeling Claims

Both the US and Canada classify products and define claims based on a product's regulatory category (Figures 1 and 2). The terminology differs, however, between the two regulatory systems.

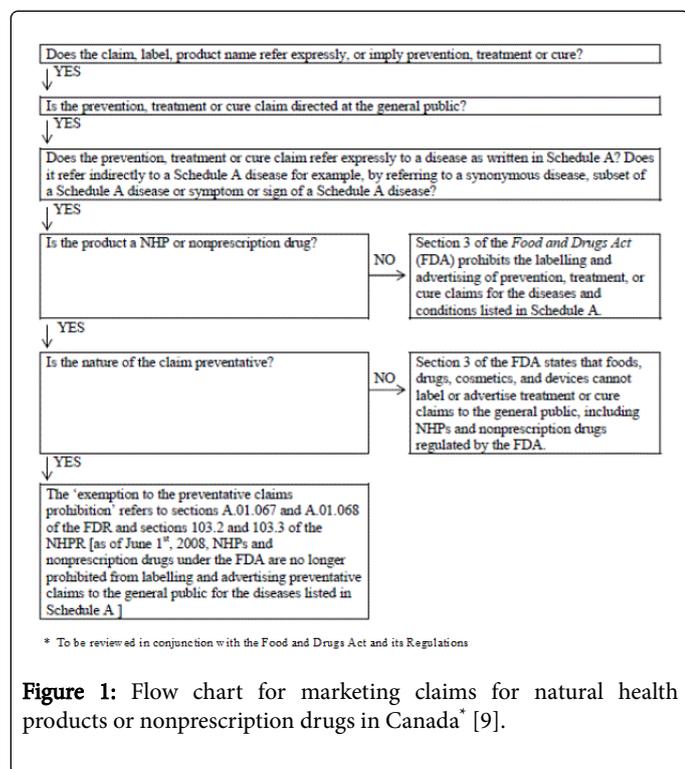


Figure 1: Flow chart for marketing claims for natural health products or nonprescription drugs in Canada [9].

Health claims

According to Canadian regulation, a health claim is any statement that indicates the intended beneficial effect of a product when used in accordance with its recommended conditions of use. The term “recommended use or purpose” is often used interchangeably with “health claim” or “indications for use”. The term “claim” includes the product’s therapeutic indication specifically for a disease. The term “disease” is used as a general term to include diseases, disorders, or abnormal physical states [8].

By law and regulation NHP claims can be further divided into two categories:

- Traditional health claims;
- Modern health claims.

Traditional health claims: Traditional health claims promote the product’s use or mode of action based upon the theories, experiences and beliefs of ancient practices of medicine and also on the knowledge, skills and practices of the indigenous Canadian culture. Product categories for these types of claims include homeopathic and traditional medicines. Traditional medicine specifically pertains to products that contain multiple medicinal ingredients that have a “traditional use” within a single recognized system of traditional medicine (e.g., Ayurveda, ethnomedicines of the First Nations, traditional Chinese medicine) [10]. Health Canada also requires at least 50 consecutive years of traditional use of a medicinal ingredient within a cultural belief system or healing paradigm for the product to be considered “traditional”. Traditional claims may appear on non-

traditional use products, as long as the claim meets the requirements for traditional use claims and the dosing and method of preparation represents how the product was used traditionally.

Modern health claims: Modern health claims are those that are not based on traditional medicinal use or practices. More rigorous evidence is required to support these novel claims and uses. Support must be based on clinical studies, animal and *in vitro* studies, pharmacopoeias, textbooks, peer-reviewed published articles, and regulatory authority reports [11].

In the US, a health claim describes a relationship between a food substance (a food, food component, or dietary supplement ingredient), and reduced risk of a disease or health-related condition (but not treatment or prevention). FDA must review and promulgate a regulation for an unqualified health claim. When there is insufficient evidence to support an unqualified health claim, the agency can issue guidance on the wording of a “qualified” health claim.

