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Health Canada Allows for OTC Use of 10 Naturally Sourced Ingredients

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What do oil of apiol, deanol, theobromine, *Centella asiatica*, dopamine, gold, uracil, dimethyl sulfoxide, levocarnitine, and L-tryptophan have in common?

Until recently, they were classified as prescription drugs in Canada, meaning the only way consumers could access products containing any of these ingredients was by virtue of a licensed health care practitioner writing a prescription for their use. However, with the recent passage of amendments to Schedule F of the Food and Drug Regulations, suppliers will now have the opportunity to bring these ingredients to market as natural health products (dietary supplements). These amendments came into force Nov. 24, 2011.

When the Natural Health Products Regulations became law in 2004, all naturally sourced ingredients meeting the definition of a natural health product (e.g., vitamins, minerals, amino acids, and plant and animal extracts) came under the scope of these regulations. However, products containing ingredients listed on Schedule F of the Food and Drug Regulations were explicitly excluded from the Natural Health Products Regulations. Natural health products, by definition, are only allowed to be sold for over-the-counter (OTC) uses—that is, for conditions amenable to self-care.

Sections C.01.041 to C.01.049 of the Food and Drug Regulations control the sale of medicinal ingredients listed on Schedule F—those that require a prescription for human and/or veterinary use.

Industry Concerns

The previous classification of these ingredients has caused the natural products industry much grief over the years, and with the implementation of the Natural Health Products Regulations in 2004, stakeholders thought they would see an end to the confusion and a move to change the Regulations. At that time, the Natural Health Products Directorate (NHPD) actually agreed to review the classification of carnitine and L-tryptophan, ingredients of primary importance to the industry. Monographs were written for these ingredients by consultants at the request of NHPD, but the monographs sat on a shelf and changes were not forthcoming.

Widespread confusion surrounded the legal interpretation and implementation of Schedule F of the Regulations. Did products that naturally contained Schedule F ingredients automatically become prescription products? At one point in time, shipments of blue-green algae were being turned back at the borders because of the presence of naturally occurring vitamin K. (Until 2005, all forms and dosages of vitamin K were considered to be prescription drugs.) Following this logic, it could be argued that chocolate and tea, natural sources of theobromine, should also be considered prescription drugs. The determination of whether gotu kola was a prescription drug by virtue of the presence of the "active principles of *Centella asiatica*" also flip-flopped back and forth, with shipments of the raw herb often being refused entry into Canada.

In addition, Canadian consumers were restricted in purchasing L-tryptophan and carnitine, while these ingredients were freely available over the counter in the United States. Industry had expected that the Natural Health Products Regulations would help to level the playing field and increase the number of products available to consumers in Canada. However, this discrepancy only reinforced the viability of Internet and black-market sales.

The qualifying language for L-tryptophan on Schedule F, "tryptophan, when sold as a single ingredient," served to add further confusion. This language was intended to differentiate between L-trytophan as an isolated, pure substance and L-tryptophan as one of many amino acid residues in a protein. However, it was often interpreted by industry to mean that L-tryptophan could be sold over the counter as long as it was in combination with other ingredients. It further aggravated the industry that carnitine, routinely found in meat and dairy products, nuts, seeds, and a host of other foods, and allowed to be added to foods such as infant formula, required a prescription for consumer access when sold as a supplement.

Health Canada Review

The industry lobbied extensively over the years for the revision of Schedule F. But it was not until 2008 that Health Canada initiated

its own review of naturally sourced medicinal ingredients listed on Schedule F. As part of this undertaking, the department's Drug Schedule Status Committee reviewed science assessments for 11 naturally sourced ingredients to evaluate the merit of their remaining on Schedule F based upon established criteria. The committee concluded that these 11 ingredients could be regulated in whole or in part as natural health products under the Natural Health Products Regulations.

Health Canada used the following factors to determine whether prescription status of drugs is appropriate.

Drugs will be listed in Schedule F if:

a. Individualized instructions and/or direct practitioner supervision, adjunctive therapy with scheduled drugs or routine laboratory monitoring are required;

b. There is a narrow margin of safety between the therapeutic and toxic doses, especially in populations such as geriatrics, children and pregnant or nursing mothers;

c. There are potential or known undesirable or severe side effects at normal therapeutic dosage levels;

d. They are known by experimental data to induce toxicity in animals but have not been in clinical use long enough to establish the pattern or frequency of long-term toxic effects in humans;

e. They are used in treatment of a serious disease easily misdiagnosed by the public;

f. Their use may mask other ailments;

g. They have contributed to, or are likely to contribute to, the development of resistant strains of micro-organisms in humans;

h. They possess a dependence or abuse potential that is likely to lead to harmful non-medical use;

i. They possess a high level of risk relative to expected benefits; or

j. They have a therapeutic effect based on recently elucidated pharmacological concepts, the consequences of which have not been established.

