Submitted by

Health Canada

FROM: Annette Daley

DATE: June 12, 2008

SUBJECT: Submission to the NL Task Force on Adverse Health Events

Thank you for the opportunity to contribute information to the Task Force that we hope you will find useful in your examination of the management of adverse events in the health system.

Background:
As Canada's federal authority responsible for regulating health products, Health Canada's Health Products and Food Branch (HPFB) evaluates and monitors the safety, quality and effectiveness of the thousands of human and veterinary drugs, vaccines, medical devices, natural health products and other therapeutic products available to Canadians. Within HPFB, post-market surveillance is the responsibility of the Marketed Health Products Directorate (MHPD). With more than 22,000 pharmaceutical products, 42,000 natural health products and 80,000 medical devices on the market, MHPD's creation in 2002 was driven by:

- The need for independent monitoring of health product safety--a distinct function from the pre-market approval process;
- Patients wanting to take more responsibility for their health product decisions;
- The need for more rigorous monitoring of marketed health products as a result of regulatory developments, increased international standardization and cooperation, advances in access to information, and public expectations; and
- The increased potential for adverse reactions and interactions among drugs, health products and food products.

Working collaboratively with other HPFB directorates, MHPD coordinates the monitoring of health products on the market for prompt action when safety risks are identified. It investigates the link between adverse reactions and health products, and determines cause-and-effect relationships. The link between medication incidents and safety concerns with the naming, packaging and labelling of health products are also investigated. Taking the risk tolerance of Canadians into account in its risk management decisions, it then takes appropriate action, ranging from informing the public and health care professionals of new product safety information, to recommending labelling changes or removal of a product from the market altogether.

At this time, we would like to submit three pieces of information

on MHPD's work that we feel may be relevant to the Task Force's investigation:

1. A Health Products and Food Branch (HPFB) working document i) outlining the overall relationship between patient safety related terms from a federal regulator perspective; and ii) clarifying the differences between the terms adverse reaction and medication incident.

(See attached file: Patient Safety Terminology February 2008_v4.doc)

2. Background information on Health Canada's discussions with the provinces and territories on the development of a mandatory adverse reaction reporting requirement for health care institutions for federally regulated health products. Preliminary discussions with all provinces and territories on this issue were completed in May 2008. (See attached file: hospital-based AR reporting bilateral document.pdf)

3. We would also like to provide information about a pilot that is being initiated within our marketed medical device bureau looking at a new pro-active surveillance mechanism to adverse event reporting for devices within health care facilities. This sentinel system approach (soon to be named) would engage a subset of reporters to provide high quality reports of any adverse event encountered with a medical device to Health Canada directly. They, in turn, would be provided feedback which would help them with their quality improvement activities.

(See attached file: Government of NL Task Force on Adverse Health Events. Sentinel project.doc)

MHPD would be happy to provide more information or participate in further discussions with the Task Force on any of these pieces. For additional information on either the patient safety terminology document or on the mandatory reporting issue you can contact Cindy Evans at cindy_evans@hc-sc.gc.ca. For the medical devices pilot project please contact Colleen Turpin at colleen_turpin@hc-sc.gc.ca.

Annette Daley
Regional Director, Atlantic Region / Directrice régionale, Région de L'Atlantique Health Products and Food Branch / Direction générale des produits de santé et des aliments
Tel.: 902-426-2161
Fax: 902-426-7108

Health Canada Santé Canada

Your health and safety… our priority. *Votre santé et votre sécurité… notre priorité.*

MARKETED HEALTH PRODUCTS DIRECTORATE

Patient Safety Terminology*

*This draft document has not been vetted with referenced external organizations

Supersedes:
New Document

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Draft: February 27, 2008

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N/A

Ce document est aussi disponible en français.

Canada

Purpose

A Health Products and Food Branch (HPFB) working document,

1) outlining the overall relationship between patient safety related terms from a Health Canada perspective; and

2) clarifying the differences between the terms adverse reaction and medication incident.

Patient Safety Terms from a Health Canada Perspective

Understanding patient safety key terms is critical as different sources define terms differently resulting in inconsistency and confusion.

As stated by the Royal College of Physicians and Surgeons of Canada (Jan M. Davies, Philip Hébert and Carolyn Hoffman) "If we, as professionals, and as members of society, are to learn from less than optimal events in the health system, then we need to have a common language and understanding of the terms that are central to the enterprise of patient safety."[1]

