

How We Came To This PASS

The Current Post-Approval Surveillance System in Canada

A backgrounder
by the
Canadian Treatment Action Council



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About This Document

How We Came To This PASS briefly describes how prescription drugs are tested, approved, and monitored for safety in Canada.

Related Documents

- Improving our Health: the Need to Enhance the Post-Approval Surveillance System for HIV/AIDS Drugs in Canada (CTAC discussion paper; December 2000)

Descriptions of the Canadian Treatment Action Council's "PASS Study" – an investigation of post-approval drug surveillance methods:

- The PASS Study: A Brief Overview (CTAC fact sheet; March 2006 – a condensed, 4-page summary)
- The PASS Study: A Community Report (CTAC fact sheet; March 2006 – a more detailed report)

(All of the preceding documents are downloadable in PDF format from the CTAC website, www.ctac.ca, in English and in French.)

About CTAC

The **Canadian Treatment Action Council** (CTAC) is a national, non-governmental organization directed by people living with HIV/AIDS. CTAC informs public policy and promotes public awareness on treatment access and health care issues that impact people living with HIV/AIDS.

How we came to this PASS:

The current post-approval surveillance system in Canada

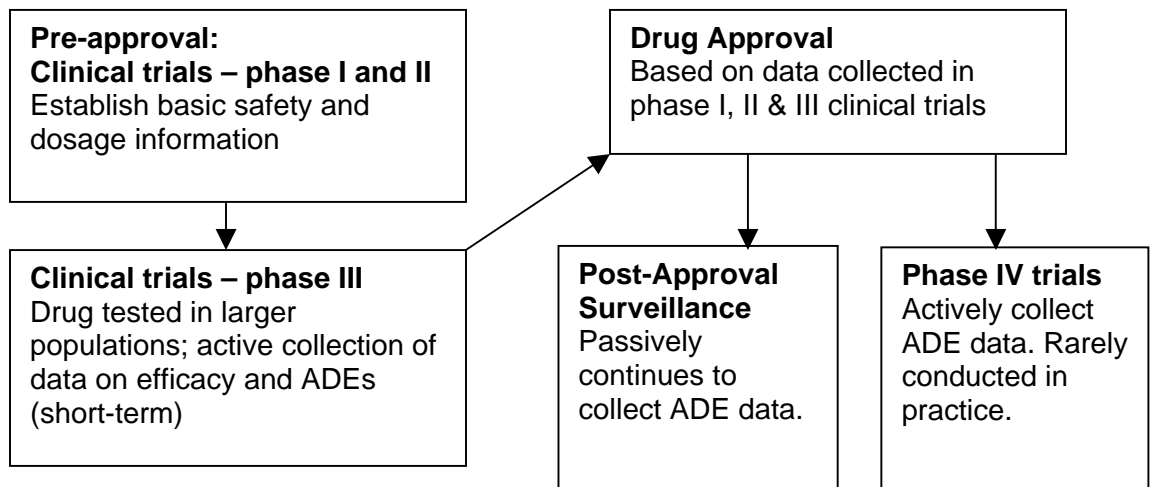
Pre-approval: How are drugs approved for sale in Canada?

Before a prescription drug is approved for marketing, it must go through *clinical trials*, which test how safe and effective it is. Information from clinical trials is submitted to Health Canada, along with other information collected during drug development, and the decision as to whether the drug is approved for sale in Canada is made based on this data. A drug cannot be sold in Canada until it has received marketing approval from Health Canada (a “Notice of Compliance” – NOC – or a conditional “NOC/C”: see page 5.) Before approval, drugs may be available through “compassionate access programs” and other special mechanisms; but unapproved drugs cannot be sold, and they are not available through regular prescriptions and pharmacy dispensing.

The manufacturing drug company submits its information to Health Canada’s Therapeutic Products Directorate (TPD) for review. (A separate body, the Biologics and Genetics Therapies Directorate (BGDT), handles “biologics” such as blood products, biotech products, and gene therapies.)

