Health Canada Santé Canada

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Provincial and Territorial Deputy Ministers of Health
Provincial and Territorial Drug Program Managers
Deans of Pharmacy
Registrars of Provincial Medical and Pharmacy Associations
Industry and Consumer Associations
Regulatory and Health Professional Associations
Other Interested Parties

Dear Sir/Madam:

Re: *Food and Drug Regulations* - Project # 1508 - Schedule F

The purpose of this letter is to provide an opportunity to comment on the proposed addition of one medicinal ingredient to Part I of Schedule F to the *Food and Drug Regulations*.

Schedule F is a list of medicinal ingredients, the sale of which is controlled under sections C.01.041 to C.01.049 of the *Food and Drug Regulations*. Part I of Schedule F lists ingredients that require a prescription for human use and for veterinary use. Part II of Schedule F lists ingredients that require a prescription for human use, but do not require a prescription for veterinary use if so labelled or if in a form unsuitable for human use.

The Drug Schedule Status Committee determines the necessity for prescription status for medicinal ingredients on the basis of established and publicly available criteria. These criteria include, but are not limited to, concerns related to toxicity, pharmacological properties and therapeutic uses of the ingredients.

Description of the medicinal ingredient:

Nicotinic acid when sold in

a) a modified-release oral dosage form providing 500 mg or more per dosage unit or per daily dose; or
b) an immediate-release oral dosage form providing more than 500 mg per dosage unit or per daily dose

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Nicotinic acid at these doses acts as a lipid metabolism regulating agent and is used for the treatment of patients with abnormally high levels of cholesterol in the blood. Diagnosis by a practitioner is required to rule out other causes of high blood cholesterol levels and to determine that other treatments have not been effective. Individualized instructions and direct supervision by a practitioner are required because nicotinic acid has been associated with liver toxicity when administered in modified-release formulations. Liver toxicity has also been associated with immediate-release formulations when administered at doses greater than 500 mg.

Modified-release dosage forms are defined in the Health Canada guidance document, ***Guidance for Industry - Conduct and Analysis of Bioavailability and Bioequivalence Studies (Part B: Oral Modified Release Formulations)***, as drug formulations that differ from conventional formulations in the rate at which the drug is released. For the purpose of this guidance, modified release dosage forms include formulations designed to meet one or more of the following objectives:

- To delay disintegration, de-aggregation, or dissolution so that the drug's rate of degradation is altered.
- To delay or decrease the rate of absorption so that the likelihood of gastrointestinal or other adverse effects is diminished (e.g., enteric-coated forms).
- To provide effective drug concentrations for a longer period of time after a single dose.
- To deliver the drug initially at a rate similar to that obtained with the conventional form, and to provide effective drug concentrations for a longer period of time.
- To minimize fluctuations in drug concentrations during the dosing interval.
- To provide, after single administration, multiple peaks and troughs in the serum concentration-time curves similar to those achieved after repeated dosing with the conventional formulation.

The degree of regulatory control afforded by Schedule F (prescription drug) status coincides with the risk factors associated with this medicinal ingredient. Oversight by a practitioner is necessary to ensure that adequate risk/benefit information is available before the drug containing the medicinal ingredient is administered and that the drug therapy is properly monitored.

Alternatives

The initial proposal, as part of Project 1451, included only the extended-release dosage form providing 500 mg or more per dosage unit or per daily dose. In light of comments received during the consultation process, the proposal was reconsidered and has been revised. The following changes have now been incorporated (see Consultation section, below, for details):

- Expanding the amendment to include immediate-release nicotinic acid providing more than 500 mg per dosage unit or per daily dose;
- Adding oral dosage form;
- Replacing the term "extended-release" by "modified-release" for consistency with the terminology used by Health Canada, and
- Removing "its salts and derivatives" from the amendment as the salts and derivatives are not used to treat high blood cholesterol and do not have the same toxicity profile.

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Any alternatives to the degree of regulatory control recommended in this revised proposal would need to be established through additional scientific information.

Benefits and Costs

The amendment would impact on the following sectors:

- **Public**

Prescription access to drug products containing this medicinal ingredient would benefit Canadians by decreasing the opportunities for improper use and by ensuring the guidance and care of a practitioner.

Another benefit is that drug products for human use containing medicinal ingredients listed on Schedule F may be covered by both provincial and private health care plans.

- **Health Insurance Plans**

Drug products for human use containing medicinal ingredients listed on Schedule F may be covered by both provincial and private health care plans.

