Health Canada Santé Canada

Foreign Risk Notification, Annual Summary Reports, and Issue-related Analysis of Safety and Effectiveness for Medical Devices

Draft Guidance Document

June 2019

Canada

Foreword

Guidance documents are meant to provide assistance on how to comply with governing statutes and regulations. Guidance documents 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. 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 relevant sections of other applicable guidance documents.

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Introduction

Health Canada is proposing regulatory changes to the *Medical Devices Regulations* (MDR) in order to strengthen the lifecycle approach to the regulation of medical devices by increasing post-market surveillance authorities. The proposed regulations were published in *Canada Gazette*, Part I, on June 15, 2019, for a 70-day comment period.

The proposed regulations are as follows:

Regulatory proposals related to the amendments made to the *Food and Drugs Act* as a result of the 2014 *Protecting Canadians from Unsafe Drugs Act* (Vanessa's Law):

- Authority to compel medical device licence holders of Class II-IV devices to conduct an assessment
- Authority to compel medical device licence holders of Class II-IV devices to compile information, conduct tests or studies or monitor experience
- New requirement for manufacturers and importers of Class II-IV devices to notify Health Canada of foreign risk communications, label changes, recalls, etc.

Regulatory proposals on monitoring and surveillance:

- Requirement for medical device licence holders of Class II-IV devices to prepare annual summary reports & notify when there are changes in the risks and/or benefits associated with the medical device
- Requirement for manufacturers of Class I devices and medical device licence holders of Class II-IV devices to provide analytical reports upon request

The information contained in this document is intended to be read alongside the proposed regulations in order for medical device manufacturers and other stakeholders to view how Health Canada intends to interpret and apply the proposed regulations. Health Canada will consider the comments made by stakeholders on both the proposed regulations and the draft guidance. Revised final guidance will be published on the Government of Canada website once the final regulations appear in *Canada Gazette*, Part II. This draft guidance document may be separated into three final guidance documents.

Consultation on the draft guidance

Any comments on the draft guidance should be sent to Health Canada by August 26, 2019.

Comments should be sent to:

Office of Policy, Risk Advisory and Advertising
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Address Locator 1912C
Ottawa, Ontario
K1A 0K9

Email: MHPD-DPSC.VL-LV@hc-sc.gc.ca

Definitions

Importer: A person, other than the manufacturer of a device, who brings a medical device into Canada for sale.

Manufacturer: As is defined in the *Medical Devices Regulations*, this term means a person who sells a medical device under their own name, or under a trade mark, design, trade name or other name or mark owned or controlled by the person, and who is responsible for designing, manufacturing, assembling, processing, labelling, packaging, refurbishing or modifying the device, or for assigning it to a purpose, whether those tasks are performed by that person or on their behalf.

Revocation: An action taken by an authority to cancel or indeterminately suspend an authorization for the purposes of mitigating or eliminating a serious deterioration in the state of human health.

Foreign Risk Notification (Sections 61.2 and 61.3)

The proposed regulatory requirements outlined in sections 61.2 and 61.3, titled "*Information- Serious Risk of Injury to Human Health*", require a medical device licence holder for a Class II-IV device and a holder of an establishment licence that imports Class II-IV devices to notify Health Canada of certain actions. For ease of reference, these requirements are referred to in this guidance document as 'Foreign Risk Notification.'

The requirements for Foreign Risk Notification are intended to: a) improve the collection and assessment of new relevant safety information in respect of any serious risk of injury to human health in certain foreign countries; and b) help determine an appropriate response in Canada to these issues. Important safety issues are more likely to be detected in markets where medical devices have been sold for a longer time, or at a higher volume. The new requirement to notify Health Canada about foreign risks would replace the requirement for manufacturers and importers of Class II-IV devices to report an incident that occurs outside of Canada via the current section 59 of the MDR (titled Mandatory Problem Reporting).

Please note that for holders of establishment licences for the sale/import of Class I devices, the mandatory problem reporting requirements under the existing section 59 would be superseded by very similar requirements under 59(1.1) of the proposed regulations (titled Incident Reporting – Manufacturers and Importers).

