Health Canada Santé Canada

Notifying Health Canada of Foreign Actions

Guidance Document for Industry

Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

Également disponible en français sous le titre :
Aviser Santé Canada des mesures prises dans les pays étrangers - Document d'orientation à l'intention de l'industrie

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Publication date: Month 2018

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Cat.: H164-250/2018E-PDF
ISBN: 978-0-660-28427-9
Pub.: 180564

Forward

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. These alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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1 Introduction

1.1 Purpose

The purpose of this guidance document is to provide manufacturers, importers and other holders of instruments of market authorization (Drug Identification Numbers (DIN) and Notices of Compliance (NOC)) under the *Food and Drug Regulations* (http://laws.justice.gc.ca/eng/regulations/c.r.c.,_c._870/index.html), with information that may be useful in achieving compliance with the regulatory requirements of notification to Health Canada of foreign regulatory actions as outlined in sections C.01.050 (2)(a), (b) and (c) and C.01.050 (3) of the *Food and Drug Regulations* (http://laws.justice.gc.ca/eng/regulations/c.r.c.,_c._870/index.html).

These foreign notification provisions are intended to improve the collection and assessment of new relevant safety information related to any serious risk of injury to human health involving regulatory issues in foreign countries, which will help determine an appropriate response in Canada to these issues. As many drugs may be marketed years in advance or in higher volume in other countries, important safety signals may be detected earlier in a foreign jurisdiction.

The intended outcome is that the Minister will have early knowledge of regulatory actions that are taken in foreign jurisdictions to mitigate serious risks of injury to human health. This will allow Health Canada to better identify and assess risks to Canadians and to take appropriate action to mitigate those risks when warranted.

Health Canada may follow up to seek further information as necessary.

1.2 Background

This regulation seeks to operationalize aspects of the safety provisions of the *Protecting Canadians from Unsafe Drugs Act* (also known as Vanessa's Law) regarding the notification to Health Canada of foreign regulatory actions, which received Royal Assent on November 6, 2014. The regulations to which this guideline applies were published in *Canada Gazette Part II* on May 2, 2018. This guideline was prepared with input received from stakeholders during and after the *Canada Gazette Part I* consultation.

1.3 Scope and Application

Adopting a risk-based approach, the requirement to notify Health Canada of foreign regulatory action applies to the following three classes of drugs:

- prescription drugs;
- drugs that are required to be sold under a prescription by Part G, the *Benzodiazepines and Other Targeted Substances Regulations* or the *Narcotic Control Act;* and
- drugs that are permitted to be sold without a prescription but that are administered only under the supervision of a practitioner.

The requirement applies only to products to which a Drug Identification Number (C.01.014.2 (1)) or notice of compliance (C.08.004 or C.08.004.01) has been assigned. Products without market authorization (e.g. still under review) are not included.

These provisions would apply not only to human drugs, but also to a veterinary drug if a foreign action were to involve a serious risk of injury to human health.

2. Interpretation

2.1 What kinds of foreign actions require authorization holders to notify Health Canada?

The holder of a market authorization (made through the assignment of a DIN or issuance of a NOC) must provide the Minister with information in respect of any serious risk of injury to health of which the holder becomes aware, that is relevant to the safety of the drug in Canada, and that is associated with certain specific actions taken in any one of the specified foreign jurisdictions. Where the Market Authorization Holder (MAH) becomes aware of more than one similar action, notification must be made of the earliest action. If a foreign Good Manufacturing Practices (GMP) issue affects a Canadian product, it is relevant. For safety/toxicity issues, all actions related to similar ingredients or molecules must be reported.

Examples include, but are not limited to:

- A manufacturing issue that pose a serious risk of injury to human health and that is communicated by one of the specified foreign regulatory authorities or a manufacturer within those jurisdictions (C.01.050(2)(a));
- serious risks related to a new contraindication or warning, that is communicated by one of the specified foreign regulatory authorities or a manufacturer within those jurisdictions (C.01.050(2)(a));
- changes that have been made to the labelling that have been communicated to or requested by one of the specified regulatory authorities in respect of serious risk (C.01.050(2)(b)) (e.g. new dosages, indications, directions for use, warning statements, contraindications, improved clarity to mitigate incorrect use);
- recalls in respect of serious risk, conducted within one of the specified foreign regulatory jurisdictions (C.01.050(2)(c));
- reassessments of market authorizations, which resulted in new or additional risk mitigation measures for a drug or the addition of enhanced vigilance requirements (e.g. changes to Risk Management Plans or Risk Evaluation and Mitigation Strategies), within one of the specified foreign regulatory jurisdictions, in respect of serious risk (C.01.050(2)(c));
- the suspension or revocation of manufacturing authorizations (e.g. site licences) within one of the specified foreign regulatory jurisdictions (C.01.050(2)(c)), in respect of serious risk; and
- the suspension or revocation of market authorizations (e.g. permission to sell) within one of the specified foreign regulatory jurisdictions (C.01.050(2)(c)) in respect of serious risk.