If the drug is approved, this information is published in its *product monograph*, which becomes the standard published reference information for that drug, including characteristics such as dosage, effectiveness, and adverse effects. The monograph becomes a ‘snapshot’ of what is known about the drug when it is approved. (Later information may be included in revised monographs, including priority safety warnings.)

After approval, information on ADEs (Adverse Drug Events – unwanted or harmful reactions to medications) is still collected, but the collection process is no longer quite so rigorous (see chart).



What is Canada's Post-Approval Surveillance System?

The system that tracks serious adverse drug events *after* the drug goes to market is called a *post-approval surveillance system*, or PASS. This may include formal “Phase IV” clinical trials, similar in structure to Phase III trials, which actively seek and collect information on drug safety and efficacy after the drug has been marketed. For the most part, however, PASS is a passive system in which drug companies and health officials only have to make limited efforts to find out about serious ADEs.

After a new drug is approved for distribution in Canada, the HPFBI (Health Product & Food Branch Inspectorate) makes sure that its manufacturer continues to meet industry quality standards in manufacturing, testing, and storage. New information about ADEs is the responsibility of the Marketed Health Products Directory (MHPD) – specifically, the Canadian Adverse Drug Reaction Monitoring Programme (CADRMP).

The CADRMP collects and monitors information about ADEs to approved drug products in Canada – including prescription and non-prescription, herbal, and homeopathic health products. This is meant to make sure that drug benefits continue to outweigh the risks, and that labelling and product information are updated to reflect new information.

At the time of the PASS Study, the CADRMP had one national office and five regional centres. (This number has now increased to seven.) If a doctor, pharmacist or other health care professional suspects a serious drug-related ADE, he or she can report it to one of these centres. Suspected ADEs can also be reported directly to the manufacturers, who are obligated to report all such information to Health Canada.

Participation by physicians and other health professionals is voluntary: they may report ADEs, but are not required to. The practical problems of (uncompensated) additional time and paperwork often make it difficult for health care professionals to use the reporting system. “Consumers” – people who actually take the medications – may report ADEs directly to drug manufacturers or the CADRMP, but very few are aware of this, and almost none actually do.

Only drug manufacturers are under mandatory requirement to report ADEs, including a “concise and critical analysis”, and an annual summary report of all ADEs. Above and beyond the annual report, reports must also be submitted when requested by the Director of the MHPD. We do not know how frequent those requests actually are.

Information reported to the CADRMP is summarized and distributed to health care professionals, health associations, and other interested parties through the quarterly *Canadian Adverse Drug Reaction Newsletter*. The Newsletter is also published in the *Canadian Medical Association Journal*, and on the Drugs & Health Products website. (See Health Canada Online box, page 6.)

Phase IV trials and NOC/Cs

In addition to the legislated PASS system, drug companies may pro-actively conduct Phase IV (“post-marketing”) clinical trials. In practice, these are not conducted very often. Theoretically, during the drug review process, the Health Products and Food Branch (HPFB) may request or demand that a drug company conduct a Phase IV trial after approval is granted, as a condition of approval. In reality, we do not know how often this happens, but there are no indications that it is frequent.

Sometimes, a drug may be “conditionally approved”. This means it is granted a “Notice of Compliance with Conditions” (NOC/C) instead of the usual Notice of Compliance (NOC) which allows a drug into the marketplace. Current policy demands that, if an NOC/C requires a Phase IV trial, the results of that trial must be filed with the HPFB for review. This will eventually ensure that HPFB is aware of these studies, will receive ongoing ADE data from them, and will be required to approve their results.

An NOC/C may also spell out post-approval commitments relating to monitoring ADEs, and may suggest ways to monitor safety. However, the policy that governs drug review does not specifically state how the HPFB makes these decisions. Advocacy towards more systematic regulation might be useful, but would likely require industry support.

Summary – Health Canada “Who does What”

Health Canada is the department of the Canadian government responsible for all areas of health, including drug regulations and monitoring. The *Food and Drugs Act* is the overall Canadian legislation by which all drug manufacturers must abide. It includes requirements for timely reporting of ADEs.