Responsible parties for Foreign Risk Notification

Health Canada is proposing the manufacturer and importer are each responsible for providing Health Canada with information under the Foreign Risk Notification requirements, unless the manufacturer provides the Minister with written authorization to permit the importer to report on its behalf (see section 61.3(1) of the proposed regulations). Manufacturers remain responsible for ensuring that the information in the incident report is both complete and accurate.

Foreign actions that require submission under Foreign Risk Notification requirements

The manufacturer of a medical device licence for a Class II-IV device or an establishment licence holder importing Class II-IV devices must provide the Minister with new information in respect of any serious risk of injury to health of which the manufacturer or importer becomes aware, that:

- involves a medical device that is authorized for sale in Canada;
- is the subject of one or more of the notifiable actions listed below; and
- has occurred in one of the specified countries or jurisdictions (see Appendix A).

With respect to the proposed sections 61.2 and 61.3 of the MDR, a notifiable action is a certain action taken in respect of a medical device related to the safety, quality, effectiveness or performance characteristics, for the purposes of mitigating or eliminating a serious risk to the health of a patient, user, healthcare professional or bystander. The notifiable actions are as follows:

- public risk communication;
- labelling change that has been communicated to, or requested by a relevant foreign regulatory agency;
- recall, including product withdrawal;
- reassessment; and
- suspension or revocation of an authorization.

Relevant Countries and Regulatory Agencies

The requirement for medical device licence holders and importers for Class II-IV devices to notify Health Canada applies only when the notifiable actions are taken by the foreign regulators of certain countries or when the medical device licence holders and importers take notifiable actions in certain foreign countries, with respect to a serious risk

related to a device marketed in Canada. The Proposed List of Regulatory Agencies and applicable foreign countries and jurisdictions for the purposes of section 61.2 of the *Medical Devices Regulations* is provided in Appendix A.

Examples of reportable foreign actions

- A regulatory agency listed in Appendix A has required that a manufacturer conduct a reassessment of a medical device authorized for sale in that country due to the finding of a new or increased serious risk of injury to health related to the use of the device. The device is also authorized for sale in Canada.
- It was identified that the labelling of a medical device authorized for sale in a country listed in Appendix A was misleading, leading to a new or increased serious risk of injury to health. As a result, the regulatory agency in that country has suspended the device authorization until a change to the labelling has been implemented. The device is also authorized for sale in Canada.
- A regulatory agency listed in Appendix A has issued a communication to the public to inform them that patients with certain characteristics should not use a medical device due to the finding of a new or increased serious risk of injury to health. The device is also authorized for sale in Canada.
- A manufacturer has identified a new or increased serious risk of injury to health related to the use of their medical device and, as a result, has withdrawn the product from the market in one or more countries listed in Appendix A. The device is also authorized for sale in Canada.

Examples of non-reportable foreign actions

- A manufacturer of a medical device authorized for sale in a country listed in Appendix A has issued a public communication. The objective of the communication is to inform about a product enhancement that has been implemented for reasons unrelated to mitigation or elimination of a serious risk of injury to health.
- A manufacturer of a medical device authorized for sale in a country listed in Appendix A has received complaints from users of their device, describing that hospitalization has taken place as a result of complications related to the use of their device. The manufacturer has concluded that it is not necessary, or has not been requested by a regulatory agency of country or jurisdiction listed in Appendix A, to undertake any of the "notifiable actions" listed above.

Information to be provided when complying with the requirements under Foreign Risk Notification

In order to comply with the proposed regulations, the medical device licence holders and/or importers for Class II-IV should provide the following information, as applicable:

- The name and contact information of the medical device licence holder and/or importer;
- The brand name and manufacturer of the foreign product;
- The brand name of the relevant Canadian product;
- The Canadian medical device licence number;
- The lot number, if applicable;
- The foreign regulatory agency that took the notifiable action and/or the foreign jurisdiction in which the action was taken;
- A description of the action taken by the foreign regulatory agency or the action taken by the company in the country;
- The reasons (or information about those reasons) for the action, including a description of the serious risk being mitigated and what is known about the root cause;
- A description of any actions being planned and/or already taken in Canada by the manufacturer in response to the serious safety issue;
- If no action has been taken in Canada by the manufacturer in response to the serious safety issue, a rationale to explain why action isn't warranted; and
- Where applicable and available within the given timeline, a reference number to a corresponding corrective action(s) along with supporting material.