This information is required to be provided to the Minister, preferably without delay, within 72 hours of the MAH receiving it or becoming aware of it so as to allow the Minister to determine if similar risks exist for those drugs in Canada and which action(s) would be required to mitigate these risks.

While Health Canada appreciates hearing about serious emerging safety issues for which foreign or domestic action is likely to occur and which are relevant to Canadian products, the regulatory requirements in subsections C.01.050(2)(b) and (c) only apply to actions that have taken place, not actions that are being contemplated.

If after notifying Health Canada of a relevant action in one country a similar action is taken in one or more other countries to address the same issue involving the same safety information, it is not necessary under this regulation for the MAH to notify Health Canada of these subsequent actions. One notification is sufficient. Examples of actions that are not similar include a situation where if in one jurisdiction a warning is added to a label and in another jurisdiction a public advisory is issued instead to address the same issue; these are considered different actions for the purpose of these regulations and both must be reported. Another example of different actions would be where in one jurisdiction a recall was issued to the wholesale level and, in another, to the retail level.

If the foreign actions are relevant to a product authorized for sale in Canada, a range of issues could possibly trigger the requirement to provide information to Health Canada.

2.1.1 Quality-related issues examples:

- A recall of a prescription drug is conducted in the United States due to a reasonable probability that the use of, or exposure to, the drug would cause serious adverse health consequences or death (i.e. a Type I recall).

- A recall of a non-prescription drug that is administered under the supervision of practitioners is conducted in Australia as the product was causing a temporary adverse health consequence in a vulnerable subpopulation.
- The Health Products Regulatory Authority in Ireland issues a safety notice indicating a contravention in GMP in the manufacturing of a prescription drug that increases the probability, nature or frequency of a serious adverse health consequence.
- The Medicines and Healthcare Products Regulatory Agency of the United Kingdom suspends a manufacturer licence for a non-prescription drug that is administered under the supervision of practitioners due to finding of a critical deficiency in GMP that poses the risk of a serious injury to health.

2.1.2 Other safety-related issues examples:

- A public warning is issued by Australian Therapeutic Goods Administration (TGA) concerning a prescription drug when it is discovered that a serious new safety concern exists when the drug is used in combination with certain foods.
- The label of a generic pain medication marketed in the United States has been changed to include warnings regarding use in children under the age of 12, relating to serious health effects.
- The license of an anticoagulant is revoked in the European Union (EU) when a rare but serious adverse reaction is discovered after many years on the market.
- A public safety communication has been issued regarding serious human health risks associated with accidental self-injection of a product while administering to an animal.
- An update of the Warnings section of a veterinary drug label has been made to mitigate serious human health risks while administering a topical product to animals.
- Marketing is suspended in France pending a safety assessment to establish the risk profile of a drug with a narrow safety range, in the context of rapidly increasing off-label use.

2.1.3 Which foreign regulatory authorities are encompassed by the requirements?

A three-part list of foreign regulatory authorities (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/foreign-actions-profile/guidance-document/list-regulatory-authorities-section-c01050-fdr.html) maintained by Health Canada has been incorporated by reference in the *Food and Drug Regulations* (http://laws.justice.gc.ca/eng/regulations/c.r.c.,_c._870/index.html).

While Health Canada appreciates hearing about actions taken in other jurisdictions to address serious risks, the regulatory requirement only applies to those countries that appear in the reference list. For a discussion of monitoring, see 2.7 below.

2.2 Key elements for consideration about serious risk

The regulations require a MAH to notify Health Canada about certain actions taken and information communicated (see 2.1) by foreign regulatory authorities ”in respect of a serious risk of injury to human health”. For a discussion of “serious risk” please refer to Annex A to *Amendments to the Food and Drugs Act: Guide to New Authorities* (https://www.canada.ca/en/health-canada/services/drugs-health-products/legislation-guidelines/amendments-food-drugs-act-guide-new-authorities-power-require-disclose-information-power-order-label-change-power-order-recall.html#a13).

Consequently, the MAH must determine if the risk meets this threshold. This determination should be made by, or in consultation with a person with sufficient medical knowledge, qualified by pertinent training or experience. For further clarification regarding personnel and training, please refer to Canada’s *Good Pharmacovigilance Practices (GVP) Guidelines (GUI-0102)* (https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/pharmacovigilance-guidelines-0102.html).

This non-exhaustive list of elements should be considered together as the starting point for making a determination of serious risk:

a The seriousness of the adverse health consequence. A serious adverse health consequence includes any untoward occurrence that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. This element should be given the most weight when making a determination of serious risk.
b A change in the nature or frequency of a serious adverse health consequence posed by the drug.
c The probability of the serious adverse health consequence upon exposure to the drug.
d The vulnerability of the patient population and/or sub-population that are exposed to the particular drug. Vulnerable populations may include, but are not limited to: children, the elderly, pregnant and lactating women, and immunocompromised patients.
e The extent of the population's exposure to the drug and the potential public health impact of the exposure.

If there is uncertainty over whether or not the seriousness of the risk meets the threshold for information sharing, it is a prudent practice to notify Health Canada of the issue.

