# *Improving our Health:*

## *The Need to Enhance the Post-Approval Surveillance System for HIV/AIDS Drugs in Canada*

***A Discussion Paper***

**prepared by**
**the Canadian Treatment Advocates Council**

**December 2000**

# Acknowledgements

The author wishes to thank the following persons for providing information during the research phase of this paper:

**Suzanne Cadden**, Glaxo-Wellcome Inc.
**Robert Peterson**, **Susanne Reid**, **Heather Setcliffe**, Health Canada

The author also wishes to thank **Louise Binder**, **Tom McAulay** and **Greg Robinson** of the Canadian Treatment Advocates Council for providing information and guidance and for critiquing early drafts of the paper.

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# Executive Summary

Canada has an inadequate and ineffective system of post-approval surveillance of drugs that have been licensed for sale. Systems for reporting adverse drug reactions are weak. This is particularly problematic with respect to HIV/AIDS drugs since they often generate more adverse reactions than other drugs. This has negative implications for the long-term health of some persons living with HIV/AIDS.

## Problems

There are many problems with the current system. The following is a summary of the problems:

### Reporting Problems

1. Pharmaceutical companies are not required to report adverse drug reactions.

2. There is no requirement for health care professionals or consumers to report serious adverse drug reactions or adverse drug reactions, nor are they actively encouraged to do so.

3. There is no formal process in place for consumers to report serious adverse drug reactions and adverse drug reactions.

4. Persons living with HIV/AIDS are not reporting to health care professionals all adverse reactions to the drugs they are prescribed.

5. Even when people living with HIV/AIDS do report adverse drug reactions to their health care professionals, these reports are often not being forwarded on to the national surveillance system either directly or through pharmaceutical companies.

6. Health care professionals are not always sure which drug may have caused an adverse reaction.

### Systemic Problems

1. The post-approval surveillance system lacks clear goals, objectives and action plans.

2. The Canadian Adverse Drug Reaction Monitoring Programme (CADRMP) is not well known to health care professionals across Canada.

3. There is a lack of consistency in the terminology used in the monitoring of adverse drug reactions.

4. The roles of federal and provincial governments around the monitoring of the ongoing effectiveness of licenced drugs are blurred

5. Post-approval surveillance is not a priority within Therapeutics Products Programme (TPP) or the Health Protection Branch. There are insufficient resources devoted to post-approval surveillance.

6. It is not clear whether a portion of the Drug Information Number (DIN) fees are being assigned to post-approval surveillance.

7. There is a lack of coordination of resources within TPP.

8. There is a lack of information-sharing.

9. There are problems with the database that is being used to record reports of drug reactions.

**Programmatic Problems**

1. Pre-marketing clinical trials fail to identify many adverse reactions.

2. Few Phase IV clinical trials are being conducted.

3. For those adverse drug reactions that are reported to CADRMP, there is no system in place to disseminate information on them to HIV/AIDS consumers and the organizations that represent them.

4. There is a lack of information coming from other countries.

## Recommendations

To improve the system and make it more responsive, the Canadian Treatment Advocates Council advances the following guiding principles and recommendations:

**Guiding Principles**

1. It should be consumer-centred.

2. It should be easily accessible.

3. It should meet Canadian needs – i.e., it should use a Canadian database and Canadian strategies for data collection.

4. It should be open and transparent.

5. It should respect individual confidentiality.

**General Recommendations**

1. TPP should develop a comprehensive strategy for post-approval surveillance of HIV/AIDS drugs. The strategy should include (a) measures to promote and facilitate the reporting of adverse reactions by manufacturers, health care professionals and consumers; (b) improved analysis of the adverse reaction data to spot trends and problem areas; (c) the commissioning of research on the causes of adverse reactions; (d) improved dissemination of the data, the analysis of the data and the results of the research; and (e) making Phase IV trials a condition of licensing of the drug. This strategy could serve as a blueprint for the post-approval surveillance of all drugs licensed for sale in Canada.

2. TPP should establish clear goals and objectives for its post-approval surveillance system.

3. Federal and provincial/territorial levels of governments should agree on their respective roles in a national post-approval surveillance system.

4. TPP should establish an advisory body whose membership includes a broad spectrum of stakeholders, including community representation. The role of the advisory body should be to advise TPP on the post-approval surveillance system.

5. TPP should keep the Federal-Provincial-Territorial Pharmaceutical Issues Committee abreast of developments with respect to the post-approval surveillance system, and should encourage joint activities, where appropriate.

6. TPP should provide an accounting of the annual Drug Information Number (DIN) renewal fees it receives, and should ensure that an appropriate percentage of these fees is allocated to the post-approval surveillance system (as per original and ongoing agreements).