It is not necessary to provide original documents that are issued to healthcare professionals or to the public (e.g., recall notices, risk communications, notifications of label change, etc.). However, the required description of the notifiable action taken must be of sufficient detail to allow for an understanding of the information included in any documents that are issued to healthcare professionals or the public. Health Canada may also request these documents subsequent to the receipt of the report from the manufacturer or importer.

Submission timelines under the Foreign Risk Notification requirements

The proposed regulations specify that a Foreign Risk Notification report shall be provided to the Minister within 72 hours of the manufacturer or importer receiving or becoming aware of a notifiable action. The Minister will then be able to confirm that adequate risk mitigation has also been implemented in Canada.

Note that the proposed regulatory requirements would only apply when a foreign action has taken place, not when action is being contemplated.

The process for informing Health Canada of notifiable actions

Health Canada is proposing that reporting take place on-line using an electronic form provided through Canada.ca. The form that is currently being used for Foreign Risk Notification requirements under the *Food and Drugs Regulations* can be viewed as an example.

Language of Foreign Risk Notification reports

Foreign Risk Notification reports must be in either English or French. Additional documents (e.g., recall notices, risk communications) relating to the issue are not required to be submitted but may be requested by Health Canada. Manufacturers and importers must provide the relevant documents in either English or French in the time requested.

Monitoring foreign regulatory actions by regulated parties

There are no specific requirements set out in the *Medical Devices Regulations* in respect of environmental scanning. Manufacturers and importers are encouraged, however, to collect safety information in ways that promote compliance with the proposed requirement to notify Health Canada of notifiable actions. This may include facilitating timely communication between themselves and their counterparts operating in the relevant countries/jurisdictions.

The documented notification monitoring process for manufacturers and importers could include, for example:

- Monitoring of safety issues and adverse effects via established processes;
- Monitoring information sources from listed authorities for relevant actions (communication of risks, changes to labelling, recalls, etc.);
- Scanning for information involving “serious risk of injury to human health”; and
- Determining relevance to devices that are administered under the supervision of a practitioner, that are sold in Canada by the medical device manufacturer.

However it is done, environmental scanning should be conducted systematically and documented in a way that enables compliance with the proposed regulations. Training for qualified people should be documented and the scanning process described in a way that enables self- and regulatory auditing.

Compliance and Monitoring

In order to comply with the requirements of the proposed regulation, the manufacturer and importer should have in place and maintain an auditable process that may be assessed during compliance verification activities. Documentation could include, for example:

- a documented process to receive, assess and report on notifiable actions. This includes relevant quality documents, such as Standard Operating Procedures.
- operational records sufficient to enable the regulator to determine compliance (showing information received and assessed, decisions and actions taken, etc.)

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 done by Health Canada.

In the event that Health Canada identifies instances of more persistent non-compliance, additional compliance and enforcement measures could be taken by the Regulatory Operations and Enforcement Branch in accordance with the risk-based approach detailed in Health Canada's Compliance and Enforcement Policy (POL-0001). In the unlikely event that a situation of non-compliance is not resolved through this approach, Health Canada may use provisions of the *Food and Drugs Act* and its associated regulations, for example seeking an injunction under section 21.5 of the *Act* to compel a manufacturer to comply with the regulations. In determining the appropriateness of exercising enforcement measures, the Department would take into consideration whether the non-compliance of a manufacturer is shown to pose a serious health risk to Canadians, as well as other factors outlined in POL-0001.