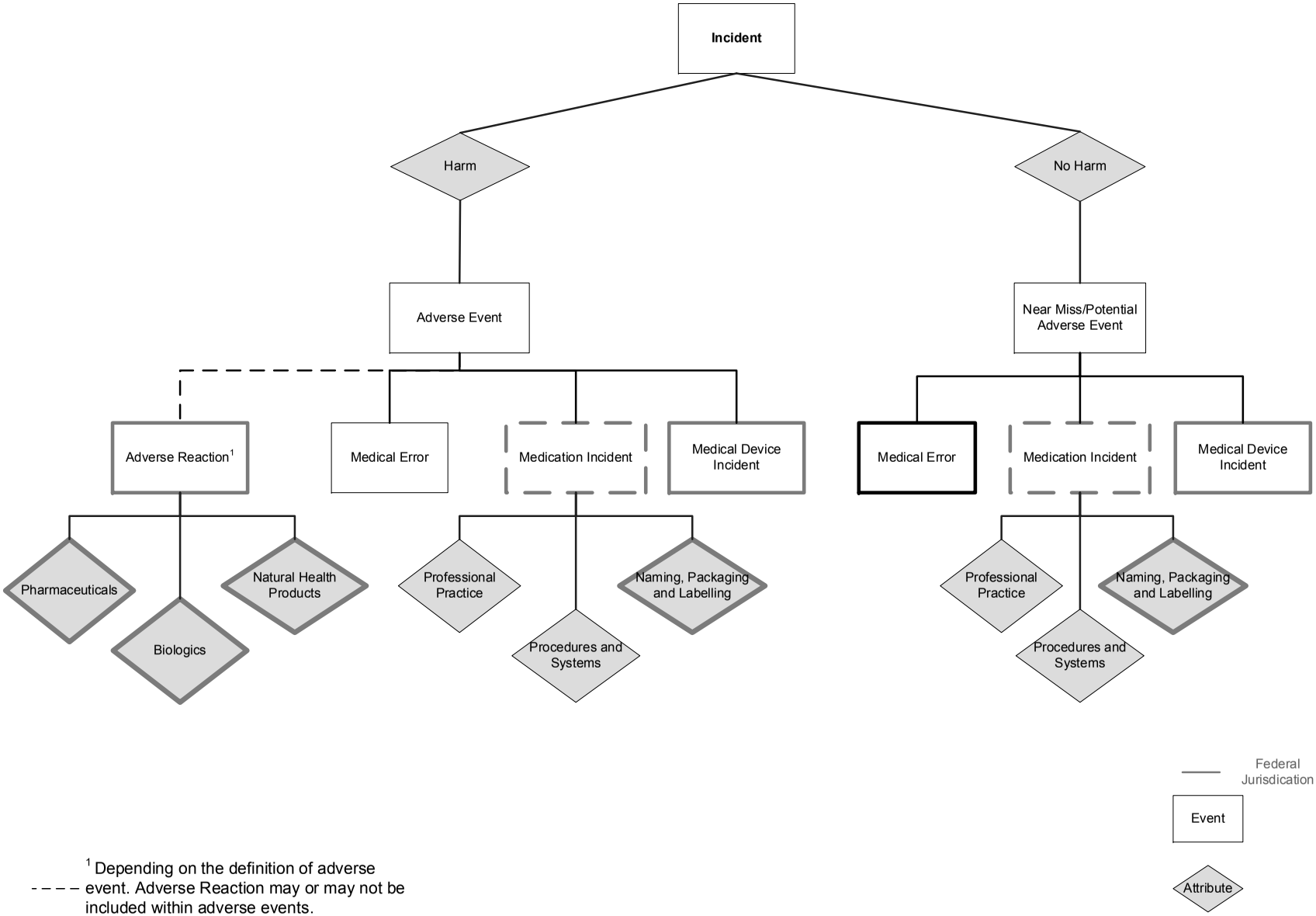
Yu, Nation and Dooley (2005) conducted an electronic search of websites of 160 organizations associated with medication safety, and found 25 different medication safety terms and 119 definitions from 33 organizations. Twenty-one different definitions alone were found for "adverse event".[2] (Refer to appendix 4 for specific examples)

Figure 1 illustrates the overall relationship between patient safety-related terms as they are used by Health Canada. Although this diagram is highly simplified and an adverse event can have more than one cause, it provides an understanding of the responsibilities that fall within the federal jurisdiction. The diagram starts with an "incident" which is defined as an event, process, practice, or outcome that is noteworthy by virtue of the hazards they create for, or the harms they cause patients. For consistency, it is suggested that the definitions of the terms following the diagram be used.

[1] Royal College of Physicians and Surgeons of Canada (Jan M. Davies, Philip Hébert and Carolyn Hoffman, Canadian Patient Safety Dictionary, October 2003, http://rcpsc.medical.org/publications/PatientSafetyDictionary_e.pdf; accessed February 11, 2008

[2] Yu, K.H., R.L. Nation, and M.J. Dooley, *Multiplicity of medication safety terms, definitions* and functional meanings: when is enough enough? Qual. Saf. Health Care, 2005. **14**(358-363).

Figure 1: Overall Relationship between Patient Safety-Related Terms From Health Canada Perspective



Defining Key Terms

Incident	Events, processes, practices, or outcomes that are noteworthy by virtue of the hazards they create for, or the harms they cause patients. (Adapted from the Royal College of Physicians and Surgeons of Canada (Jan M. Davies, Philip Hébert and Carolyn Hoffman, Canadian Patient Safety Dictionary, October 2003, http://rcpsc.medical.org/publications/PatientSafetyDictionary_e.pdf; accessed February 11, 2008)
Harm	An outcome that negatively affects the patient's health and/or quality of life.
Adverse Event	In Health Canada guidelines, policies and procedures, the term adverse event is used as defined in ICH E2D as meaning any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An Adverse Event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. (International Conference on Harmonization, Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting E2D, November 2003, http://www.ich.org/LOB/media/MEDIA631.pdf, accessed February 11, 2008)
Near Miss	An incident that could have resulted in unwanted consequences, but did not because either by chance or through timely intervention, the event did not reach the patient. Sometimes referred to as potential adverse event. For example, a nurse reports that there are two medications used for refractive eye surgery, both made by the same pharmaceutical company, and both come in similar packaging and the labels are very similar (same colours blue and white) which could easily be mistaken for each other because of similar packaging. This is reported without any harm actually occurring. (Canadian Medication Incident Reporting and Prevention System. Key Definitions for the Canadian Medication Incident Reporting and Preventions System. Ottawa, 2005)
Medical Error	Failure to complete a planned action as it was intended, or when an incorrect plan is used in an attempt to achieve a given aim. For example, wrong site surgery, wrong patient. (Adapted from the Canadian Patient Safety Institute, Canadian Patient Safety Dictionary, October 2003, http://rcpsc.medical.org/publications/PatientSafetyDictionary_e.pdf; accessed February 11, 2008)
Medical Device Incident	Any occurrence involving a medical device which encompasses actual or potential occurrences of device failure. *(Health Canada Guidance Document, Mandatory and Voluntary Problem Reporting for Medical Devices, July 2001)*
Adverse Reaction	Adverse drug reaction as defined in the *Food and Drug Regulations* is a noxious and unintended response to a drug, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function. For example, (1) A patient who

experiences a hypersensitivity reaction to penicillin who was not previously known to be allergic to penicillin; (2) A patient who experiences rhabdomyolysis following treatment with a cholesterol lowering agent (statin).

Adverse reaction as defined in the *Natural Health Products Regulations* is a noxious and unintended response to a natural health product that occurs at any dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying an organic function.

Adverse reaction as defined in the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* is an undesirable response in the recipient to transplanted cells, tissues or organs, including the transmission of a disease or disease agent.

Medication Incidents

Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Medication incidents may be related to drug products, professional practice, procedures and systems including, prescribing, order communication, product naming, packaging or labelling, compounding, dispensing, distribution, administration, education, monitoring and use. The term "medication incident" is synonymous with medication "error", but less "punitive" in its connotation. (Adapted from the National Coordination Council on Medication Error Reporting and Prevention, What is Medication Error?, http://www.nccmerp.org/aboutMedErrors.html; accessed February 11, 2008)

Critical Incident*

A serious adverse health event including, but not limited to, the actual or potential loss of life, limb or function related to a health service provided by, a regional health authority or health care organization. (Saskatchewan, *The Critical Incident Regulations*. 2004, Government of Canada.)

