Health Canada Santé Canada

How Adverse Reaction Information on Health Products is Used

What is an adverse reaction (AR)?

Adverse reactions are undesirable effects to health products. Health products include drugs, medical devices and natural health products. Drugs include both prescription and nonprescription pharmaceuticals; biologically-derived products such as vaccines, serums, and blood derived products; cells, tissues and organs; disinfectants; and radiopharmaceuticals.

Reactions may occur under normal use conditions of the product. Reactions may be evident within minutes or years after exposure to the product and may range from minor reactions like a skin rash to serious and life-threatening events such as a heart attack or liver damage.

What is the regulatory framework for ARs?

In Canada, the legislative requirements for the post approval surveillance of health products are covered under the *Food and Drugs Act and Regulations*. These may be accessed at:
http://www.hc-sc.gc.ca/fn-an/legislation/acts-lois/index_e.html

The *Food and Drug Regulations* define an adverse drug reaction as 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.

A serious adverse drug reaction is defined as a noxious and unintended response to a drug, which occurs at any dose and requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death.

How are ARs detected once a health product is available for sale in Canada?	Patients, health professionals, manufacturers and health product regulatory authorities work together to monitor ARs. Voluntary reporting by health professionals and consumers of suspected reactions is the most common way to monitor the safety and effectiveness of marketed health products to obtain information regarding ARs. These individual reports may be the only source of information concerning previously undetected ARs or changes in product safety and effectiveness profiles to marketed health products.
Why are ARs monitored?	All health products have risks and benefits. Before a product is marketed, safety and efficacy experience is limited to its use in clinical trials. However, these initial clinical trials mostly detect common and frequent ARs. Some important reactions may take an extremely long time to develop or occur infrequently. In addition, the controlled conditions under which patients use health products in clinical trials (e.g., under direct medical supervision without necessarily significant exposure to other products and or underlying diseases), do not necessarily reflect the way the product will be used in real life conditions once it is marketed. Continued monitoring of ARs is thus essential to maintain a comprehensive safety and effectiveness profile of health products made available to Canadians.

How is AR information being collected in Canada?	National adverse reaction reporting activities are coordinated by the Marketed Health Products Directorate of Health Canada. Reports are currently collected by seven Regional AR Centres (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Québec and Atlantic) in addition to the National Office (Ottawa, Ontario). Regional Centres perform an initial review of the quality and completeness of the reports which are then processed and further analyzed at the National Office. Manufacturers are legally responsible to provide Health Canada with any important safety information for health products they sell in Canada. Additional information regarding health product safety and effectiveness may also be obtained through: • post-marketing studies conducted by manufacturers or health care institutions; • active surveillance activities which include the regular periodic collection of case reports from health professionals and health facilities; • publications in scientific journals; • collaboration with patient groups, academic institutions, professional associations in Canada and internationally; • risk-communications from regulatory agencies in other countries.
What feedback information is provided to reporters of ARs ?	Regional Adverse Reaction Centres currently provide acknowledgements and monthly updates to reporters concerning new information derived from AR reports.

The *Canadian Adverse Reaction Newsletter*, a quarterly publication, alerts health professionals and consumers to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk-benefit evaluations and regulatory decisions are undertaken.

The Newsletter is distributed to :

- Physicians: by mail with the *Canadian Medical Association Journal.*
- Pharmacists, other health professionals and interested parties: by mail
- Public: on the Web at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/index_e.html and by email to subscribers of the MedEffect e-Notice electronic mailing list.

New safety and effectiveness information derived from AR reports is disseminated in health product Advisories issued by Health Canada and/or manufacturers to health professionals and the public as well as in updated official Product Monographs.

How to subscribe to the MedEffect e-Notice mailing list?

To receive the *Canadian Adverse Reaction Newsletter* and health product Advisories by email, join Health Canada's MedEffect e-Notice mailing list. Go to : http://www.hc-sc.gc.ca/dhp-mps/medeff/subscribe-abonnement/index_e.html and click "subscribe".

What type of information is collected in AR reports ?

Reports contain relevant information about the patient characteristics and details about the reaction(s) suspected to be associated with the health product(s), the general finding(s), the treatment and final outcome(s). Information about the identity of the patient and the health care provider is kept confidential. Disclosure of data is only done in accordance with the provisions of the *Access to Information Act*.

How is the information processed?	AR reports are analyzed to discover potential health product safety signals. A signal is considered to be the preliminary indication of a product-related issue. The identification of a signal is not by itself the proof of the association of an AR to a health product, but it triggers the need to further investigate a potential association. Signals must be carefully evaluated in order to confirm or to disprove the potential association between the product and the AR.
How are signals identified and analyzed from AR reports?	Signals may be identified through the systematic review of AR reports and any other additional information on product safety. Potential signals need expert evaluation before any actions are undertaken. The subsequent preliminary evaluation of the signal determines the likelihood of the association between the reaction and the health product. Typical information which must be taken into account includes the frequency, severity, plausibility, quality of the information contained in the reports, amount of product used, time needed for appearance of the reaction, underlying diseases, simultaneous use of other medications, and evidence of disappearance or reappearance of the reaction once the product was discontinued or reintroduced. Additional investigative studies and consultations with other regulatory agencies are often necessary to confirm the health product-AR relationship.