Annual Summary Reports (Sections 61.4 and 61.5)

The annual summary report (ASR) is intended to be a comprehensive assessment of all known safety information for a licensed medical device. Sections 61.4 and 61.5 of the proposed regulatory changes to the *Medical Devices Regulations* (MDR) require medical device licence holders to complete ASRs on the safety and effectiveness of their devices.

ASRs are not considered an information-gathering tool. Rather, ASRs are intended to be a standard post-market vigilance tool to contribute to the detection of changes in the benefits and risks of a product. As such, the use of ASRs will help in the early detection of potential safety signals, which will promote better safety and effectiveness for medical devices on the market in Canada.

According to the proposed section 61.4, medical device licence holders are required to prepare the ASRs for Class II-IV devices. An ASR is required for each medical device licence, whether the licence relates to a medical device family, a medical device group, a medical device group family or a single medical device.

ASRs are not required for Class I devices.

Timelines for preparing ASRs

The proposed regulations specify that ASRs must be prepared for a 12-month period. This 12-month period should begin on the date of issuance of the medical device licence. For example, if the licence is issued on December 1, 2019, then the 12-month period for which the ASR would be prepared would be December 1, 2019 to November 30, 2020. For products already licensed, this 12-month period should begin on the anniversary of the issuance of the device licence. For example, if the device was licensed on February 1, 2012, then the 12-month period for which the ASR should be prepared is from February 1 to January 31.

ASRs must be completed annually for each year that the device is licensed. ASRs must be completed within 90 days of the end of the 12-month period.

Contents of an ASR

ASRs prepared by manufacturers should contain the information identified in this guidance.

Health Canada is aware that many manufacturers already gather and analyze the information proposed to be included in an ASR. Given this, different formats are acceptable for the preparation of ASRs. Information in the ASR may vary depending on the data known to the licence holder.

ASRs prepared by licence holders should contain the sections identified below. If a section cannot be completed, this should be noted and justified with reasons, for example, a lack of new information.

Information specific to the Canadian context is considered an important part of the ASR and should be included. However, in order to give the most fulsome view of the risks and benefits of the device, inclusion of information that stems from use of the device outside Canada should also be included when available.

Introduction

The licence holder should identify the device(s) covered under the ASR, including licence number and details on the medical device(s), medical device group(s), medical device family (families), and/or medical device group family (families). The licence holder should also identify the time period for which the ASR is being completed.

Summary of Changes

The licence holder should summarize any changes made to the device (design, labelling, intended use, etc.) since the last ASR was completed or in the last 12 months. The licence holder should also identify any applications for a licence amendment under section 34 of the MDR made to Health Canada or recalls issued in Canada in relation to the device during that time.

Analysis

As identified in the proposed section 61.4(1)(a) to (d), the licence holder must consider the elements below when preparing the critical analysis:

- possible adverse effects associated with the use of the medical device;
- problems related to the performance characteristics or safety of the device, including any complaints received by the manufacturer, importer or distributor after the device was first sold in Canada (e.g., problems referred to in section 57(1)(a) of the MDR);
- incidents relating to a failure of a medical device or a deterioration in its effectiveness, or any inadequacy in its labelling or in its directions for use that has led to the death or a serious deterioration in the state of health of a patient, user or other person or could do so were the incident to recur (e.g., incidents referred to in section 59(1) of the MDR); and
- serious risks of injury to human health that are relevant to the safety of the medical device and that are referred to in the proposed subsection 61.2(2).

Licence holders should consider the above information in light of the number of devices sold or patient exposure (i.e., denominator data to help assess the risk of the device).

In addition, the following types of evidence should also be included in the analysis when they are available to the licence holder:

- clinical evidence updates (the consideration of any new relevant clinical data from published sources, device-related investigations, or ongoing clinical studies);
- information related to effectiveness;
- product- or issue-specific information; and
- publicly-available safety information.

If there is other information that would be helpful to include in order to provide a fulsome picture of what is known about the risks and benefits of the device, then the licence holder should include it.