7. Information on the post-approval surveillance system should be included in medical schools and programmes for continuing education (for physicians and other health care professionals).

8. TPP should analyze incoming reports of drug reactions on a timely basis, and prepare synopses based on these analyses.

9. TPP should develop and implement mechanisms to ensure timely, broad and effective dissemination of adverse drug reaction synopses to all stakeholders. The synopses should be provided to one or more community-run newsletters as well as peer-reviewed scientific journals.

10. TPP should promote the development of a system for the international collection, analysis and sharing of information on serious adverse drug reactions and adverse drug reactions.

11. TPP should standardize the terminology it uses for the monitoring of adverse reactions.

12. TPP should ensure that its post-approval surveillance activities are centralized in one or two divisions within the Bureau of Licensed Product Assessment and are well-coordinated.

13. TPP should ensure that information is shared between the officials involved in pre-marketing approval of drugs and those involved in post-approval surveillance.

**Recommendations Specific to Gathering Data on Adverse Reactions**

1. The Regulations should be altered to require drug manufacturers to report adverse drugs reactions as well as serious adverse drug reactions.

2. The post-approval surveillance system should include effective mechanisms for consumers, health care professionals and other stakeholders to report drug reactions and drug reactions.

3. TPP should develop local, regional and national strategies to solicit reports of drug reactions from health care professionals.

4. TPP should develop local, regional and national strategies to solicit reports of drug reactions from consumers and organizations that represent consumers.

5. TPP should ensure that its strategies for soliciting reports of drug reactions address issues specific to women (e.g., menstrual, menopause, hormonal, pregnancy) and other population groups.

6. A comprehensive education programme should be developed for people reporting drug reactions.

7. TPP should ensure that its database systems are upgraded to accommodate increasing number of reports of drug reactions and to facilitate analysis of the data.

8. TPP should ensure that the reports of drug reactions continue to be entered on its database system on a timely basis.

9. TPP should embark on more pilot projects to test various methods of gathering data on drug reactions.

10. TPP should endeavour to obtain information on drug reactions on a regular basis from other countries.

# Section I
# Introduction

Many of the drugs that have been approved for sale in Canada, perhaps as many as half, have serious side effects that are not detected prior to licensing. Frequently, drug interactions and beneficial side effects also go undetected. Canada currently has an inadequate and ineffective system for post-approval surveillance, a term that describes the monitoring of drugs after they have been licensed for sale. Systems for reporting adverse drug reactions are weak. As well, Phase IV clinical trials – trials conducted after a drug is licensed – are rarely undertaken.

Drugs for the treatment of HIV/AIDS probably generate more adverse reactions than other drugs. Because they are so urgently required, HIV/AIDS drugs are often approved following relatively short clinical trials based on surrogate marker outcomes. As a result, the long-term side effects of these treatments, and the interactions between these treatments and other drugs, are not usually identified during the trials. This has negative implications for the long-term health of some persons living with HIV/AIDS.

The goals of post-approval surveillance include:

- ❑ recognizing, as early as possible, new safety and effectiveness information;
- ❑ refining and adding to information on suspected or known reactions and interactions;
- ❑ reviewing the merits of one drug compared with other drugs and other types of therapy;
- ❑ communicating the information in a way that improves therapeutic practice; and
- ❑ identifying the beneficial effects of drugs.

Canada's system of post-approval surveillance does not adequately meet these goals.

The purpose of this discussion paper is to explain the concerns that persons living with HIV/AIDS and their representatives have with the current system of post-approval surveillance and to suggest ways in which the system can be improved.

After this Introduction, Section II of the Paper provides definitions of some of the terms commonly used in any discussion of this topic. This is followed in Section III by a description of the current system of post-approval surveillance in Canada. Section IV summarizes the findings of some of the major reports on this topic produced in Canada in the last ten years. The problems with the current system are outlined in Section V. Finally, in Section VI, some conclusions and recommendations are presented.

## Limitations

This is a discussion paper. As such, it is designed to provoke discussion of the issues around post-approval surveillance of HIV/AIDS drugs. Further work will be required to describe the issues in more detail and to find definitive solutions to the problems with the current system.

## Note About Terminology

The terms “post-marketing surveillance,” “post-approval surveillance,” and “pharmacovigilance” are often used interchangeably (see Section II Definitions). The first two of these terms are the ones most commonly used. We have chosen to use the term “post-approval surveillance.” We believe that it is the more accurate term. “Post-marketing surveillance” can be construed to mean surveillance that occurs only after a drug has left the market; this would be an incorrect interpretation.