Sentinel Event*

Any unanticipated event in a healthcare setting resulting in death or serious physical or psychological injury to a person or persons, not related to the natural course of the patient's illness. Sentinel events specifically include loss of a limb or gross motor function, and any event for which a recurrence would carry a risk of a serious adverse outcome. (The Joint Commission, Sentinel Event Policy and Procedures, July 2007, http://www.jointcommission.org/NR/rdonlyres/F84F9DC6-A5DA-490F-A91F-A9FCE26347C4/0/SE_chapter_july07.pdf; accessed February 12, 2008)

* Term not included in diagram, but defined for additional clarity

Table 1 further illustrates the differences between the terms adverse reaction and medication incident.

	Adverse Reactions	Medication Incident
Focus	Primary focus of regulatory agencies and post-market surveillance	Primary focus of patient safety organizations and healthcare system stakeholders such as the Canadian Patient Safety Institute and the Institute for Safe Medication Practices Canada
Scope	• Harm directly caused from an administration of a drug. An adverse event of which nature or severity is not consistent with the product information. • Mostly unpreventable, unintended response to an approved health product given at usual doses; result not from an error but from the intrinsic properties of the product	• Inappropriate use of product that may or may not result in harm. • Preventable; a result of the care provided. Prevention results from improvements in the medication use system
Regulatory Applications	Under the *Food and Drug Regulations:* Adverse Drug Reaction Reporting C.01.016, C.01.017; New Drugs C.08.007, C.08.008 *Natural Health Products Regulations:* Reaction Reporting Section 24 (see appendix 1 Adverse Reaction Regulatory Requirements) *Safety of Human Cells, Tissues and Organs for Transplantation Regulations Section 47and 48*(see appendix 1 Adverse Reaction Regulatory Requirements)	Primarily non-regulatory, voluntary (see Appendix 2 – Regulatory considerations relating to health product naming, packaging and labelling) Saskatchewan , Manitoba and Quebec: Mandatory critical incident reporting (see Appendix 3 Provincial Activities)
Nature of reports	• Identifiable information for reporter is required (but not for the patient). • Could be used in a legal proceeding, parts of the report are subject to Access to Information	• Anonymity of reporter is assured. • Reporting of all events are encouraged including near misses • Focussed on systems issues
Management	• Successful management relies upon compliance and enforcement potentially through standards/accreditation process • Benefit-Risk Assessment • Updating labelling can highlight potential adverse reactions and approximate frequency to reduce their occurrence in the future.	• Successful management including changes to health care delivery within institutions relies on building a culture of safety, the development of standards and accreditation through for example the Canadian Council on Health Services Accreditation (CCHSA) • Management of risks due to product naming, packaging and labelling • Root Cause Analysis (RCA) or Failure Mode and Effects Analysis (FMEA)

Examples of Medication Incidents that fall under the Federal Jurisdiction:

Naming, Packaging or labelling

- Manufacturer's label design inhibits proper product recognition and selection. Example: Print size too small, font style is too ornate, expiry dates are unclear.

- Manufacturer's packaging or container design elements that look similar to those of another drug product and inhibit the proper selection

- Sound-alike drug names: The brand or generic name of a drug product is similar in pronunciation (it is phonetically similar) to another drug product. Example: hydromorphone and morphine

- Look-alike (Spelled-alike) drug names: The brand or generic name of a drug product is similar in spelling to another drug product name. Example: Losec and Lasix

More specific examples:

(1) Medication Incident relating to Look-Alike Sound-Alike Health Product name confusion - A patient in labour was administered epinePHRINE instead of epheDRINE. The patient experienced severe hypertension and nausea.

(2) A patient with known allergy to penicillin receives penicillin instead of amoxicillin and experiences a hypersensitivity reaction to penicillin.

Examples of Medication Incidents that fall under the Provincial/Territorial Jurisdiction:

Professional practice, Procedures and Systems

- Abbreviations: Written miscommunication due to the use of abbreviations for information pertaining to the drug product. Example: drug name, dosage rout of administration, latin abbreviations for frequencies such as QD (daily) or OD (once daily)

- Leading zero omitted: Absence of a leading zero in front of a fractionated amount. Example: ".5" may be interpreted as "5"

- Increased workload: Increase in the volume of work that a healthcare provider is assigned or expected to do in a specified time period

- Physical environment: Distractions/frequent interruptions, lighting, noise level, room temperature, workflow design, workspace design

More specific examples:

(1) A physician used the letter “u” for “units”, which was misinterpreted as “0” (zero) by a nurse resulting in a 10-fold overdose error.

(2) Drug D was ordered to infuse at 100 ml/hr, but was administered at 40 ml/hr

Appendix 1: Adverse Reaction Regulatory Requirements

Adverse Drug Reaction Reporting – *Food and Drugs Act and Regulations*

The Food and Drug Regulations (C.01.016, C.01.017, C.08.007, C.08.008), set forth regulatory requirements for manufacturers to report adverse drug reactions and to report unusual failure in efficacy of new drugs to Health Canada.

C.01.016.

(1) No manufacturer shall sell a drug unless the manufacturer, with respect to any adverse drug reaction or any serious adverse drug reaction known to the manufacturer that occurs after this section comes into force, furnishes to the Director
   (a) a report of all information in respect of any serious adverse drug reaction that has occurred in Canada with respect to the drug, within 15 days after receiving the information; and
   (b) a report of all information in respect of any serious unexpected adverse drug reaction that has occurred outside Canada with respect to the drug, within 15 days after receiving the information.

(2) The manufacturer shall, on an annual basis and whenever requested to do so by the Director, conduct a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to a drug referred to in subsection (1) and prepare a summary report in respect of the reports received during the previous twelve months or received during such period of time as the Director may specify.

(3) Where, after reviewing any report furnished pursuant to subsection (1) and any available safety data relating to the drug, the Director considers that the drug may not be safe when used under the recommended conditions of use, the Director may, for the purpose of assessing the safety of the drug, request in writing, that the manufacturer submit
   (a) case reports of all adverse drug reactions and serious adverse drug reactions to that drug that are known to the manufacturer; and
   (b) a summary report prepared pursuant to subsection (2).

(4) The manufacturer shall submit the case reports and summary report referred to in subsection (3) within 30 days after receiving the request from the Director.