Exceptions will be considered for drugs, which:

k. Are required to be readily available under emergency circumstances where it is not practical to obtain a prescription (such as adrenalin in insect bite kits);

l. Are rarely used without a practitioner's supervision, and where the need for free availability outweighs the need for protection under Schedule F, such as insulin and nitroglycerin; or have potential to produce dangerous interactions with other drugs or food constituents but effective labelling can minimize the risk.

A list of factors for listing drugs on Schedule F is available at the Health Canada website.

In discussions with Health Canada personnel, it became apparent that documentation explaining why many of these ingredients had been placed on Schedule F either could not be located or did not exist. Compliance with the Schedule F factors is lacking for many of these ingredients. For example, for oil of apiol, deanol and its salts and derivatives, and theobromine and its salts, the recent Health Canada science review confirmed that "none of the factors for listing on Schedule F were found to apply."

The proposed regulatory amendments were put forward in three groupings.

Project 1577 reviewed the application of Schedule F factors to oil of apiol, deanol and its salts and derivatives, theobromine and its salts, and *Centella asiatica* extract and its active principles. The review of available science revealed that none of the criteria for Schedule F listing applied to any of these four ingredients, and it was therefore recommended that they be removed completely from Schedule F. The Health Canada committee made the following comments to support its recommendations.

1. Oil of apiol: A wide margin of safety exists between the therapeutic and toxic doses. The common presence of apiol oil in foods (essential oils of parsley seed, dill seed, fennel seed, sassafras root bark, and other plant species) indicates a lack of toxicity at doses likely to be found in herbal medicines.

2. *Centella asiatica* extract and active principles thereof (derived from gotu kola): There is a wide margin of safety between therapeutic and toxic doses. These substances pose a low risk of undesirable or severe side effects.

3. Deanol (and its salts and derivatives), also known as dimethylaminoethanol or DMAE, is a naturally sourced chemical found in salmon roe, shellfish, and fish oils. Available scientific literature indicates that deanol does not have a narrow margin of safety between therapeutic and toxic doses.

4. Theobromine (and its salts) is a naturally occurring chemical substance found in cocoa and chocolate. Toxicity from theobromine is very rare and is only seen at very high doses in humans. It does not pose a high level of risk relative to expected benefits.

The "Regulations Amending the Food and Drug Regulations (1577 — Schedule F)" can be viewed at the *Canada Gazette* website.

Project 1651 reviewed the available evidence for dopamine and its salts, gold and its salts, and uracil and its salts, and the need to retain prescription status via Schedule F. The committee concluded that nonprescription status should be allowed for all strengths, doses, dosage forms, and uses that do not meet the factors for listing on Schedule F. The following recommendations and supporting statements were made.

1. Dopamine and its salts: Prescription status will be retained for dopamine and its salts when sold for administration by injection. All other dosage forms and routes of administration at any

strength and for any use are exempt from prescription status. Dopamine is inactive in the body when administered orally; however, allowing OTC use for oral administration will mitigate issues that arise with ingredients that might naturally contain trace amounts of dopamine.

2. Gold and its salts: Prescription status will be retained for gold and its salts when sold for administration by injection; any other dosage form or route of administration at any strength and or any use are exempt from prescription status. This revision to Schedule F will avoid unintentionally subjecting products containing trace amounts of gold to prescription requirements when it is not necessary.
3. Uracil and its salts: Prescription status will be retained for uracil and its salts when sold for the treatment of cancer; all other uses at any strength, dosage form, or route of administration are exempt from prescription status. Uracil is found in all living organisms, so listing in Schedule F without qualifiers in inappropriate.
4. Lovastatin was initially included in this proposal but was removed based upon information submitted during the initial consultation. The review of lovastatin will now proceed separately as Project 1668. It was originally proposed that the listing for lovastatin would be revised to retain prescription status for all strengths and dosage forms except when lovastatin was sold in an oral dosage form that provides less than 1.0 mg per dosage unit or per daily dose. Oral dosage forms containing less than 1.0 mg of lovastatin would be exempt from prescription status. The proposed exemption for less than 1.0 mg is only 10 percent of the lowest therapeutic dose of 10 mg of lovastatin. This would allow red yeast rice products containing only trace amounts of lovastatin to be marketed as natural health products in Canada. Red yeast rice is derived from yeast grown on rice and is used as food in some Asian countries. It contains several substances, including lovastatin, known to reduce cholesterol.