The **Health Products and Food Branch (HPFB)** is the main branch of Health Canada responsible for drugs, biologics, food and nutritional products, and other similar products. Within the HPFB, the **Therapeutic Products Directorate (TPD)** is the federal authority that approves and regulates pharmaceutical drugs.

In 2002, a **Marketed Health Products Directorate (MHPD)** was created, which is responsible for “monitoring and collecting all adverse reaction and medication incident data”¹. All adverse events are now reported to the MHPD through the **Canadian Adverse Drug Reaction Monitoring Program (CADRMP)**.

In addition, the **Health Product & Food Branch Inspectorate (HPFBI)** monitors adherence to good manufacturing practices in the production, testing, and storage of drugs.

¹ From the MHPD website (see next page).

Health Canada Online

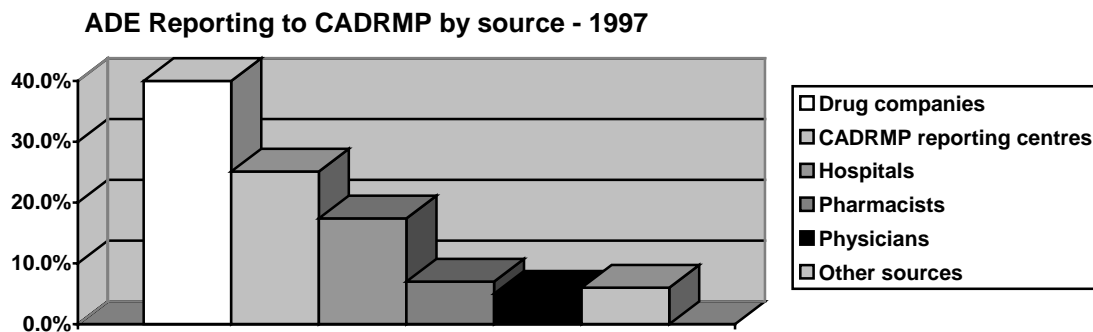
Health Canada's departments, programs, and consumer information sites pertaining to drug monitoring, are available online. Key sites include:

- www.hc-sc.gc.ca/index_e.html (Health Canada main page)
- www.hc-sc.gc.ca/dhp-mps/index_e.html (Drugs and Health Products)
- www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/mhpd-dpsc/index_e.html (Marketed Health Products Directorate - MHPD)
- www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index_e.html (Canadian Adverse Drug Reaction Monitoring Program [CADRMP] – MedEffect (Adverse Reaction Database))

Stats: How much is the current PASS system used?

Up to the year 1997, the CADRMP was receiving between 4,200 and 4,500 ADE reports from Canadian sources per year. Most of these came from drug manufacturers (see chart).

In 2002, Health Canada received 8,566 domestic reports of suspected adverse reactions to health products, mostly from pharmacists and physicians, and often from the manufacturer and the Regional Adverse Reaction Centre. Of these, 5,889 were classified as serious. (This is the total number of adverse reports for *all* drugs; only about 65 are related to antiretrovirals.)



Reporting of adverse reactions in Canada has increased over the past five years. When the PASS Study began, an estimated backlog of 18,000 adverse drug reaction reports dated back five years, which had not been entered into a database. According to the TPD, limitations are set by the Food and Drug Regulations, and by under funding. Other problems seem to include difficulties developing an adequate database, and the lack of consolidation of resources for ADE reporting in the Health Products and Food Branch.

Improvements: What's been proposed?

In 1998, the Health Protection Branch (as it was then called) formed a Working Group on HIV/AIDS to examine pre-approval and post-approval surveillance of HIV/AIDS drugs.

This group was formed to:

- define issues on adverse drug reaction reporting (the weaknesses and barriers, lessons learned from other jurisdictions, and proposed solutions);
- outline issues in information generation and dissemination on ADEs (current practices, and proposed improvements);
- examine current and future resource issues (comparative studies with other countries, a proposed HIV/AIDS pilot study, and other suggested initiatives); and
- to define where to proceed to next.