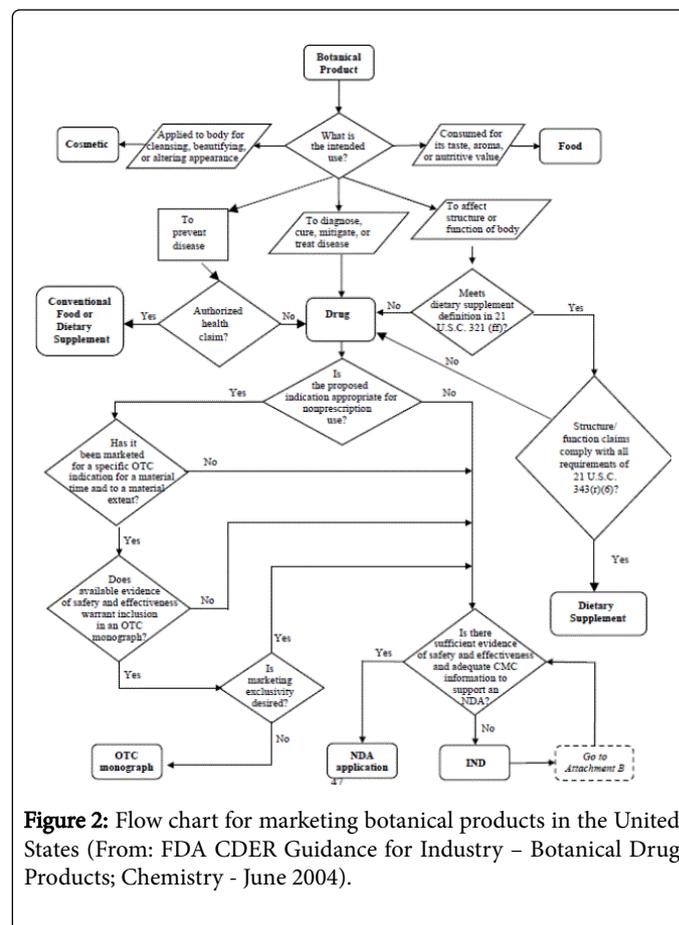


Figure 2: Flow chart for marketing botanical products in the United States (From: FDA CDER Guidance for Industry – Botanical Drug Products; Chemistry - June 2004).

Structure Function (SF) claims

SF claims describe an effect of the product on a structure or physiological function in the human body. They may also describe a mechanism of action, e.g. “antioxidant”.

Canadian NHPs may bear SF claims that describe health maintenance (e.g., “maintains healthy gums”) as well as the treatment of disease or conditions (e.g., “reduces blood cholesterol”). Such claims may also be worded for “general health support” when the product contains an essential nutrient.

In the US both drugs and dietary supplements can affect the structure or function of the body, although only drugs are permitted to describe SF effects on diseases or other abnormal conditions. According to DSHEA dietary supplements are prohibited from making explicit or implicit “disease” (drug) claims. Use of an SF claim for a dietary supplement also requires the inclusion of a disclaimer: “The FDA has not evaluated this claim. This product is not intended to diagnose, mitigate, treat, cure or prevent disease”. A manufacturer, packer, or distributor that wishes to market a dietary supplement with a nutritional deficiency, SF, or general well-being claim must have substantiation that the claim is truthful and not misleading. Notification of such claims must be submitted to FDA within the first 30 days of marketing.

Therapeutic claims

Unlike US dietary supplements which are regulated as “foods”, Canadian NHPs can claim therapeutic effects that are related to the diagnosis, treatment and mitigation or prevention of a disease, disorder, or abnormal physical state or its symptoms in humans. Such claims, however, are limited to nonserious conditions or diseases, that is, those not listed in Health Canada’s Schedule A [9].

While the regulatory pathway for a botanical to achieve therapeutic claims that require a prescription in Canada remains somewhat murky, the US has already approved two botanical “new” drugs, both of which are available only by prescription. Veregen[®] (sinicatechins) ointment, 15% (Medigene-Germany) was approved by FDA in 2006 as a topical proprietary extract of green tea for the treatment of genital and perianal warts [12,13]. Fulyzaq[™] (crofelemer) 125 mg tablet (Salix Pharmaceuticals-USA), “a proprietary oral extract from the *Croton lechleri* tree...” was approved by FDA in 2012 [14]. Both drugs underwent the New Drug Application (NDA) premarket review process and are produced in compliance with pharmaceutical Good Manufacturing Practices [14,15].

Safety

For both regulatory systems “safety” is a relative term. Safety depends on the product category and the product’s intended use, as expressed in the product claims. Both NHPs and drugs require a “benefit to risk” assessment. Such an assessment does not pertain to foods (including US dietary supplements) or cosmetics.

During its review Health Canada requires that NHP sponsors address potential risks: severity and seriousness, probability or frequency, and inherent risks of the medicinal ingredients. Safety risks can be mitigated by advisory information on the NHP product label: warning statements or contraindications for mild to moderately harmful outcomes. Safety evidence for non-medicinal ingredients may be requested and must be appropriate to the route of administration and exposure. The safety requirements for non-medicinal ingredients generally mirror those of medicinal ingredients. However, when risk or uncertainty is identified, additional evidence may be requested to help characterize the risk. In addition the product sponsor may cite a monograph as the sole source of information in support safety and efficacy of the product. Monographs can be used to make either “modern” or “traditional claims,” or they may refer to the risk-based level of evidence for finished products making “modern” claims [8-10].

