Health Canada Santé Canada

Therapeutic Products Directorate
Holland Cross, Tower "B"
6th Floor, 1600 Scott Street
Address Locator # 3106B
OTTAWA, Ontario
K1A 0K9

07-114042-470

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

Dear Madam/Sir:

Re: Proposed amendment to the *Food and Drug Regulations*, Project No. 1470, Non-medicinal Ingredients in drug product formulation

This provides you with an opportunity to comment on the Health Products and Food Branch's (HPFB) proposal, Project 1470, to amend the *Food and Drug Regulations* (Regulations) to require the submission of full formulation data for drug products regulated solely by Division 1. This would include both prescription and non-prescription drug products for human and veterinary use. Currently, the formulation requirements in the *Food and Drug Regulations* are limited to "active" or medicinal ingredients, and non-medicinal ingredients (NMIs) that are used in drug products as colouring agents or preservatives. The proposed regulatory requirement is anticipated to enhance Health Canada's ability to respond to circumstances of health safety concern in a timely and efficient manner.

Strategy

Several sources of potential risk may be associated with drug products of unknown formulation, including: 1) animal & human-sourced materials, e.g., material sourced from Bovine Spongiform Encephalopathy(BSE); 2) NMIs or excipients, with a potential to aggravate allergies and sensitivities to individuals; and 3) substances that may result in toxicity.

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Health Canada administers the *Food and Drug Regulations* as an important instrument to manage the risks of drug products and their ingredients. For drugs that must comply with the New Drug Regulations of Division 8, a requirement exists to supply full formulation information including medicinal and non-medicinal ingredients (NMIs) as well as any changes to formulations throughout the life cycle of the drug. In contrast, Division 1 requires only that sponsors supply information on medicinal ingredients and NMIs related to colouring agents and preservatives. Furthermore, under Division 1 drug sponsors may change their drug product formulation with respect to NMIs, that are not colouring agents or preservatives, without notifying Health Canada.

For Health Canada to properly assess the potential risk to the health of Canadians it requires knowledge of all ingredients present in all drug products regardless of the regulatory division that applies to that particular product.

Pre-Market DIN [1] Submission

For new DIN submissions regulated under Division 1, drug manufacturers would be required to provide, in addition to medicinal ingredients and NMIs used as colouring agents and preservatives, the name and quantity for all other NMIs used in the formulation of the drug product.

Post-Market Changes to Division 1 DINs

For drug products already marketed in Canada, formulation information would be collected through the DIN annual notification process.

Drug product manufacturers would be required to submit formulation information for drug products solely regulated by Division 1, as well as any updates, changes or revisions to the formulation of drug products already marketed in Canada. Health Canada will not be requiring sponsors of drug products who have already complied with the 2004 and subsequent voluntary requests, to resubmit the formulation information, except in circumstances of updates or revisions to the previously submitted information.

Furthermore, it is proposed that changes to formulation that are related to NMIs be treated as 30-day notifications similar to the treatment of changes to colouring ingredients, which may not necessarily involve the process of filing a new DIN application as per C.01.014.4 (b) of the *Food and Drug Regulations*.

A one year transition period is proposed for drug manufacturers to submit formulation data in accordance with revised requirements for currently marketed drug products.

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1 DIN: Drug Identification Number.

Current formulation provisions in the Food and Drug Regulations

The drug product formulation requirements for Division 1 include:

- a list of medicinal ingredients required by section C.01.014.1.(2)(e):a quantitative list of the medicinal ingredients contained in the drug by their proper names or, if they have no proper names, by their common names;

- those NMIs that serve as colouring agents under section C.01.014.1.(2)(h): the name and quantity of each colouring ingredient that is not a medicinal ingredient;

- those NMIs that serve as preservatives under section C.01.004(2) (b)& (c): ...a quantitative list of any preservatives present therein by their proper names [...] & ...mercury or a salt or derivative thereof as a preservative [...]

Proposed changes to the Food and Drug Regulations

The scope of the proposed regulatory amendment is tailored to drug products that are solely regulated by Part C, Division 1 of the *Food and Drug Regulations*, for human and veterinary use.

This amendment will require the submission of complete quantitative and qualitative formulation information for drug products, including all medicinal and non-medicinal ingredients used in formulation.

Options Considered

Option #1: Status quo

Health Canada would continue to collect NMI formulation data on voluntary basis.

Option #1 is not recommended as the voluntary approach has met with varied success and Health Canada is limited in its ability to enforce compliance of this request.