What other tools are used to detect potential signals?	Signals may also be recognized by performing periodic analysis of the collected AR reports with statistical tools which enable the detection of a higher than expected number of suspected reports for particular marketed health products. Statistical calculations enable the comparison of the number of reports with a particular product and reaction with the total number of reports already contained in the AR database. In other words, this places any suspected report in perspective by providing the background context of the previously entered reports in the database as well as similar symptoms from underlying disease(s). Unfortunately, the size and functionality of the current Canadian AR database does not allow the performance of this type of analysis. A project to partner with the United States Food and Drug Administration's more powerful database for AR analysis is currently underway and may make more complex analysis possible.
How many reports does it take to make a signal?	There is no fixed formula, method or specific number of reports required to make a signal. Each single case has to be looked at and considered as unique. Gathering all relevant evidence will ultimately determine the nature of the signals and their relative priority for further evaluation. Most health product regulators and experts in pharmacovigilance have stated nevertheless, that more than one report is usually needed to generate a signal. Health products are used worldwide and it is more difficult for a relatively small country (e.g., Canada) with a population of about thirty million compared to a larger country (e.g., USA, with a population ten times higher than that of Canada) to generate and evaluate signals for rare adverse reactions. Active international collaboration is critical to support the signal generating capabilities.

What are the limitations of AR information?	ARs to health products are considered to be suspicions, as a definite causal association often cannot be determined. In some cases the reported clinical data may be incomplete, the given reaction may be due to the underlying disease or to another coincidental factor. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown. Quantitative comparisons of health product safety cannot be made from spontaneous AR reports because multiple factors affect reporting (e.g., length of time a product is on the market, market share, publicity about an AR, regulatory actions). Spontaneous reporting systems are most suited to detect signals of potential safety issues for marketed health products. However, in certain situations additional epidemiological studies or head-to-head comparative controlled clinical trials are needed.
How much information is needed to initiate a regulatory action?	Regulatory actions must be based on scientific analysis of case series and are taken according to the regulatory framework in place. This implies an evaluation of the signal and the appropriate benefit-risk review of the information available. Active partnerships among all stakeholders, including scientific experts, health professionals, industry, other regulatory agencies as well as consumers is commonly needed to provide all the essential information on the ARs to enable regulatory actions. Actions may vary depending on the nature, the seriousness and the frequency of the reaction, as well as on the intended use of the health product, the benefit obtained from its use versus the risks and the availability of alternative therapies.

What are the possible actions taken by health product regulatory authorities?

Possible regulatory actions vary from continuing observation of health products to cancelling the marketing authorization in Canada. Other possibilities include :

- postmarketing studies;
- comprehensive re-assessment of the risk and benefit profile of the health product;
- product labeling changes (including addition of contraindications, warnings, precautions or supplementary AR information in the product information or Product Monograph);
- altered packaging to clearly identify risks and instructions on the use of the product;
- dissemination of information to health care professionals and consumers about the risks (e.g., letters, advisories, publications, specialized internet sites);
- addition of "warnings" in patient information leaflets;
- issuing public alerts; or
- conducting market withdrawals.

These actions or market interventions may be done by Health Canada or the sponsor of the health product or both parties.

How to obtain AR Reporting Guidelines?	Various health professional and manufacturer AR reporting guidelines listed below are available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/guide/index_e.html Drugs: • Canadian Adverse Drug Reaction Monitoring Program Guidelines for the voluntary reporting of Adverse Drug Reactions by health professionals; • Guidelines for Reporting Adverse Reactions to Marketed Drugs (Vaccines excluded) for the Mandatory Reporting by the Canadian Pharmaceutical Industry Medical Devices: • (Draft) Mandatory and Voluntary Problem Reporting for Medical Devices Vaccines: • Guidelines for Reporting Adverse Events Associated with Vaccine Products

For further information

You can reach the National Office at:

Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Health Canada
A.L.: 0701C
Ottawa, (ON)
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Telephone: (613) 957-0337
Fax: (613) 957-0335
Email: cadrmp@hc-sc.gc.ca
Or visit our website:
http://www.hc-sc.gc.ca/dhp-mps/medeff/index_e.html

Health professionals and consumers may report ARs toll free to Health Canada at:

Tel: 866 234-2345
Fax: 866 678-6789
Your call will be directed to the appropriate AR Regional Centre.

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