Conclusion

As per the proposed section 61.4(4), the medical device licence holder must assess the benefits and risks of their device and determine whether a change has occurred compared to what was known during the previous reporting period (or at the time of licensing if there has been no prior ASR for the product). These changes include whether:

- there has been a decrease in any of the benefits of the device;
- the risks are more likely to occur;
- the consequences for patients or users may be more serious, if a risk occurs; or
- a new risk has been identified (e.g., emergent off label uses, risks identified with long-term use).

The licence holder must document their conclusions in the ASR. If none of the above was identified, the licence holder must document this in their conclusion.

When to send an ASR to Health Canada

In accordance with the proposed section 61.4(6), if in preparing the ASR, the licence holder concludes that there has been a change in what is known about the benefits and risks associated with the device, the licence holder must send the ASR to Health Canada. In this situation, the licence holder must inform Health Canada of this conclusion in writing within 72 hours of reaching the conclusion, in accordance with section 61.2(3) of the proposed regulations. The notification must include the most recent completed ASR and a cover letter indicating that the information is being sent to fulfill the reporting requirements in the proposed section 61.4(6).

When not to send an ASR to Health Canada

Licence holders should not send ASRs to Health Canada if they determine that there has been no change in what is known about the benefits and risks associated with the device.

Other possible reporting actions

As a result of the preparation of an ASR, the licence holder may conclude that action is necessary to comply with the MDR. For example, this may include the requirement to:

- submit an application for a medical device licence amendment under section 34 of the MDR for a significant change amendment that could include relevant changes to manufacturing, design, software, labelling, etc.; or
- provide information on or before undertaking a recall of a device as per section 64 of the MDR.

In these situations, the licence holder:

- must submit the necessary information to Health Canada (e.g., in accordance with the existing requirements of MDR section 34 and/or section 64);
- must document in the ASR that this information was submitted as a result of their conclusion(s);

When would the Minister request ASRs

The Minister may, for the purposes of determining whether the medical device meets the applicable requirements of sections 10 to 20 (safety and effectiveness requirements) of the MDR, request one or more of the ASRs from the licence holder, as well as the information used to create them. The Minister may request that the licence holder submit the ASRs to Health Canada within 30 calendar days of the request, unless otherwise specified. For example, the licence holder may be required to submit the ASR in less than 30 days if the information is required on an expedited basis to determine whether the medical device poses a serious and imminent risk to human health.

Retention time for ASRs

As per the proposed regulations, licence holders must retain copies of ASRs for seven (7) years. All ASRs must be maintained by the licence holder on site or be easily accessible. During inspections, licence holders must make the ASRs available to inspectors upon request.

Request for Analysis: Changes to Sections 25 and 39

The existing information-request provisions in the MDR, sections 25 and 39, permit Health Canada to request information or samples to determine whether the medical device meets the applicable safety and effectiveness requirements. The proposed regulations include changes to these sections of the MDR to give the Minister the additional ability to request analysis from manufacturers of Class I devices and medical device licence holders for Class II-IV devices during a post-market safety review for a Class I-IV device.

Health Canada initiates post-market safety reviews when a potential safety issue (i.e., a signal) is identified through various means, such as post-market incident reporting, scientific literature, or information exchanged between foreign regulators, etc. The Minister may request that an analysis be completed by a manufacturer when it is needed as part of the post-market review of safety and effectiveness in response to a signal regarding the device.

For Class I devices, the manufacturer is responsible for completing the analysis and submitting it to Health Canada.

For Class II-IV devices, the medical device licence holder (referred to as the manufacturer in section 39 of the MDR) is responsible for completing the analysis and submitting it to Health Canada.

Information that could be included in an analysis

The Minister expects to receive a concise, critical analysis as specified by the request. A request for analysis could contain, but is not limited to, the following information:

Relevant device incidents

The manufacturer of a Class I device, or the medical device licence holder, should consider all complaints, incidents, or other evidence of adverse effects in its possession that relate to the identified issue. Information specific to the Canadian context is considered essential as part of the analysis. Inclusion of information that stems from use of the device outside Canada should also be included, when available.