Canada’s NHP product licensing system also requires premarket evaluation by Health Canada, depending on the level of risk of the health condition. Studies range from controlled clinical studies for

“high risk” categories; “phase 2” studies for “medium risk” conditions; and at least some clinical data for “low-risk” conditions. Similar to the US, Canada requires two “head-to-head” clinical trials to support comparative therapeutic claims [8,10].

A modern health claim requires scientifically valid clinical evidence demonstrating the effect of the product or its components under conditions that reflect the actual conditions of use and exposure. Depending on the specific claim, Health Canada may require additional qualifying statements to provide sufficient context and clarification for consumers [10].

US consumer products, those sold DTC, which include food, dietary supplements and nonprescription drugs, must have “absolute” safety: a risk profile that permits the product to be properly administered by a consumer in the absence of a “learned intermediary”. The initial assumption for all drugs, including nonprescription drug ingredients considered “Generally Recognized as Safe” (GRAS), is that their benefit based on the intended use outweighs any risk to the user.

With very few exceptions, botanicals entering the US market as drugs will be considered as “new” drugs, which are defined as any drug that is “...not generally recognized as safe and effective under the conditions prescribed, recommended or suggested in the labeling” [6]. Even though the botanical may have a long history of use, FDA may require additional safety data, both nonclinical and clinical, to support a particular indication, novel route or new population [3,17]. For new drugs, the initial regulatory step in the US pathway requires the filing of an Investigational New Drug (IND) application to initiate clinical studies in the US. The final regulatory step in the development process is submission of a New Drug Application for premarket approval [3,6,15].

Efficacy

Botanicals sold as Canadian NHPs bearing therapeutic claims must demonstrate therapeutic efficacy based on one or a combination of ingredients. Controlled clinical evidence is required, although studies can be observational or experimental in design. Prior to study initiation, protocols must be submitted under a Clinical Trial Application (CTA), which must be reviewed and authorized by the Nonprescription and Natural Health Products Directorate [7,8].

For the US, the requirement that a product show efficacy depends on the regulatory route. Drugs and medical devices that are required to undergo premarket approval must show safety and efficacy. However, the concept of “efficacy” is inapplicable to products sold as conventional foods, dietary supplements, cosmetics, or as medical devices that are “substantially equivalent” to precedent devices under Section 510 k of the FDC Act.

The legal requirements for botanical “new” drugs are no different from those for any other drug, as described above. FDA can approve a new drug when it has been shown to be safe and effective for its intended use, as demonstrated by substantial evidence, defined as “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved”. These data must show that the “drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling....” The sponsor

must also show that the drug is lot-to-lot consistent, which for botanical drugs can somewhat be challenging [13].

Finally, although FDA is responsible for the label of all products, it is only responsible for the advertising and promotion of prescription products. Advertising and promotional claims of DTC products are under the aegis of the US Federal Trade Commission.

Manufacturing and Quality

Neither the FDA nor Health Canada have “special rules” for botanicals over other ingredients. However, both regulatory systems have identified category-specific requirements. FDA and Health Canada can request that the sponsor provide detailed information about the botanical raw source material, product characteristics and quality, safety, including nonclinical toxicology studies, and clinical safety and efficacy, depending on the product’s intended use.

Both agencies require manufacturers to adopt processes that serve to optimize the lot-to-lot consistency of a raw material, ingredient, or

product, which includes identity, purity, and impurities, such as heavy metals, aflatoxins and pesticides. Botanical raw material should conform to Good Agricultural and Collection Practices (GACPs), which may be those set by the World Health Organization (WHO) [18]. NNHPD refers to a product as “standardized” if it is manufactured to meet consistently a predetermined concentration of a specific marker or set of markers. Markers are chemically defined constituents or groups of constituents that can be followed during the manufacturing process irrespective of their correlation with therapeutic activity [7,10]. FDA has described similar requirements in the agency’s botanical guidance document [6].

Conclusion

Botanical ingredients and products have many market channels potentially available to them in both the US and Canadian domestic markets. Selection depends on the route of administration, safety, and most importantly, the intended use or promotional claims (Table 1).