2.3 What kind of information needs to be included?

In order to comply with the regulations it is expected that MAHs provide the following information, as applicable:

- The name and contact information of the Canadian MAH and importer;
- The brand name and manufacturer of the foreign product ;
- The brand name and DIN(s) of the relevant Canadian product(s);
- Relevant lot number(s) and expiration date(s), if known;
- The foreign regulatory authority that took the action and/ or the foreign jurisdiction in which the action occurred;
- The action taken by the foreign regulatory authority or the action taken by the company in the foreign jurisdiction;
- The foreign site where the issue arose (if different from the manufacturing site);
- The reasons (or information about those reasons) for the action (i.e. product quality/GMP vs. product safety/adverse reaction/unsafe use);
- A description of how that the issue that resulted in foreign action is relevant to the safety of product(s) sold in Canada;
- A declaration that the issue related to the action poses a serious risk to human health (see 2.2); and
- Any actions already taken in Canada by the authorization holder in response to the serious safety issue.

It is not necessary to provide original documents (recall notices, risk communications, notification of label change, etc.). However, these may be requested subsequently by Health Canada.

The electronic on-line form (see link below in section 2.4) is designed to prompt and capture the necessary information.

2.4 What is the process for notifying Health Canada of foreign actions?

Reporting will take place on-line using an electronic on-line form provided by Health Canada (https://health.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/foreign-regulatory-actions-safety-risk.html).

2.5 Language of notification reports

Notification reports must be in either English or French. Additional documents (e.g. recall notices, risk communications) relating to the issue are not required by regulation but may be requested by Health Canada and provided, if available, in their existing language.

2.6 Are regulated parties required to monitor foreign regulatory action?

Although there are no specific regulations requiring environmental scanning, MAHs are encouraged to collect safety information in ways that promote compliance with this regulation such as by accelerating communications between themselves and their affiliates operating in the select foreign regions. For example, a MAH could ensure that the local affiliates in the relevant countries are informing their global Head Office of the kind of issues and products referred to in the regulation, and determine the relevance of the actions to products sold in Canada.

Companies who are not affiliated with foreign companies would also be expected to conduct sufficient monitoring to meet the intent of the regulation. The documented process for any MAH could include, e.g.:

- Monitoring of safety issues and adverse events via required pharmacovigilance activities;
- Monitoring information sources from listed authorities for relevant activities (communication of risks, changes to labelling, recalls, etc.);
- Screen for information involving "serious risk of injury to human health";
- Determine relevance to prescription or non-prescription drugs that are administered under the supervision of a practitioner, that are sold in Canada by the MAH.

However it is done, environmental scanning should be conducted systematically and documented in a way that would enable compliance with the regulations. Training records for qualified people should be documented and the process described in a way that would enable self- and regulatory auditing. For additional information on expectations for environmental scanning under the drug regulations, please refer to the *Preparing and Submitting Summary Reports for Marketed Drugs and Natural Health Products - Guidance Document for Industry* (https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/medeffect-canada/preparing-submitting-summary-reports-marketed-drugs-natural-health-products-guidance-industry.html). For guidance on documentation, please refer to Canada's *Good Pharmacovigilance Practices (GVP) Guidelines (GUI-0102)* (https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/pharmacovigilance-guidelines-0102.html).

2.7 How will compliance be monitored and assessed?

The MAH is encouraged to have in place and maintain an auditable process that may be assessed during an inspection. Documentation could include, for example:

- a documented process to receive, assess and report on foreign regulatory actions within the scope of the regulation. This would include relevant quality documents such as Standard Operating Procedures.
- operational records sufficient to enable the regulator to determine compliance (showing information received, assessed, decisions and actions taken, etc.) of the local MAH.

This capacity may be assessed during inspection. As well, compliance with these regulations may also be verified through reconciling incoming reports with information gathered by Health Canada through other means, such as Mutual Recognition Agreements with foreign regulatory authorities or environmental scanning in house. For further guidance on the documentation of auditable processes, please refer to Canada's *Good Pharmacovigilance Practices (GVP) Guidelines (GUI-0102)* (https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/pharmacovigilance-guidelines-0102.html).

The online reporting tool will automatically generate a confirmation of the information submitted, which the MAH may maintain.

2.8 Will submitted information reports be publicly accessible?

Information submitted to Health Canada is subject to the *Privacy Act* (http://laws.justice.gc.ca/eng/acts/P-21/index.html). As these reports are intended to supplement existing regulatory monitoring, documents received and generated under this requirement will be handled and shared according to current transparency provisions relating to the results of safety reviews and establishment licensing decisions. These include:

- Regulatory transparency and openness: https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness.html,
- Safety Reviews: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews.html,
- New Safety Reviews: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/new.html, and the
- *Amendments to the Food and Drugs Act: Guide to New Authorities* (s. 21.1; Power to require and disclose information, etc.): https://www.canada.ca/en/health-canada/services/drugs-health-products/legislation-guidelines/amendments-food-drugs-act-guide-new-authorities-power-require-disclose-information-power-order-label-change-power-order-recall.html#a8