# Section II
# Definitions

To better understand the issues involved in any discussion of post-approval surveillance, it is useful to define the various terms used. Some of the definitions presented below are based on documentation provided by Health Canada and on textbooks on this topic. The definitions have been divided into three categories:

- ❑ drug interactions and reactions;
- ❑ surveillance and reporting; and
- ❑ other.

## Drug Interactions and Reactions

**DRUG INTERACTION**
A drug for which the pharmacokinetics or pharmacodynamics (see definitions below) are altered by the presence of another drug.

**ADVERSE DRUG REACTION**
**DRUG SIDE EFFECT**
A noxious and unintended response that occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function.[1]

**SERIOUS ADVERSE DRUG REACTION**
A noxious and unintended response to a drug that requires in-patient hospitalization or prolongation of existing hospitalization; or causes congenital malformations; or results in persistent or significant disability or incapacity; or is life-threatening or results in death.[2]

**UNEXPECTED ADVERSE DRUG REACTION**
**SERIOUS UNEXPECTED ADVERSE DRUG REACTION**
An adverse drug reaction or a serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out on the label of the drug.[3]

**SIGNAL**
An event or series of events that indicate a new or evolving adverse effect of a drug.

## Surveillance and Reporting

**SURVEILLANCE**
The ongoing systematic collection, analysis, and interpretation of health data essential to the planning, implementation and evaluation of (public) health practices, closely integrated with the timely dissemination of the data to those who need to know.

**ACTIVE SURVEILLANCE**
A surveillance system or study where responsible authorities seek out events occurring in a population.

**PASSIVE SURVEILLANCE**
A surveillance system or study where responsible authorities do not seek out events occurring in populations, but rely instead on spontaneous or voluntary reporting.

**POST-APPROVAL SURVEILLANCE**
**POST-MARKETING SURVEILLANCE**
**PHARMACOVIGILANCE**
Continued monitoring of a drug after it has been licensed for public use. The monitoring is designed to provide information on the actual use of the drug for a given indication and on the occurrence of side effects, adverse reactions and drug interactions.[4] Sometimes these terms are used more narrowly to refer only to monitoring adverse reactions.[5]

**PHASE IV TRIAL**
A surveillance trial designed to estimate the frequency of uncommon side effects, toxicity or interactions (also called expanded safety trials in drug development).[6] Sometimes the term is used more broadly to refer to controlled prospective trials that monitor comparative efficacy, effectiveness and ongoing safety.[7]

**CONTINUING ASSESSMENT**
Refers to the study of a new drug throughout its clinical life, beginning at the clinical trial stage and ending only when the drug is withdrawn from the market.[8]

**SPONTANEOUS REPORTING**
**VOLUNTARY REPORTING**
Notification of suspected adverse reactions to drug products or other therapeutic products to a centralised agency on a spontaneous or voluntary basis, usually by practising health professionals.[9]

## Other

**CONFIRMATORY TRIAL**
An adequately controlled clinical trial in which the hypotheses are stated in advance and evaluated. As a rule, confirmatory trials are necessary to provide firm evidence of efficacy or safety.[10]

**DRUG EFFECTIVENESS**
A term used to describe how well treatments work in a real world setting. Effectiveness is a composite assessment of various factors such as drug efficacy; patient adherence; provider adherence to practice, standards or guidelines; and coverage (access to treatment) for those in need of treatment.

**DRUG EFFICACY**
The ability of a therapeutic product to bring about the intended beneficial effects for individuals in a defined population with a given medical problem, under ideal conditions.[11]

**INTERNATIONAL CONFERENCE ON HARMONIZATION (ICH)**
An initiative that brings together the regulatory authorities of Europe, Japan and the United States, and experts from the pharmaceutical industry in these three regions, to discuss scientific and technical aspects of drug product registration. The objective is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and the requirements for drug product registration. Canada is an observer to the ICH process.

**PERIODIC SAFETY UPDATE REPORT (PSUR)**
A report that provides information on the world-wide safety experience with an active substance at specific times following its approval for use. The format and content of this report have been agreed upon by the International Conference on Harmonization.

**PHARMACODYNAMICS**
The branch of pharmacology that deals with the effect and the reactions of drugs within the body.[12]

**PHARMACOLOGY**
The scientific study of the composition, use and effects of drugs and medicines.[13]

**PHARMACOEPIDEMIOLOGY**
The study of the distribution and determinants of drug-related events in populations, and the application of this study to efficacious drug treatment.[14]

**PHARMACOKINETICS**
The branch of pharmacology that deals with the absorption, distribution, and elimination of drugs by the body.[15]