Item	United States	Canada
Product Categories	Foods (including dietary supplements) Food additives Color additives Scents (fragrances) Cosmetics Nonprescription drugs (including homeopathic drugs) Prescription drugs Biologics Medical devices	Foods Food-like NHPs (fortified foods, energy drinks, bars etc.) Food additives Cosmetics Natural Health Products (including Homeopathic drugs) Nonprescription drugs Prescription drugs Biologics Medical devices Disinfectants and sanitizers with disinfectant claims
Allowed claims for products categories	Depends on “intended use”: Food: no claims; health claims; nutrient content, etc. Dietary supplements: nutrient content; claims of “wellbeing”; structure or function claims; health claims Drugs/Biologics: disease claims (to “diagnose, treat, prevent, mitigate or cure”) and/or affect the structure or function of the body; Devices: no claims or disease claims (devices primarily exert effects through a physical- not chemical- means)	Depends on “recommended conditions of use”: Food: no claims, health claims; nutrient content NHPs: Health claims including structure-function, risk-reduction, and therapeutic or treatment claims; claims may be traditional and/or modern Drugs/Biologics - disease claims and/or affect the structure or function of the body; “diagnose, treat, prevent, mitigate of cure” Devices: disease claims
level of evidence for botanical drugs and nhps	Botanical drugs: strong evidence of safety and efficacy obtained through a series of “adequate and well-controlled” studies; requires both nonclinical studies and clinical studies.	NHPs: level of evidence to support safety and efficacy varies for each claim; ranges from traditional references, and observational studies, to randomized clinical trials Data to support a health claim should be appropriate to support the strength of the claim
Require Pre-market approval	“New” drugs and biologics, some (Class III) medical devices	All NHPs, new drugs and biologics, some medical devices
Clinical trials for Safety	For GRAS applications, new drug and biologics approval; some medical devices (Class III)	May be requested to help characterize the risk
Clinical trials for Efficacy	“New” drugs and biologics	All products, except foods.
Regulatory Filings	Medical devices, based on claims Foods: No pre-market approval for conventional foods “GRAS” determinations: for ingredients “generally recognized as safe” intended to be used for foods, or drugs Health Claims: petition	NHPs, depending if the claims are traditional or modern health claims CTA: Clinical Trial Application - to initiate clinical studies NHPs: Product License Application (PLA), Terms of Market Authorization (TMA) OTC: Market Authorization: Drug Identification Number (DIN)

	Structure-Function Claims: 75 day notice "New" drugs: IND: Investigational New Drug application – to initiate clinical studies; allowance to proceed NDA: New Drug Application – request to market "new" drug; pre-market approval	Drugs: IND and NDS (New Drug Submission) -similar to US. Market Authorization: DIN, Natural Product Number (NPN)
Regulation of Advertising/Promotion	Direct to consumer: Federal Trade Commission Prescription: Food and Drug Administration	Health Products and Food Branch (HPFB) Inspectorate Health Canada
Intellectual Property Protections	Market Exclusivity (FDA) Patent-term restoration (under Hatch-Waxman Act) (USPTO) Other: Copyright, trademarks, trade secrets	Market exclusivity for drugs Other: trademarks, trade dress, trade secrets, patents, brand promotion and protection
Approval time	Foods, dietary supplements: no premarket product approval; some claims, (e.g., health claims, structure-function) are subject to specific processes, such as promulgation of a regulation, or pre-market 75-day notification Same as other drugs, depending on whether the NDA receives Standard or Priority review (generally 6–18 months)	For simple products that mirror existing NHPD monographs 10 days NPN: within 60 days of filing an application For products with unique ingredients and health claims: NPN in 180 days
Path to Market	Depends on the market channel (foods, dietary supplements, drugs, etc.)	Differs for NHP and similar OTC products or prescription drugs

Table 1: Comparison of Canadian and United States regulation of botanicals.

Canada's unique NHP category allows botanicals to make general health promotion, traditional and modern health claims, structure-function, and in some cases, therapeutic claims. Canadian NHPs are consumer health products, sold without a prescription. As such they are restricted from making claims regarding serious medical conditions.

The US permits botanicals in any regulatory category for which the requirements can be met. As drugs, botanicals can be developed for prescription use only for serious and life-threatening conditions and can be administered by any conceivable route. Within the past decade FDA has approved two NDAs for prescription botanical new drugs. Both drugs met all of the legal requirements for drugs in the US. Regardless of the amount of prior human use, the US regulatory process requires documented evidence of both safety and efficacy, a requirement no different from any other drug.

Both systems are continuing to refine their guidance and policies on botanicals. In 2016, FDA revised its industry guidance on botanical drug development. Health Canada recently published guidance on the quality parameters for NHPs. Even more recently there have been announcements from Health Canada proposing a new structure for classifying products based on a product's risk. Health Canada is currently requesting public commentary on its proposal to not subject "low risk" "self-care" consumer products to review [16,19].

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