Option #2: Discontinue Current Voluntary Formulation Request

Health Canada would no longer ask sponsors to voluntarily provide formulation information.

Option #2 was not recommended as it does not meet Health Canada's needs to possess full and current formulation data available for even a reduced sub-set of the existing DIN products.

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Option #3: Use Division 2 to request NMI formulation data

Sponsors could be required to comply with Division 2 of the *Food and Drug Regulations* that apply to Good Manufacturing Practices (GMPs) to supply complete formulation data.

Option #3 was not recommended as it would entail a necessarily broad and perhaps confusing, interpretation of Division 2. It would not build on the processes already in place as a result of the voluntary requests in 2004 and subsequent DIN Updates in the Annual Notification Process.

Option #4: Request NMI formulation data through regulatory amendment to Division 1 (Recommended)

Amend the requirement under Division 1 of the *Food and Drug Regulations* to require the submission of complete qualitative and quantitative formulation data, including a list of all NMIs in a drug product, as well as the source of any human or animal derived NMIs or medicinal ingredients. This requirement would apply to all new DIN applications and drug products for which a DIN has previously been issued.

Option #4 is the recommended approach as it is expected to provide Health Canada with the information required to make NMI safety assessments and allow for enforcement of compliance when necessary. It also builds on the voluntary reporting process that has been in place since 2004.

Benefits and Costs

The amendment is expected to impact the following sectors:

Health Canada

Health Canada will have access to full formulation information on all drug products marketed in Canada. This information would be easily accessible and readily available to Health Canada should a situation of health safety concern or emergency emerge. This approach is consistent with Health Canada's mandate in protecting the health and safety of Canadians. Additionally, when full formulation data pertaining to a drug product is available, Health Canada is better positioned to assess the status of NMIs and their potential risk to health.

Investments may need to be undertaken by Health Canada in technology upgrades, training and human resources.

Industry

The proposed regulatory amendment is expected to positively influence drug review and approval processes, in that it could increase reviewers access to formulation information, and ensure that safety requirements for drug products solely regulated by Division 1 are subject to comprehensive assessment standards and are based on quality data.

The financial impact on industry is not anticipated to be major, since drug sponsors are currently required to keep written specification on marketed drug products in conformity with GMP provisions of Division 2 in the *Food and Drug Regulations*. Moreover, drug sponsors have already submitted information for almost 50% (12,193 DINs) of drug products marketed in Canada following Health Canada's Submission and Information Policy Division (SIPD) annual voluntary request. Therefore, following the implementation of the regulatory amendment, the cost of submitting information on all NMIs used in drug products solely regulated by Division 1, is expected to be similar to the current cost incurred by industry for submitting formulation information through the voluntary request. Finally, drug sponsors who have already complied with the voluntary request will not be required to resubmit the formulation information, except in circumstances of updates or revisions for the previously submitted information.

Federal government

There would be minimal increases in government costs to ensure compliance.

Compliance and Enforcement

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

Consultation

This issue has been consulted upon broadly within Health Canada, receiving ongoing input from the Drug Product Formulation Working Group.

Industry Associations have been made aware of this proposed regulatory amendment through the Therapeutic Product Directorate's Bilateral Meeting Program. Furthermore, the broader range of external stakeholders are being consulted through this early consultation letter.

Additionally, drug manufacturers have been requested to submit formulation information voluntarily since 2004 as part of the annual DIN notification mail out. The 2007 DIN annual notification mail-out also advised drug manufacturers of the regulatory amendment in question.

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This letter is being sent by email to stakeholders, and is also being posted on the Health Canada website at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/legislation/acts-lois/notice-avis/index_e.html and the Consulting With Canadians website at http://www.consultingcanadians.gc.ca/ cpcPubDepartments.jsp?DeptID=73&lang=en&Type=current.

Any comments regarding this proposed amendment should be addressed as follows within **60** days following the date of posting of this letter on the Health Canada website.

Project No. 1470
Policy Division
Bureau of Policy, Science and International Programs (BPSIP)
Therapeutic Products Directorate (TPD)
Holland Cross, Tower B
2nd Floor, 1600 Scott Street
Address Locator 3102C5
Ottawa ON K1A 0K9
Telephone: (613) 948-4623 (refer to Project No. 1470)
Facsimile: (613) 941-6458 (refer to Project No. 1470)
Email: regaff_access@hc-sc.gc.ca

Yours sincerely,

Original signed by

Supriya Sharma
Acting Director General