The "Regulations Amending the Food and Drug Regulations (1651 — Schedule F)" can be viewed at the *Canada Gazette* website.

Project 1656 dealt with the science surrounding dimethyl sulfoxide, levocarnitine and its salts and derivatives, and L-tryptophan, when

Status Summary of Naturally Sourced Ingredients

MI = medical ingredient; NMI = non-medical ingredient

Ingredient	Regulatory Jurisdiction			
	Canada	**United States**	**Australia**	**United Kingdom**
Oil of apiol	Non Prescription	Non Prescription	Non Prescription	Prescription MI
Deanol (its salts and derivatives)	Non Prescription	Non Prescription	Prescription MI	Non Prescription
Theobromine (and its salts)	Non Prescription	Non Prescription	Non Prescription	Non Prescription
Centella asiatica extract and active principles thereof	Non Prescription	Non Prescription	Non Prescription	Non Prescription
Dopamine (and its salts)	Prescription only when sold for administration by injection	Prescription MI	Prescription MI	Prescription MI
Gold (and its salts)	Prescription only when sold for administration by injection	Dietary Supplement Use	NMI use in prescription and non-prescription drugs	Not listed as a medicine (prescription, pharmacy, or general sale)
Uracil (and its salts)	Prescription only when sold for the treatment of cancer	No approved drugs containing uracil	Prescription MI	Not listed as a medicine (prescription, pharmacy, or general sale)
Dimethyl sulfoxide	Prescription status only when sold for veterinary use or when sold for the treatment of interstitial cystitis or scleroderma in humans	Prescription MI	Prescription MI	Prescription MI
Levocarnitine (and its salts and derivatives)	Prescription status only when sold for the treatment of primary or secondary levocarnitine deficiency	Prescription MI with exemptions for non-prescription use	Prescription MI with exemptions for non-prescription use	Prescription MI with exemptions for non-prescription use
L-tryptophan (when sold as a single ingredient)	Prescription status when sold (a) for human use in oral dosage form at a concentration of more than 220 mg per dosage unit or per daily dose, as a single ingredient or in combination with other ingredients; or (b) for human or veterinary use as a single ingredient intended for any route of administration other than oral	Limited approval for use as a nutrient (dietary supplement)	Available as a prescription MI in preparations labeled with a recommended daily dose of 100 mg or less	Prescription MI with exemptions for dietary supplementation and external use

sold as a single ingredient, and the need to control their availability through prescription status. The following recommendations and comments were made.

1. Dimethyl sulfoxide: Prescription status is to be retained for veterinary use or when sold for the treatment of interstitial cystitis or scleroderma in humans. All other human uses at any strength, and in any dosage form are exempt from prescription status.
2. Levocarnitine and its salts and derivatives: Prescription status will be retained when it is sold for the treatment of primary or secondary levocarnitine deficiency; all other uses, strengths, dosage forms, and routes of administration are exempt from prescription status.
3. L-tryptophan: Prescription status will be retained for when it is sold (a) for human use in oral dosage form at a concentration of more than 220 mg per dosage unit or per daily dose, as a single ingredient or in combination with other ingredients; or (b) for human or veterinary use as a single ingredient intended for any route of administration other than oral.

The "Regulations Amending the Food and Drug Regulations (1656 — Schedule F)" can be viewed at the *Canada Gazette* website.

In general, comments received from stakeholders during the initial consultations, although limited, were supportive of the proposed amendments. The one exception was a lack of support from two respondents for the revision to the listing for lovastatin. Lovastatin is currently widely available in Canada as a prescription drug for the treatment of high cholesterol. However, work on this proposal is continuing, and a revised proposal is expected in the near future. Stakeholders supported all other recommendations for the 10 other ingredients discussed above, and regulatory amendments to that effect came into force on Nov. 24, 2011.

Other Regulatory Jurisdictions

Most of the changes made to the status of the 10 ingredients bring their classifications into line with major trading partners such as the United States, Australia, and the United Kingdom (see table, page 3). Where classifications differ, it is important to note that Canada has the authority to evoke additional controls under the Natural Health Products Regulations. Although these ingredients are now allowed for OTC use in natural health products under specific circumstances, the premarket review process for natural health products requires that the safety and efficacy of all medicinal ingredients in each proposed formula must be demonstrated to Health Canada's standards with human clinical evidence. Where potential safety concerns exist, they could be mitigated through the use of lower dosages, specified durations of use, target populations, and/or cautions, warnings, and contraindications on the product label. Natural health products are only issued a license by Health Canada once safety, efficacy, and quality are confirmed.

These amendments are a positive step forward in providing suppliers with new options for product formulation and increasing the availability of products to consumers. However, it remains to be seen how many will appear in product formulations in the coming years.

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