- **Provincial Health Care Services**

The provinces may incur costs to cover practitioners' fees for services. However, the guidance and care provided by the practitioners would reduce the need for health care services that may result from improper use of drug products for human use that contain medicinal ingredients listed on Schedule F. The overall additional costs for health care services should therefore be minimal.

Compliance and Enforcement

This amendment would not alter existing compliance mechanisms under the provisions of the *Food and Drugs Act* and *Food and Drug Regulations* enforced by the Health Products and Food Branch Inspectorate.

Consultation

As noted above, the proposal to add nicotinic acid to Schedule F was initially part of Project 1451, which included proposals for two other medicinal ingredients. A direct notice of Project 1451 was provided to stakeholders on May 18, 2005 with a 75-day comment period.

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The proposed wording for nicotinic acid in Project 1451 was, “Nicotinic acid and its salts and its derivatives in an extended release formulation providing 500 mg or more per dosage form or per daily dose”. Comments were received from four stakeholders. One respondent expressed support for the proposed amendment. However, three respondents raised questions about the proposed listing for nicotinic acid. No concerns were expressed regarding the proposed listings for the other two medicinal ingredients. Consequently, the nicotinic acid proposal was removed from Project 1451, and is proceeding as this separate amendment.

The proposed wording of the Schedule F listing for nicotinic acid has been revised following further consideration by the Drug Status Scheduling Committee in response to the comments received from the Project 1451 consultation. These comments are summarized below with Health Canada’s responses:

1. One respondent requested that the proposed Schedule F listing be revised to include nicotinic acid in an immediate-release oral dosage form providing 500 mg or more per dosage unit or per daily dose. The respondent cited information indicating that immediate-release nicotinic acid 500 mg is associated with adverse effects.

Response

- The proposed amendment has been revised to include immediate-release nicotinic acid at doses **greater than 500 mg**.
- While immediate-release nicotinic acid in doses of 500 mg or less has been associated with adverse or undesirable effects such as flushing, dizziness, increased heart rate and shortness of breath, these effects are not immediately life threatening and are reversible on discontinuation of treatment.
- A review of reports from the Canadian Adverse Drug Reaction Monitoring Program database revealed that, between 1965 and 2006, none of the adverse events reported by patients taking immediate-release nicotinic acid at 500 mg were associated with symptoms of liver toxicity or other serious adverse drug reactions. Adverse events that are not considered to be serious adverse drug reactions could be managed by appropriate label information.
- The *Food and Drug Regulations* define a serious adverse drug reaction as a “noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death”.

2. One respondent expressed concerns that listing nicotinic acid on Schedule F would restrict the ability of naturopaths to treat patients with nicotinic acid.

Response

- The recommendation to add nicotinic acid to Schedule F is based on evidence of liver toxicity. Nonprescription status is not appropriate for these formulations and strengths of nicotinic acid as it means that they would be available to the general public without the intervention of a practitioner.
- The *Food and Drug Regulations* define practitioner as "a person authorized by the law of a province of Canada to treat patients with any drug listed or described in SCHEDULE F to the Regulations". Issues concerning the licensing and regulation of naturopaths as practitioners should be directed to the appropriate provincial/territorial jurisdiction.

3. One respondent questioned why the new dosage form of nicotinic acid is being proposed for addition to Schedule F and whether there are plans to add other nicotinic acid products to Schedule F.

Response

- Nicotinic acid is being proposed for addition to Schedule F based on information that these strengths and dosage forms are associated with liver toxicity.
- Immediate-release oral dosage forms providing more than 500 mg per dosage unit or per daily dose have been added to the revised proposal.

The process for this consultation with stakeholders is described in the Memorandum of Understanding (MOU) to streamline regulatory amendments to Schedule F, which came into effect on February 22, 2005. The MOU is posted on the Health Canada website.

This letter is being sent by email to stakeholders and is also being posted on the Health Canada website and the *Consulting With Canadians* website.

Any comments regarding this proposed amendment should be addressed as follows within **75** days following the date of posting of this letter on the Health Canada website. The policy analyst for this project, Karen Ash, may be contacted at:

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Final Approval

In accordance with the MOU process, it is anticipated that this amendment will proceed directly from this consultation to consideration for final approval by the Governor in Council, approximately 6 to 8 months from the date of posting of this letter on the Health Canada website. If approved by the Governor in Council, publication in the *Canada Gazette*, Part II, would follow. The amendment would come into force on the date of registration.

Yours sincerely,

Original signed by

Neil Yeates
Assistant Deputy Minister