Depending on the nature of the issue and the information considered necessary to inform decision-making, the Minister may specify, for example:

- the years for which device complaints and/or incidents should be included;
- jurisdictions that are of interest;
- the requirement to include patient outcomes; and
- whether non-serious events should be considered in addition to serious events.

Exposure data/Sales data

Exposure data or sales data are necessary for inclusion in order to determine reporting rates. Depending on the product, it may be more relevant for the manufacturer of a Class I device or medical device licence holder to include the number of procedures or uses, or how many healthcare facilities have been impacted, if known.

Labelling

Information provided to users related to the identified potential issue should be included, such as the most recent Canadian version of the labelling, including the Instructions for Use, additional warnings or contraindications to maintain safety and effectiveness, and any other materials provided to the user.

Clinical evidence

Any clinical evidence updates should be added, including:

- new relevant clinical data from published sources or device-related investigations;
- clinical study outcomes from completed or ongoing studies, which could include patient specific outcomes;
- pre-clinical safety data;
- clinical studies to support claims;
- pre-clinical test data and analysis to confirm safety; and
- additional clinical results (e.g., long-term follow-up studies, etc.).

Trends of device malfunctions, quality issues and results obtained under various analyses

Any information relating to device malfunction and quality issues should be included. Examples of analysis could include, but are not limited to, root cause analysis, failure modes and effects analysis, and fault tree analysis.

Conclusion

The Class I device manufacturer or medical device licence holder should include their conclusions with regard to the identified issue, while considering how the issue impacts the overall safety and effectiveness of the device and whether mitigation strategies are needed to address any risk(s).

Risk mitigation measures

If the Class I device manufacturer or medical device licence holder concludes that mitigation strategies are necessary, then they should indicate the mitigation strategies that have been taken or that they intend to take. They should also consider any actions taken or planned in response to the problems reported (as referred to in paragraph 57(1)(b) of the MDR, Complaint Handling) and any root causes identified and/or actions taken, or planned, as a result of the investigation of incidents (as referred to in section 61.2 of the MDR, Information – Serious Risk of Injury to Human Health).

Timeframe for submitting an analysis to Health Canada

The request for analysis should specify the timeframe in which the analysis should be submitted to the Minister by the manufacturer (Class I) or the medical device licence holder (Classes II-IV). The default time period for submitting an analysis would be 30 days from the date of the request. However, the Minister could ask for the report in less than 30 days if the information is required on an expedited basis to determine whether the medical device poses a serious and imminent risk to human health.

Compliance

Should a medical device licence holder fail to comply with a request for analysis under section 39 of the MDR, the Minister could suspend the medical device licence for devices from Class II-IV. The Minister could also order a stop sale (under section 25(2)) of Class I devices should a manufacturer not comply with a request for analysis.

Appendix A: Proposed List of Regulatory Agencies for the Purposes of Section 61.2 of the Medical Devices Regulations

Regulatory Agency	**Country / Jurisdiction**
Therapeutic Goods Administration of the Department of Health and Ageing	Australia
National Health Surveillance Agency (ANVISA)	Brazil
United States Food and Drug Administration	United States of America
Pharmaceuticals and Medical Devices Agency and the Ministry of Health, Labour and Welfare	Japan
European Commission Directorate-General for Internal Market, Industry, Entrepreneurship and Small and Medium Enterprises	Europe
Health Sciences Authority	Singapore
Swissmedic	Switzerland
Paul Ehrlich-Institute of Germany	Germany
Agence nationale de sécurité du médicament et des produits de santé	France
Health Products Regulatory Authority	Ireland
National Medical Products Administration	China
Russian Ministry of Health	Russia
Ministry of Food and Drug Safety	South Korea
Medical Products Agency	Sweden
Medicines and Healthcare Products of Regulatory Agency	United Kingdom
Medicines Evaluation Board of the Netherlands and the Dutch Health Care Inspectorate	Netherlands
Medicines and Medical Devices Safety Authority (Medsafe) of the Ministry of Health	New Zealand
Ministry of Health of the United Mexican States	Mexico