C.01.017.

The manufacturer shall maintain records of the reports and case reports referred to in section C.01.016 for auditing purposes.

New Drugs (C.08.007, C.08.008)

C.08.007.

Where a manufacturer has received a notice of compliance issued in respect of a new drug submission or abbreviated new drug submission or a supplement to either submission, the manufacturer shall establish and maintain records, in a manner that enables an audit to be made, respecting...

(h) any unusual failure in efficacy of that new drug.

C.08.008.

No manufacturer shall sell a new drug unless the manufacturer has, with respect to all the manufacturer's previous sales of that new drug, furnished to the Minister...

(c) within 15 days after the receipt by the manufacturer of information referred to in paragraphs C.08.007(g) and (h), a report on the information received.

Adverse Reaction Reporting – *Natural Health Products Regulations*

The Natural Health Products Regulations under section 24 set forth regulatory requirements for licensees (as opposed to manufacturers).

Reaction Reporting (Section 24)

Section 24.

24.(1) A licensee shall provide the Minister with

(a) a case report for each serious adverse reaction to the natural health product that occurs inside Canada, within 15 days after the day on which the licensee becomes aware of the reaction; and

(b) a case report for each serious unexpected adverse reaction to the natural health product that occurs inside or outside Canada, within 15 days after the day on which the licensee becomes aware of the reaction.

(2) A licensee who sells a natural health product shall annually prepare and maintain a summary report that contains a concise and critical analysis of

(a) all adverse reactions to the natural health product that have occurred inside Canada; and

(b) all reactions for which a case report is required to be provided under subsection (1), that have occurred

(i) during the previous 12 months, and

(ii) at a dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying organic functions in humans.

(3) If after reviewing a case report provided under subsection (1) or after reviewing any other safety data relating to the natural health product, the Minister has reasonable grounds to believe that the natural health product may no longer be safe when used under the recommended conditions of use, the Minister may request that, within 30 days after the day on which the request is received, the licensee
(a) provide to the Minister a copy of any summary report prepared under subsection (2); or
(b) prepare and provide to the Minister an interim summary report containing a concise and critical analysis of
(i) all adverse reactions to the natural health product that have occurred inside Canada, and
(ii) all reactions for which a case report is required to be provided under subsection (1), that have occurred
(A) since the date of the most recent summary report prepared under subsection (2), and
(B) at a dose used or tested for the diagnosis, treatment or prevention of

Adverse Reaction Reporting – *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*

Pursuant to the Safety of Human Cells, Tissues and Organs for Transplantation Regulations, establishments and "source establishments" are required to:

47. (1) Subject to subsection (2), an establishment that is not a source establishment and that has reasonable grounds to believe that an unexpected adverse reaction has occurred must immediately take all of the following steps:
(*a*) determine the donor identification codes of the transplanted cells, tissues or organs;
(*b*) identify and quarantine any other cells, tissues and organs in its possession that could potentially cause an adverse reaction in the same way as the transplanted cells, tissues or organs; and
(*c*) notify the following establishments:
(i) the relevant source establishment, and
(ii) if the cells, tissues or organs were imported, the establishment that imported them.

48. (1) A source establishment that has reasonable grounds to believe that an unexpected adverse reaction has occurred that involves cells, tissues or organs for whose processing it is responsible must immediately take all of the following actions:
(*a*) quarantine any implicated cells, tissues and organs in its possession;
(*b*) send a notice described in subsection (2) to all of the following establishments:
(i) if the implicated cells, tissues or organs were imported, the establishment that imported them,

(ii) any source establishment from which it received the donor referral, if applicable,
(iii) any source establishment to which it made a donor referral, and
(iv) any establishment to which it distributed implicated cells, tissues or organs; and

(*c*) initiate an investigation into the adverse reaction.

Mandatory Problem Reporting – *Medical Devices Regulations*

Pursuant to Part 1, section 59 of the Medical Devices Regulations, manufacturers and importers of medical devices are required to:

59. (1) Subject to subsection (2), the manufacturer and the importer of a medical device shall each make a preliminary and a final report to the Minister concerning any incident that comes to their attention occurring inside or outside Canada and involving a device that is sold in Canada and that
(a) is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labelling or in its the directions for use; and
(b) 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 it to recur.

Pursuant to PART 2, Section 77 of the Medical Devices Regulations (Custom-made Devices and Medical Devices to be imported or sold for special access) health care professionals are required to:

77. The health care professional referred to in subsection 71(1) shall, within 72 hours after the occurrence of an incident described in section 59 involving a medical device for which an authorization has been issued pursuant to section 72, report the incident to the Minister and to the manufacturer or importer of the device, and specify the nature of the incident and the circumstances surrounding it.

Appendix 2:
Regulatory Considerations Relating to Health Product Naming, Packaging and Labelling

Pre-market:

a) Product naming

Authority is considered to be present to refuse to issue a Drug Identification Number (DIN) (new drugs and drugs other than new drugs) and/or Notice of Compliance (NOC) (new drugs only), as applicable. [see subsection C.08.002.(1), C.08.002.(2), C.08.002.(3) and C.01.014 to C.01.014.3 of the *Food and Drug Regulations*]. Section 9 of the *Food and Drugs Act* may also confer authority. It states *(1) No person shall label, package, treat, process, sell or advertise any drug in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety.*

b) Product labelling

The *Food and Drug Regulations* require that the written text of all labels and package inserts to be used in connection with a drug be provided in a drug submission as part of the information required to assess the safety and effectiveness of a product.

Specifically, subsection C.01.0141(2)(m) of the *Food and Drug Regulations* states that: *(2) An application under subsection (1) shall be made to the Director in writing and shall set out the following information (among other items):*
(m) The written text of all labels and package inserts to be used in connection with the drug and of any further prescribing information stated to be available on request.

In additions, subsection C.01.014.2 (2) (b) states that: *(2) Where the Director believes on reasonable grounds that a product in respect of which an application referred to in section C.001.014.1 has been made (b) is a drug but that its sale would cause injury to the health of the consumer or purchaser or would be in violation of the Act or these Regulations, he may refuse to issue the document referred to in subsection (1)* (ie. a DIN).