The group met several times and developed recommendations. These were presented to, and endorsed by, the HIV/AIDS and other stakeholder communities.

Summary: PASS in Canada – Barriers & Creative Solutions

Barriers to PASS

Due to the factors outlined above, we know that adverse effects of AIDS drugs are underreported in Canada. As a glaring example, the Therapeutic Products Directorate only received four reports of “fat redistribution” (attributed to the use of protease inhibitors) in 1998. Meanwhile, numerous published reports estimate lipodystrophy to occur in anywhere from 25% to 70% of PHAs on antiretroviral therapy.

Before initiating the PASS Study, CTAC identified the following barriers to effective PASS in Canada (by analyzing the existing literature, and through the consultation process):

- The current PASS does not capture new and evolving ADEs to approved HIV/AIDS treatments in a complete and timely manner.
- Although PHAs are openly discussing their experiences with drugs within the HIV/AIDS community, these effects are often not recognized or captured by health professionals or by the present Canadian PASS.
- Even when people living with HIV/AIDS do report adverse health effects to their health care professionals, these effects are often not reported to the present Canadian PASS.
- The existing legislation and Regulations from the *Food and Drugs Act* only require pharmaceutical companies to report ADEs. Consumers and health care professionals are not required to report ADEs, though they may do so voluntarily. This system has seriously underestimated new and evolving adverse effects.
- There is no organized, comprehensive method for keeping consumers informed about evolving drug side effects. Treatment information programs in ASOs may try to keep PHAs informed, but not through any direct partnership with Health Canada. It is up to the expertise of individual health professionals to stay informed and keep their patients informed.
- Terminology used to monitor ADEs is not always consistent.

This is not a complete list of barriers; however, these are the ones addressed by CTAC's PASS Study. The PASS Study was done in the hopes that community-generated ideas could offer creative suggestions for improvement in monitoring antiretroviral ADEs.

Creative Solutions and Recent Initiatives

Outside of the PASS Study, the community is taking many other active steps – such as community forums, support/information exchange groups, and Internet chat lines (such as LIPIDLIST, an Internet forum about lipodystrophy and related complications).

See CTAC's backgrounder, *Improving our Health: the Need to Enhance the Post-Approval Surveillance System for HIV/AIDS Drugs in Canada*, for further information on PASS-related initiatives.

Another Health Canada pilot project, in partnership with The University of Ottawa Health Services, was implemented in 2002. This project included three phases:

1. Proof of Concept (one local sentinel site),
2. Validation (in a select group of sentinel sites), and
3. Integration (into the HIV/AIDS service community).

This study looked at 68 patients of various ethnicities between 18 and 55+ years old. The Proof of Concept analysis (Phase 1) tested a patient-centred ADE reporting scheme (patients reporting to a health care nurse), and one directed at clinic nurses to extract data from patients' charts. It showed that PHAs on medications were prepared to report their adverse drug events (ADEs), that such reporting would work, and that "patient-centred reporting" could be a viable alternative/addition to the existing Health Canada PASS system.

In June 2005, Health Canada announced that it would be holding consultations on developing a mandatory system for reporting adverse reactions. To begin this process, a discussion paper entitled, *Designing a Mandatory System for Reporting Serious Adverse Reactions*, has been posted on Health Canada's web site². The Health Canada press release states: "Currently, adverse reaction reporting by health professionals is voluntary, unlike the mandatory reporting of serious adverse reactions that is required of manufacturers. Yet health professionals are in an ideal position to observe adverse reactions experienced by their patients and to report them in a clear and scientific way... [however] the design for reporting adverse reactions cannot put an undue burden on our health care professionals."³ Wider consultations with stakeholders and the public will continue.

² ³ Health Canada press release, [Hwww.hc-sc.gc.ca/ahc-asc/media/nr-cp/2005/2005_68_e.html](http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2005/2005_68_e.html)