# Section III
# Description of the Current System

In Canada, the licencing process for new drugs and the post-approval surveillance of licensed drugs, including the monitoring of adverse drug reactions, is governed by Health Canada under the *Food and Drugs Act* and its accompanying Regulations. The Therapeutic Products Programme (TPP), Health Canada, reviews submissions from drug companies on the safety, efficacy and quality of new drugs before approving them for marketing in Canada. The drug review process involves a complex balancing of evidence on the risks and benefits of a new drug. After a drug is licenced for marketing, TPP continues to monitor the new drug for safety, effectiveness and quality through its Bureau of Licensed Product Assessment. Data on adverse drug reactions are gathered by the Canadian Adverse Drug Reaction Monitoring Programme (CADRMP), which is part of the Bureau's Adverse Reaction and Medication Error Assessment Division. The Bureau is in the process of establishing an Active Surveillance, Research and Product Utilization Review Division. (See Appendix A for organization charts of TPP and of the Bureau of Licensed Product Assessment.)

Regulations issued under the *Act* require that manufacturers of a drug provide the Director of TPP at Health Canada with any information they have on serious adverse drug reactions. The Regulations require that reports of serious adverse drug reactions occurring in Canada, and serious unexpected adverse drug reactions occurring outside Canada, be submitted within 15 days after the information is received.

Although manufacturers are required to report serious adverse drug reactions known to them, there is nothing in the *Act* that obliges health professionals (or any other stakeholders) to report such reactions. As a result, some serious adverse drug reactions go unreported.

Manufacturers are also required to conduct a concise and critical analysis of both serious adverse drug reactions and adverse drug reactions annually (and whenever requested by TPP) and to prepare a summary description of all reports of drug reactions received in the previous 12 months. TPP can request copies of the summary descriptions as well as the individual reports of drug reactions.[16] In practice, TPP seldom asks for these descriptions to be provided.

## Voluntary System

The reporting system for adverse drug reactions relies primarily on physicians, pharmacists and other health care professionals voluntarily providing the information to the manufacturer or to CADRMP. Consumers can report adverse drug reactions directly to CADRMP, but this is rare. Most drug manufacturers have post-approval units; however, it is not known whether the work of these units extends to compiling information from the voluntary reporting system and fulfilling the regulatory requirements of the *Food and Drugs Act*.

Guidance for health care professionals is provided in the Report of Adverse Reaction Suspected Due to Drugs, Cosmetics and Biological Products (Vaccines Excluded), a reporting form

prepared by Health Canada (see Appendix B). This form states that the following adverse effects should be reported:

- **all suspected** adverse reactions to drugs which are unexpected – i.e., not consistent with product information labeling;
- **all suspected** adverse reactions to drugs which are serious – i.e., death or reactions that contribute to significant disability or illness, result in hospitalization, prolong hospitalization or require significant medical intervention; and
- **all suspected** adverse reactions to **recently marketed drugs** (on the market for less than five years) regardless of their nature or severity.[17]

(Underlined and bold text is as per the form.)

The form also states that causality (i.e., proof that a drug caused an undesirable patient effect) is not a requirement for reporting an adverse drug reaction. It says that health care professionals should issue a report if the event is suspected of being drug-related, particularly if the event is unusual in context of the illness.[18]

Health care professionals may report adverse drug reactions directly to the national office of CADRMP; to any of its six Regional Adverse Drug Reaction Reporting Centres (Atlantic, Saskatchewan, British Columbia, Ontario, Quebec, Other Provinces and Territories); or to the drug manufacturer.

## Role of CADRMP

The role of CADRMP is to collect and monitor adverse drug reaction information to ensure (a) that the benefits of a drug continue to outweigh the risks; (b) that labeling and product information for a drug product are continually updated; and (c) that Canadians and health care professionals are informed on a regular basis of adverse reactions to drugs licenced in Canada.[19,20]

CADRMP monitors adverse reactions to all licenced drug products, including non-prescription drugs, herbal products and homeopathic products. Reports of adverse reactions are entered onto the Canadian Adverse Drug Reaction Database. The information provided to CADRMP is rolled up into reports that are distributed quarterly to health care professionals, health associations and other interested parties via the Canadian Adverse Drug Reaction Newsletter. An issue of the Canadian Adverse Drug Reaction Newsletter is included in Appendix C. Reports are also published regularly in the Canadian Medical Association Journal and are available on the TPP website (<http://www.hc-sc.gc.ca/hpb/drugs/>).