C.08.002(2)(j) of the *Food and Drug Regulations* states that: *(2) A new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following: (j) a draft of every label to be used in conjunction with the new drug.*

C.08.002.1(2)(a) of the *Food and Drug Regulations* states that: *(2) An abbreviated new drug submission shall contain sufficient information and material to enable the Minister to assess the safety an effectiveness of the new drug, including the following: (a) the information and material described in paragraphs C.08.002(2)(a) to (f) and (j) to (l).*

The list of items explicitly set out in the above sections of the Regulations regarding what must be included in the submission is not a *finite* list. The Regulations make it clear, through the use of the word 'including' in the sections quoted above, and by provisions such as that in sections C.08.002(3)(d) and C.08.002.1(3)(d), that the Minister can request any additional information or material respecting the safety of the drug.

Specifically C.08.002(3)(d) (for a new drug) and C.08.002.1(3)(d) (an abbreviated new drug) state that: (3) *The manufacturer of a new drug shall, at the request of the Minister, provide the Minister, where for the purposes of a new drug submission/abbreviated new drug submission the Minister considers it necessary to assess the safety and effectiveness of the new drug, with the following information and material: (d) any additional information or material respecting the safety and effectiveness of the new drug*.

Based on the above, authority is considered to be present to refuse to issue a DIN and/or NOC, as applicable, if proposed labels lead to confusion with another drug, are lacking important safe use information, if confusing/unclear label presentation could result in safety concerns when the product is put to use post authorization, or if any other label-related patient safety issues are uncovered during the assessment of a submission.

c) Product packaging

On a pre-market basis, the authority of the *Food and Drug Regulations* which permit the Minister to request any additional information or material respecting the safety and effectiveness of a new drug, may enable assessment of a product's packaging from a safe use perspective. [Refer to C.08.002(3)(d) and C.08.002.1(3)(d) cited above under labelling].

It is much easier to use the above noted regulatory authorities on a proactive, pre-market assessment basis to the extent that safety issues can be anticipated prior to a product actually being marketed, than retrospectively post product approval. However, since not all safety issues related to product naming, packaging or labelling (NPL) can be foreseen, it stands to reason that some will have to be addressed on a post-marketing basis as well.

Post-market:

Section 9 of the *Food and Drugs Act* which states: *(1) No person shall label, package, treat , process, sell or advertise any drug in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety. (2) A drug that is not labelled or packaged as required by, or is labelled or packaged contrary to, the regulations shall be deemed to be labelled or packaged contrary to subsection (1)*, may confer authority to mandate changes to an approved drug's packaging or labelling if related safety issues come to light post marketing.

The *Food and Drug Regulations* state in section C.01.013: *(1) Where the manufacturer of a drug is requested in writing by the Director to submit on or before a specified day evidence with respect to a drug, the manufacturer shall make no further sales of that drug after that day unless he has submitted the evidence requested.*
(2) Where the Director is of the opinion that the evidence submitted by a manufacturer, pursuant to subsection (1), is not sufficient, he shall notify the manufacturer in writing that the evidence is not sufficient.
(3) Where, pursuant to subsection (2), a manufacturer is notified that the evidence with respect to a drug is not sufficient, he shall make no further sales of that drug unless he submits further evidence and is notified in writing by the Director that further evidence is sufficient.

(4) A reference in this section to evidence with respect to a drug means evidence to establish the safety of the drug under the conditions of use recommended and the effectiveness of the drug for the purposes recommended.

Regulatory authority to mandate change to a drug's NPL once an NOC and/or DIN has been issued by Health Canada is more limited on a post-marketing basis. Upon becoming aware of and assessing a safety concern to determine actual or potential risk associated with the NPL of a drug following issuance of an NOC and/or DIN for a drug, HPFB can use section C.01.013 of the *Food and Drug Regulations* to require the manufacturer to establish the safety of the drug under its recommended uses by submitting, by a specified date, evidence sufficient to establish the safety of a drug under the conditions of use for which the drug is recommended. When sufficient evidence is not so provided, the Director may direct the manufacturer to make no further sales of the drug.

Appendix 3:
Provincial Activities

Saskatchewan

The government of Saskatchewan requires the reporting and investigation of critical incidents in healthcare as of September 15, 2004.[3] A regional health authority or a healthcare organization must report any critical incident within 3 business days after the day of occurrence or it becomes aware of the incident. A critical incident is defined as "*a serious adverse health event including, but not limited to, the actual or potential loss of life, limb function related to a health service provided by, a program operated by, a regional health authority(RHA) or a healthcare organization (HCO)"*.[4] The authority or the organization also has to investigate the incident and submit a written report that describes the incident, contributing factors, actions taken and recommendations to the minister of health.

In February 2003, Saskatchewan Health delivered the first Root Cause Analysis (RCA) workshop to facilitate its efforts to promote patient safety in the province. Workshops held in subsequent three years ensured that RCA is exposed all regions. In 2005, increasing demands for the RCA workshop prompted Saskatchewan Health to approach the Canadian Patient Safety Institute (CPSI) for promoting the tool nationally. In collaboration with Saskatchewan Health and the Institute for Safe Medication Practices Canada (ISMP Canada), the CPSI developed the Canadian Root Cause Analysis Framework in 2006.[7]

Manitoba

The Regional Health Authorities and Manitoba Evidence Amendment Act, which became effective of November 1, 2006, requires a health corporation or organization to report any critical incident to the regional health authority, and the authority to notify the minister. A critical incident is defined as "*an unintended event that occurs when health services are provided to an individual and results in a consequence to him or her that*

> *(a) is serious and undesired, such as death, disability, injury or harm, unplanned admission to hospital or unusual extension of a hospital stay, and*
>
> *(b) does not result from the individual's underlying health condition or from a risk inherent in providing the health services"*.[5]

In March 2005, Manitoba provided support to its regions to attend the Canadian Root Cause Analysis Framework workshop. Health authorities have begun to implement the method to better investigate and prevent critical incidents. The health authorities in the province are learning from aggregated patient data using Root Cause Analysis and Failure Mode Effects And Analysis (FMEA) to improve patient safety and quality of care.[6] The Winnipeg Regional Health

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[3] Saskatchewan, *The Critical Incident Regulations*. 2004, Government of Canada.
[4] Hoffman, C., et al., *Canadian Root Cause Analysis Framework*. 2006: CPSI, ISMP Canada and Saskatchewan Health.
[5] Canada, *The Regional Health Authorities Amendment and Manitoba Evidence Amendment Act*. 2006, Queen's Printer.

[6] Beard, P. and L. Smyrski, *Reporting for Learning and Improvement: The Manitoba and Saskatchewan Experience.* Healthcare Quarterly, 2006. **9**(Special Issue): p. 61-64.

Authority's Patient Safety Team also had a Human Factors Leader in critical incident reviews and FMEA over the period of 2005-2006.[7]

Quebec

In December 2002, the Quebec government adopted Bill 113 which defines healthcare facilities' obligations on disclosure of incidents and accidents, creation of risk and quality management committee, and on the development of a local registry. The committee is responsible for identifying and analyzing incident or accident risks, ensuring support is provided to the patient, and establishing a monitoring system for the analysis and prevention of incidents and accidents.[7] The regulation also requires every institution in Quebec to transmit an annual report of its activities related to risk and quality management to the Minister.[8]

[7] Winnipeg Regional Health Authority. *Regional Integrated Patient Safety Strategy*. 2007 April [cited 2007 August 10]; Available from: http://www.wrha.mb.ca/healthinfo/patientsafety/ripss.php.

[8] Quebec, *An Act respecting health services and social services*. 2002, Government of Canada.

Appendix 4
Definitions of Adverse Event

Provided below are examples of inconsistencies in the definition of adverse event:

The landmark study on the adverse events among hospital patients in Canada by Baker et al. (2004) defines the "adverse event" as "an unintended injury or complication that results in disability at the time of discharge, death or prolonged hospital stay and that is caused by health care management rather than by the patient's underlying disease process".[9]

The World Health Organization defines adverse event as "Any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment.[10]

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO), USA defines "adverse event" as "an untoward, undesirable, and usually unanticipated event, such as death of a patient, an employee, or a visitor in a health care organization. Incidents such as patient falls or improper administration of medications are also considered adverse events even if there is no permanent effect on the patient.".[11]

The Royal College of Physician and Surgeons of Canada, Canadian Patient Safety Dictionary recommends "adverse event" to be defined in one of the following ways

1. An unexpected and undesired incident directly associated with the care or services provided to the patient;
2. An incident that occurs during the process of providing health care and results in patient injury or death;
3. An adverse outcome for a patient, including an injury or complication.

Not only do some definitions refer solely to adverse events relating to medication treatment, other definitions do not consider adverse reactions are included within adverse events. To further complicate matters, professionals and organizations may have their own interpretation of the term.

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[9] Baker, G.R., et al., *The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada.* Canadian Medical Association Journal, 2004. **170**(11): p. 1678-1686.

[10] World Health Organization. *Safety of Medicines - A Guide to Detecting and Reporting Adverse Drug Reactions – Why Health Professionals Need to Take Action*. 2002 [cited 2008 February 11]; Available from: http://www.who.int/medicinedocs/index.fcgi?sid=rQ6TWIlB9ee80ca700000000474e0a12&a=d&d=Jh2992e.

[11] The Joint Commission. *Sentinel Event Glossary of Terms*. 2008 [cited 2008 February 11]; Available from: http://www.jointcommission.org/SentinelEvents/se_glossary.htm.

Provincial/Territorial Bilateral Discussion Document:
A Hospital-Based Adverse Reaction Reporting System

Background

In 2005, Health Canada began consultations with provinces and territories, health professionals, industry, international regulatory bodies and the Canadian public on a set of preliminary issues associated with creating a mandatory adverse reaction (AR)[1] reporting system for health professionals. Health Canada's consultation discussion paper noted that the input received could be used to develop practical options, such as targeted mandatory reporting rather than an all-inclusive requirement, to assess and refine during subsequent phases of consultations.

During the first phase of consultations many stakeholders cited the inability of a broad regulatory requirement to directly address the principle barriers to reporting. However, the Department is currently examining the feasibility and advantages of a hospital-based reporting system as a better way to address the key reporting barriers and increase the reporting of serious adverse reactions to federally regulated health products.

Because health care services are delivered through the provincial and territorial programs, this initiative must be carefully integrated across jurisdictions. With this in mind, the Department intends to consult provincial and territorial governments prior to presenting a more detailed proposal to other stakeholders.

The principal questions at this time are (I) whether a system of hospital-based mandatory reporting would be best placed under federal or provincial regulation, and (ii) whether a non-regulatory approach could be effectively used (e.g. developing accreditation standards for healthcare facilities).

Meeting Objectives

To meet with health officials from provinces and territories (P/T) on a bilateral basis in order to:

- provide an update on results of our investigation regarding mandatory reporting (MR) of ARs by health professionals;
- introduce the plan to investigate a hospital-based AR reporting system;
- learn about whether P/T's have any mandatory reporting systems in place for their hospitals and if so for what issues;
- gage input and views into the feasibility of a hospital-based AR reporting system from P/T's perspective including dynamics such as administration/regulatory oversight,

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[1] An adverse reaction (AR) is a *non-preventable* adverse event and occurs when a patient experiences a noxious and unintended response to a drug, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function. Health Canada collects reports of ARs to pharmaceuticals, biologics (including fractionated blood products as well as diagnostic and therapeutic vaccines), natural health products, and radiopharmaceuticals, in order to monitor inherent product safety, as opposed to errors in the medication process.

compliance and enforcement, and quality of reporting;

Meeting Outcomes

- synthesize P/T input into a discussion document to share for comment from the greater stakeholder community; and
- ensure P/T governments are included in the overall policy development process.

Approach

We suggest that officials be invited from both the Ministries and Regional Health Authorities, with a focus on the Ministries since they may be best positioned to comment on issues concerning regulatory oversight.

Format/Agenda:

A general guideline consists of the following:

- Summary of results for the investigation of MR by health professionals and continuing investigation of a hospital-based AR reporting system;
- Presentation of our hospital-based AR reporting system proposal and consultation plan;
- Posing of a series of questions to stimulate discussion and solicit P/T views on the feasibility of a hospital-based AR reporting system (see Appendix A); and
- Opportunity for P/T officials to ask Health Canada questions and share any experiences (e.g. AR reporting, hospital systems, mandatory reporting systems)

The meeting will be informal and about half a day (3 hours maximum).

Appendix A

Examples of Key Questions/Items for Discussion for Bilateral Meetings:

Introductory remarks

As part of Health Canada's ongoing efforts to improve adverse drug reaction (ADR) reporting, we are investigating the advantages of different models for mandatory reporting, including the feasibility of a hospital-based AR reporting system. An important part of our research involves consulting with provincial and territorial health regulatory authorities such as yourself, our partners in protecting the health of Canadians, to gain your feedback and insights on the feasibility of a hospital-based AR reporting system. Your views are extremely important in helping us determine the best course of action in the pursuit of this investigation.