In 1999, the national office of CADRMP received a total of 5,688 reports from Canadian sources (2,999 serious adverse drug reaction reports and 2,689 adverse drug reaction reports). Of the 5,688 reports, 48% were provided by manufacturers, 44% by the regional reporting centres, and

8% by other sources. With respect to the types of individuals who initiated the reports, the breakdown is as follows:

- ❏ pharmacists [37%];
- ❏ physicians [25%];
- ❏ other health care professionals (e.g., nurses, dentists, coroners) [26%];
- ❏ consumers [9%]; and
- ❏ other [2%].[21]

At the beginning of 1998, there were indications that CADRMP had a large backlog of reports of serious adverse drug reactions – i.e., reports not entered onto the Canadian Adverse Drug Reaction Database. TPP says that all serious adverse drug reaction reports are now being processed in a timely manner; that all Canadian reports received since January 1, 1998 have been entered onto the Canadian Adverse Drug Reaction Database; and that all serious adverse drug reaction reports received between 1965 and January 1, 1998 have been entered either on the Canadian Adverse Drug Reaction Database or onto a separate tracking database.[22]

## Advisory Committees and Working Groups

The work of several advisory committees and working groups influences the post-approval surveillance activities of TPP.

**Advisory Committee on Management.** This committee provides management and policy advice to the Director of TPP, including guidance on the TPP Pharmacovigilance Strategy. There is a consumer representative on this committee; however, this person is not an HIV/AIDS-related consumer.

**Expert Advisory Committee (EAC) on Pharmacovigilance.** This committee "...provides the directorate with on-going and timely advice on issues related to post-approval safety, quality and effectiveness of drug products."[23] More specifically, it "....identif(ies) specific issues and concerns, provide(s) advice on matters of science and policy, assess(es) adverse drug reaction reports and drug product complaints, and evaluate(s) drug safety issues related to misuse, abuse or off-label use..."[24] In 1997, the EAC on Pharmacovigilance replaced the former Canadian Adverse Drug Reaction Advisory Committee, the mandate of which was limited to the monitoring of adverse effects after the drugs were licensed. The EAC on Pharmacovigilance has eight members selected from family and clinical medicine, pharmacy, pharmacology, pharmacoepidemiology, geriatrics, pediatrics, and poison information and control.

**Working Group on HIV/AIDS.** This group was established by TPP in 1998 to examine pre-approval and post-approval systems for HIV/AIDS drugs. The working group set up a Sub-Group on Post-Market Surveillance that met once by teleconference (November 1998) and once face-to-face (January 1999). The mandate of the sub-group was: (a) to define issues on adverse drug reaction reporting (the weaknesses and barriers, lessons learned from other jurisdictions, and proposed solutions); (b) to outline issues in information generation and dissemination on adverse drug reactions (current practices, and proposed improvements); (c) to examine current and future resource issues (comparative studies with other OECD countries, a proposed HIV/AIDS pilot study, and any other suggested initiatives); and (d) to recommend future

directions. After the face-to-face meeting in January 1999, the sub-group ceased to exist and its mandate was taken up by the full working group. In October 1999, the working group produced a series of recommendations on the drug review process of TPP, including some on post-approval surveillance (see Appendix D). The working group was disbanded in 1999.

**Advisory Committee on Product Licensing Review.** This multi-stakeholder group was set up to oversee the implementation of the recommendations of the Working Group on HIV/AIDS.

**Public Advisory Committee.** In the process of being formed, this committee is designed to improve accountability and transparency within the Therapeutics Products Programme. A working group is currently developing the Committee's terms of reference. There are about 40 people on the working group, representing various stakeholders (except the drug industry).

## Pilot Project

In 1998, TPP established the Enhanced Post-Marketing Surveillance of HIV/AIDS Drug Therapies Pilot Project to develop and test alternate methods and formats for reporting adverse drug reactions to HIV/AIDS drugs. The pilot project consists of three phases: Phase 1 – Proof of Concept (in partnership with a selected field site); Phase 2 – Validation (in partnership with a select group of sentinel sites); and Phase 3 – Integration (in partnership with HIV/AIDS community services). In Phase 1, TPP partnered with the Health Sciences Divisions of the University of Ottawa to develop and assess two alternate reporting methods: (a) patient self-reporting of adverse drug reactions and (b) extracting adverse drug reaction data from patient charts. This phase has been recently completed; a summary evaluation report is in the final stages of review.[25]

# Section IV
# Previous Reports on Post-Approval Surveillance

A number of reports produced by and for Health Canada have reviewed the objectives of post-approval surveillance and the way in which the Therapeutics Products Programme (TPP) monitors the ongoing safety, quality and effectiveness of drugs after they have been licensed. Several pivotal reports are reviewed in this Section.

**HLYNKA J.N. DEVELOPING A NATIONAL POST-MARKETING PHARMACEUTICAL SURVEILLANCE PROGRAMME (PPSP). JUNE 1991.[26]**
*Consultant report to Bureau of Pharmaceutical Surveillance, Drugs Directorate, Health Protection Branch, Health and Welfare Canada. Also referred to as the Hlynka Report.*

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The Hlynka Report was commissioned as a result of a commitment by the former Drugs Directorate (now part of TPP) to develop a new Post-Marketing Pharmaceutical Surveillance Programme (PPSP). The Report is a blueprint for the development of a PPSP. It includes: (a) specific objectives; (b) the components of PPSP required to meet the objectives; (c) a programme structure; (d) a list of the participants or stakeholders that should be involved in the development of PPSP; and (e) the developmental priorities of the programme.