Items for Discussion

Value and Impact of Proposal

- What is your initial reaction to our proposal for a hospital-based AR reporting system?
- Could you see your jurisdiction supporting this proposal?
- What features of a hospital-based AR reporting system might increase the likelihood of success (i.e. increasing quality and quantity of serious AR reports from health facilities)?
- From your perspective, what would be the key challenges in developing and implementing such a reporting system?
- What barriers might exist to implementing this system broadly and consistently across jurisdictions?

Linkages to Health Facilities

- What types of hospitals do you think should be included in such a system (e.g. all hospitals, acute care hospitals, hospitals with over x number of beds, other)?
- Do you see any opportunity in building our proposed system upon existing reporting infrastructures present in hospitals?
- Is there an opportunity to share with us any cost/impact assessments developed for existing reporting systems? (e.g. critical incident reporting)
- What are some of the problems we might encounter in clearly defining these facilities?

Regulatory Oversight and Administration

- In terms of regulatory oversight, in your opinion what would be the best approach (e.g. federal regulation, provincial regulation, a non -regulatory approach such as standards/guidelines or other)?
- In terms of administration, how would you see the role of provincial health authorities and the Ministries themselves? How about Health Canada (NCR and Regions)?
- What are the issues around promoting and monitoring compliance as you see them?

Quality of Reports

- Do you have any thoughts of how we could encourage high quality reports (e.g. accreditation)?

Final Thoughts

- What advice would give to us as we continue our investigation?

Prepared by: Derek Wade
October 29, 2007
Head, Unit 3, Policy and Regulatory Affairs
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada

Government of NL Task Force on Adverse Health Events: Call for Submissions
Date: June 13th, 2008
Submitted by:
Colleen Turpin, RN BScN, M.Ed
Project Manager
Marketed Pharmaceuticals & Medical Devices Bureau (MPMDB)
Marketed Health Products Directorate (MHPD)
Health Products and Food Branch (HPFB)
Health Canada (HC)
Tel: 613-957-9029
Email: colleen_turpin@hc-sc.gc.ca

Task Force Questions:

1) How can we improve the current approach used by our health and community services system to manage adverse events?
The Task Force could investigate a new pro-active approach offered by Health Canada for reporting medical devices adverse events. A pilot to use a sentinel approach (subset of health care professionals who report and act as 'guards' for all) to post market surveillance for medical devices is currently being planned by Health Canada for 2008-2009.

We are looking for volunteer user facilities, acute or community based within Canada, to participate in reporting any adverse event or 'near misses' to Health Canada that occur with any medical device within your organization. This will help us better understand how organizations use devices, how problems are perceived and reported, and what characteristics of the system contribute to a particular event to potentially mitigate risk at an earlier stage.

Participation in such a pilot would help the facility by:

- further developing its quality management/risk management approach to medical devices safety
- learning from 'near misses'; incorporate into own quality assurance activities
- creating/further developing infrastructure/mechanisms/policies/communication tools for adverse event reporting that could be used for other health care products
- impacting manufacturing processes or licensing requirements or assisting in own purchasing processes
- having access to awareness campaigns/education; providing information to front line users about safe medical device usage and reporting
- avoiding duplication of reporting; report would be provided to manufacture/other governmental agencies as needed
- creating a communication link with Health Canada; being privy to early warnings and participating in auditing of devices prior to failure or events within your facility
- developing a sense of community with other Sentinel users, mechanism to share information with other facilities.

2) In particular, are there gaps in how the system identifies, assesses, discloses, and takes action on adverse events?

MHPD is unaware of any gaps that are particular to the NL health system but has identified a lack of standardized reporting infrastructures within other facilities across Canada.

A variety of different processes within facilities have been encountered while investigating the background for this project. Typically there is some structure on how serious adverse events, particularly medication errors or falls are handled within institutions and reported upwardly to the corporate organization. There are less formalized processes around other health products and particularly medical devices if the outcome of the event was not of a serious nature. The collection of similar events to identify potential wide spread problems and/or warnings to other departments as 'lessons learned' happens less frequently. The distribution of equipment recalls, advisories from Health Canada and development of associated action plans are inconsistent across organizations.

Participation in the sentinel pilot for reporting adverse events from medical devices may provide structure where none existed before, or support current mechanisms that are already in place. There are opportunities here to obtain the same goals but flexibility in how to obtain them.

3) Are there gaps in how the system coordinates and communicates when it is managing an adverse event?

Within facilities across Canada, the distribution of equipment recalls/device advisories and development of associated action plans are inconsistent across organizations. Some facilities do this well but use foreign reports more so than domestic information. This may result in needless work to prepare action plans to recalls/advisories that may not affect the Canadian marketplace.

Provincially there may be mechanisms to report centrally, but MHPD is unsure if there are processes to provide the facility with information back about the event that has been reported. Potential areas of feedback that are being considered for the sentinel systems are regular newsletters, early notification of recalls/advisories, and warnings about other reports received at other sentinel reporting sites to determine the magnitude of problem. This will provide methods to pro-active surveillance for medical device problems within your institution.

Participation in the sentinel pilot for reporting adverse events from medical devices will provide early access to information about potential issues with devices on the Canadian market. This coordinated effort in communication may assist in the safe use of medical devices within the organization.

Recommendation: Task Force to investigate NL's participation in the pilot project for a sentinel system for medical device adverse event reporting.

Background (from Sentinel Business Case/internal document Health Canada/2008):

Introduction

Canadians consume over $3 billion in medical devices annually. There are over 80, 000 devices currently licensed for sale in Canada (MDS, 2008). Medical devices are largely based on technology. As advances are made in technology, the number of devices and their complexity will increase. For these reasons, it is expected that the medical devices industry will continue to grow in the future, both in size and in importance.

The increasing complexity of medical technology, perhaps coupled with economic pressures and organizational change within health care institutions, increases the potential for unanticipated and unintended consequences. Adverse medical device events have found to occur 83.7 times per 1,000 US hospital admissions (Samore et al, 2004). Hospitals have internal reporting systems but the information is rarely shared with other institutions, so the impact on improving medical device safety is limited.

These changes demand that surveillance of marketed devices moves from a reactive to proactive stance. This proactive strategy includes an understanding of how organizations use devices, how problems are perceived and reported, and what characteristics of the system contribute to a particular event.

Problem Statement

Health Canada's Marketed Health Products Directorate (MHPD) has insufficient post-market surveillance tools and limited information sources to adequately monitor, assess and identify safety issues with marketed medical devices.

Current problem reporting for medical devices relies on a system of spontaneous reports from all sources, and mandatory reporting by manufacturers and importers of medical devices. Despite these measures, which may be characterized as 'all data' or universal reporting systems, there are recognized deficiencies in the quantity and quality of information gathered about the effectiveness and safety of marketed devices

Voluntary reporting rates for medical device adverse events have been historically very low in Canada (317 in 2007 compared to 4624 mandatory reports received in our Canadian reporting system- MDS) and, as a result, the Auditor General (2004) states that Health Canada is not able to adequately identify adverse events via this passive surveillance system.

In contrast to universal data systems, sentinel systems are an alternative strategy designed to increase the quantity and quality of problem reports from a subset of user facilities. Through training and education, sentinel reporters deliver high quality data which is more sensitive and timely, and which permits proactive interventions.

Current Situation

Currently, Health Canada requires that manufacturers and importers of devices make preliminary and final reports to Health Canada concerning any incident involving their device that:

a) is related to the failure or deterioration of the device or inadequacies in the labelling or directions for use; and

b) has led to the death or serious deterioration in the health of a patient, user or other person; or could have led to a death or serious deterioration in the health of a patient, user or other person.

The Inspectorate is responsible for compliance and enforcement activities such as monitoring recalls of medical devices as they pertain to the mandatory reports received. Medical Devices Bureau (MDB) is responsible for the pre-market evaluation and licensing of the medical devices. MDB also plays a role in safety surveillance; they have a health hazard evaluation unit comprising of a lab and evaluators.

MHPD evaluators monitor the recalls, mandatory and voluntary reports in the MDS database for emerging safety trends. This risk assessment activity is encumbered by receiving belated, vague and incomplete information.

What is a Sentinel System?

A Sentinel system uses a group of dedicated, trained user facilities to report high quality data about adverse events associated with medical devices to the regulator. Through the review of this rich data source, the post market evaluators will be able to look for emerging safety trends. The safety of Canadians will be impacted by better quality risk assessments and earlier regulatory interventions. Providing citizens with timely information to make informed health choices will help them maintain and improve their health.

A Sentinel system will be an important source of product safety evaluation and provide:

- this pro–active surveillance approach fulfills AG's recommendations for MDP program
- delivers high quality reports about adverse events of medical devices, creating an early warning system for emerging safety trends
- produces better quality risk assessments and earlier regulatory interventions; providing citizens with timely information to make informed health choices will help them maintain and improve their health
- creates awareness of hospital staff not to be complacent about device problems that stimulates reporting to HC and manufacturers
- quality improvement information gained from sentinel alerts could be transferable to institutions
- supports Branch objective to use similar approach to post market surveillance as other international regulators; opportunity to share information
- user 'clinical community' rather than manufacturer relationship driven process
- may provide for safer product development and licensing in the future

One major benefit of a Sentinel system is that this pro-active strategy will provide a better understanding how organizations use devices, how problems are perceived and reported, and what characteristics of the system contribute to a particular event to potentially mitigate risk at an earlier stage.

Scenario

This initiative would include an on-line report form for the users to enter adverse events, a repository for the reports and adequate evaluation resources to complete and code reports while looking for emerging safety trends to report potential post market signals to MHPD evaluation staff on a regular basis. These reports are transferred to the universal reporting system for medical devices (MDS) to share with our partners in Medical Device Program (MDP). The reports would also be shared with the manufactures eliminating the need for facilities to duplicate reporting. Various types of feedback could be trialed in the pilot so as to determine best value to provide incentive for reporting.

Conclusion:

MHPD would be happy to provide more information or participate in further discussions with the Task Force or any other group that is interested in this sentinel project in the future.

Annex A: Acronyms

AE- Adverse Event
AG -Auditor General
FDA- Food and Drug Administration
HC- Health Canada
HPFB-Health Products and Food Branch
HPFBI- Health Products and Foods Branch Inspectorate
IM/IT- Information Management/Information Technology
MDB- Medical Devices Bureau
MDP- Medical Device Program within Health Canada (pre market, post market, inspection/compliance & enforcement bureaus)
MDS- Medical Device System (Health Canada's Medical Device application/licensing/incident tracking system)
MHPD- Marketed Health Product Directorate
MPMDB- Marketed Pharmaceuticals and Medical Devices Bureau
OIMT- Office of Information Management and Technology
US- United States

Annex B: Glossary of Terms

Act

"Act" means the *Food and Drugs Act*.

Adverse Event (AE)

In Health Canada guidelines, policies and procedures, the term adverse event is used as defined in ICH E2D as meaning any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An Adverse Event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. (International Conference on Harmonization, Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting E2D, November 2003, http://www.ich.org/LOB/media/MEDIA631.pdf, accessed February 11, 2008)

Device

"medical device" means a device within the meaning of the Act, but does not include any device that is intended for use in relation to animals.

Evaluator

Person performing the evaluation of the post market signals; also reviewer.

Health Care Facility

"health care facility" means a facility that provides diagnostic or therapeutic services to patients. It includes a group of such facilities that report to one common management that has responsibility for the activities carried out in those facilities.

Health Care Professional

"health care professional" means a person who is entitled under the laws of a province to provide health services in the province.

Manufacturer:

"manufacturer" 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 to it a purpose, whether those tasks are performed by that person or on their behalf.

Post-Market Surveillance

The continued monitoring for, and the study of effects and other safety and effectiveness related aspects of health products that have been marketed to the public.

Recall

"recall" , in respect of a medical device that has been sold, means any action taken by the manufacturer, importer or distributor of the device to recall or correct the device, or to notify its owners and users of its defectiveness or potential defectiveness, after becoming aware that the device

(*a*) may be hazardous to health;

(*b*) may fail to conform to any claim made by the manufacturer or importer relating to its effectiveness, benefits, performance characteristics or safety; or

(*c*) may not meet the requirements of the Act or these Regulations.

Signal

Refers to 'reported information on a possible causal relationship between and adverse event and a health care product, the relationship being unknown or incompletely documented previously'. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information

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