The Hlynka Report described the scope of post-approval surveillance as broader than the monitoring of adverse effects to licenced drugs. It said that such surveillance should extend to both the use and effects of drug products. Hlynka recommended that post-approval surveillance include three programme components: monitoring adverse drug reactions, drug use review and drug post-approval evaluation. He proposed that a Bureau of Pharmaceutical Surveillance be established, with a Division of Post-Marketing Surveillance that would contain three sections corresponding to the three programme components: a Drug Utilization Review Section, an Adverse Drug Reaction Reporting Section, and a Post-Market Evaluation Section. The role of the Canadian Adverse Drug Reaction Reporting Advisory Committee (CADRAC), which at that time was an advisory body to the directorate, was to be limited to input into post-marketing evaluation, adverse drug reaction signal assessment and evaluation, and Phase IV studies. Although the Report identified patients and consumers as stakeholders, it did not propose that representatives of this group be added to CADRAC; the Report assumed that their interests could be represented by others involved in the development of the PPSP.

The Hlynka Report provided some useful information on the scope and roles of the recommended programme components. It defined drug utilization review as "the retrospective measurement of patterns of drug use."[27] Hlynka identified this as a national role and differentiated it from drug use evaluation, which he defined as "the comparison of patterns of drug use to some pre-determined standards..." to detect over-use, under-use and contraindications to the use of specific drugs, and which he saw as a provincial responsibility.[28]

Hlynka identified the features of post-approval evaluation as:

- ❑ the assessment and evaluation of signals generated from an adverse drug reaction reporting system;
- ❑ coordinated, controlled prospective protocols for the monitoring and evaluation of the safety and effectiveness of drugs as part of drug regulatory requirements, either in response to pre-market studies or as a result of an adverse drug reaction signal; and
- ❑ research centres (public and private) to support the features described in the two bullets above.

The Report recognized the breadth of surveillance required to extend the information gained in pre-market clinical trials to the study of a greater number of patients on an ongoing basis, over a longer term, and in real-world conditions that are not achieved during clinical trials (e.g., different populations, different degrees of adherence to drugs, different prescribing practices of physicians).

The Report prescribed the development of regional centres in Canada to improve spontaneous adverse drug reaction reporting, investigation of reports, and education of health care providers. The adverse drug reaction reporting system proposed by Hlynka included spontaneous reporting (this is the same passive system of surveillance in existence today) and a programme of controlled monitoring[**] for adverse drug reaction reporting. Unfortunately, Hlynka did not discuss the controlled monitoring component, stating only that "... the potential of controlled monitoring studies are unknown at this time..."[29]

**GAGNON, ET AL. WORKING IN PARTNERSHIPS...DRUG REVIEW FOR THE FUTURE, REVIEW OF THE CANADIAN DRUG APPROVAL SYSTEM. JULY 1992**[30]
*Consultant Report to the Drugs Directorate, Health Protection Branch, Health and Welfare Canada. Also referred to as the Gagnon Report.*

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The Gagnon Report recognized that there is often limited information on the safety and efficacy of drugs prior to marketing. The Report described the evaluation of drug safety, efficacy and effectiveness as a continuum of knowledge that begins with the pre-market development of a drug and extends over its market history. Gagnon recognized that the performance of a drug while on the market needs to be assessed through a number of indices that extend beyond the voluntary submission of suspected adverse drug reaction reports, and that there needs to be a timely and appropriate response to such reports.

Like the Hlynka Report, the Gagnon Report recommended the consolidation of the adverse drug reaction reporting activities which were spread throughout the Health Protection Branch. It recommended a new unit at the national level (the Pharmacovigilance Unit) that would "...be responsible for adverse drug reaction reporting, liaison and support for Regional Centres, Drug

[**] Controlled monitoring can refer to a registry of each person who fills a prescription. The use of the registry involves calling patients who have filled a prescription regularly to inquire about any adverse drug reactions they have experienced to the medication(s) they are taking. Controlled monitoring has also been used in the context of conducting Phase IV trials.

Use Review initiatives, international programmes such as the World Health Organizations Adverse Reaction Monitoring Scheme and support for CADRAC."[31]

The Report recommended that post-approval surveillance include the quality of a drug as well as its adverse effects and effectiveness, and outlined the range of actions required within a system of post-approval surveillance, from education to regulation.

While Gagnon supported the encouragement of voluntary reporting of adverse drugs reactions, he also said that "the provinces and the federal government should hold discussions with health professionals' associations to study the feasibility of mandatory Adverse Drug Reaction reporting."[32] As well, Gagnon recommended that the conditional approval of drugs for life-threatening conditions should include the provision for continued post-marketing studies and for reviews of the product after specified time periods.

**STRATEGIC PRIORITIES PROJECT (DISCUSSION PAPER), PROJECT C-3, CANADIAN ADVERSE DRUG REACTION ADVISORY COMMITTEE (CADRAC). MARCH 1996.**
*Internal report, Drugs Directorate, Health Protection Branch, Health Canada*

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For the most part, this paper examined the role and function of the CADRAC, the mandate of which, at the time, largely centred on adverse drug reactions reporting. By this time, previous reports, such as Hlynka and Gagnon, were articulating that the scope of post-approval surveillance needed to be more comprehensive. This paper appears to have been conducted after a new Expert Advisory Committee on New Active Substances (EACNAS) had been created. The mandate of the EACNAS and CADRAC overlapped in the area of post-approval surveillance.

The paper evaluated a range of options that would assign the mandate of post-approval surveillance to either the EACNAS or CADRAC, or that would see the two committees share the responsibility. The paper concluded that "...coordinating all post-approval surveillance activities together in one bureau (the Bureau of Drug Surveillance), which is advised by a single competent EAC (i.e., CADRAC or its nominal successor), is critical for the development of an integrated, efficient and effective national approach to post-approval surveillance of drug products in Canada." The paper recommended retaining CADRAC, changing its name to reflect broader terms of reference, and limiting the EACNAS to focussing on pre-approval issues and sharing findings with the revamped CADRAC. The paper suggested several possible names for the revamped committee, including the Expert Advisory Committee on Post-Approval Surveillance and the Expert Advisory Committee on Pharmacovigilance.

**PRODUCT LICENSING FRAMEWORK III (DRAFT). JUNE 1998.**[33]
*Internal report, Therapeutic Products Programme, Health Canada*

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The Product Licensing Framework outlined a process for pre-market review and linked this review to post-approval reporting. According to the system proposed in this document, drugs that receive a favourable pre-market review and a licence to market would be assigned to one of three post-approval reporting schedules. The reporting schedules would determine which reports would have to be filed, the reporting frequency and the frequency of TPP's review of the

assigned reporting schedule (for possible schedule reassignment). The framework proposed three post-approval reports: a Periodic Safety Update Report, an Adverse Drug Reaction Summary Report, and a Product/Substance Summary Report. It is important to note that this framework would not alter the current system of voluntary post-approval surveillance of adverse effects of licenced drugs. To date, none of the proposals in the Framework document have been implemented.

**HEALTH PROTECTION BRANCH POLICY ON CONDITIONAL LICENCES. MAY 1998.**[34]
*Internal document, Therapeutic Products Programme, Health Canada*

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This constituted a new policy on the issuance of Notices of Compliance with Conditions(NOC/C). The purpose of the policy was to provide patients who have catastrophic or severely debilitating disease with earlier access to promising new drugs. While earlier access can benefit patients, there are potential risks resulting from the limited amount of clinical research conducted prior to approval of the drug. Knowledge of the continued efficacy, effectiveness and adverse effects of the drug will continue to evolve after it is released on the market. In recognition of this fact, the NOC/C policy requires a "sponsor's written commitment to pursue confirmatory trials acceptable to the Therapeutic Products Programme."[35] The policy specifically refers to these confirmatory trials in reference to the continued efficacy of the drug. However, the policy leaves the nature and scope of the confirmatory studies to the discretion of the TPP. The policy also requires that the sponsor submit adverse drug reaction reports to the TPP in accordance with regulations and guidelines; this appears to refer to the same voluntary reporting system that is in place currently. This policy allows TPP to withdraw a drug given an NOC/C from the market if confirmatory trials requested by TPP on the safety and effectiveness of a drug are not completed and submitted to TPP in a timely fashion.

This policy may lead to more confirmatory trials; however, more time is required to determine whether the policy will be effective in this regard.

# Section V
# Problems with the Current System

The passive adverse drug reaction surveillance system in place to this day is not capable of capturing, analyzing and disseminating complete, accurate and timely information on new and evolving adverse drug reactions to approved HIV/AIDS treatments (or on beneficial side effects and drug interactions). There are many problems with the current system. A number of them are defined and discussed below. The problems have been grouped into three categories:

- ❑ reporting;
- ❑ systemic; and
- ❑ programmatic.

## Reporting Problems

### *1. Pharmaceutical companies are not required to report adverse drug reactions.*

Under the Regulations, drug manufacturers are required to report only serious adverse drug reactions. They may report some adverse drug reactions as well, but we believe many adverse drug reactions go unreported. Reporting of adverse drug reactions is important because it can help to detect trends and because adverse drug reactions can develop into serious adverse drug reactions.

### *2. There is no requirement for health care professionals or other stakeholders, including consumers, to report serious adverse drug reactions or adverse drug reactions, nor are they actively encouraged to do so.*

Under the Regulations, only pharmaceutical companies have an obligation to report, and even then, only in the case of serious adverse drug reactions.

### *3. There is no formal process in place for consumers to report serious adverse drug reactions and adverse drug reactions.*

Even when consumers and the organizations that represent them decide that they would like to provide a report on a serious adverse drug reaction or adverse drug reaction, there is no formal process in place for them to follow. Consumers do not know who to contact, where to send the information or exactly what information is required.

### *4. Persons living with HIV/AIDS are not reporting to health care professionals all adverse reactions to the drugs they are prescribed.*

Although information on many adverse drug reactions is shared within personal support networks at the local level, it is not being recognized or captured in a timely fashion by health care professionals and the current Canadian post-approval surveillance system. The extent of this under-reporting has not been quantified.

### 5. *Even when people living with HIV/AIDS do report adverse drug reactions to their health care professionals, these reports are often not being forwarded on to the national surveillance system either directly or through pharmaceutical companies.*

The current voluntary reporting system is extremely passive. Even if a severe adverse drug reaction occurs, physicians are not always reporting the event to the Canadian Adverse Drug Reaction Monitoring Programme (CADRMP). For example, in 1998, a person who had been hospitalized for severe weight loss attributed to antiretroviral medication determined that his or her physician had not reported the hospitalization (an adverse event) to CADRMP. It was not until this person had taken the adverse drug reaction reporting form to the physician and had it completed that the event was reported. There is no incentive for physicians to report events to CADRMP; physicians are not reimbursed for their time to complete reporting forms and no personnel is provided to investigate reports and complete them in physicians' offices.

### 6. *Health care professionals are not always sure which drug may have caused an adverse reaction*.

With multiple drugs in use, health care professionals cannot always tell to which drug they should attribute an adverse reaction, so they may not report the reaction.

Under-Reporting

The problems outlined above all contribute to the under-reporting of adverse drug reactions. The extent of under-reporting is illustrated by the following examples:

- Following the introduction of protease inhibitors in Canada in the fall of 1997, persons living with HIV/AIDS began to recognize profound adverse effects of these drugs that were either unaccounted for or underestimated (in terms of prevalence) in clinical trials. Some of these effects included lipodystrophy, gastrointestinal effects (nausea, vomiting, heartburn and diarrhea), and metabolic side effects such as hyperlipidaemia and overt or subclinical diabetes. None of these adverse effects were identified through the post-approval surveillance system.

- In the first half of 1998, there were only four reports of fat redistribution attributed to the use of protease inhibitors, as reported in the July 1998 Canadian Adverse Drug Reaction Newsletter. Yet there have been countless anecdotal reports of fat redistribution problems; scientists have recognized the problem and are busy looking for solutions.

It may not be practical to design a system that completely captures all adverse effects. A more reasonable goal might be to design a system that would detect a new problem that is occurring regularly or frequently, and that would then trigger further investigation to determine the extent of the problem and identify what response is required.

## Systemic Problems

### *1. The post-approval surveillance system lacks clear goals, objectives and action plans.*

Several reports commissioned by Health Canada have proposed goals and objectives for a post-approval surveillance system, as well as actions to achieve these goals and objectives (see Section IV – Previous Reports on Post-Approval Surveillance). In addition, the Working Group on HIV/AIDS produced a series of recommendations in October 1999 (see Appendix D). The department has yet to act on these reports and recommendations.

### *2. CADRMP is not well known to health care professionals across Canada.*

CADRMP's low profile means that health care professionals are not very knowledgeable about the systems for reporting drug reactions and disseminating this information. Many physicians do not know when and where to report the adverse effects of drugs. The location of the CADRMP regional centres are not well known to some provincial officials involved in the distribution of HIV/AIDS drugs.

### *3. There is a lack of consistency in the terminology used in the monitoring of adverse drug reactions.*

Some of the definitions overlap and some of the terms have diverse uses. This has a negative impact on efforts to collect data on adverse reactions.

### *4. The roles of federal and provincial governments around the monitoring of the ongoing effectiveness of licenced drugs are blurred*

While the monitoring of adverse effects of approved drugs is clearly a federal responsibility, the responsibility for other components of post-approval surveillance, such as the monitoring of the effectiveness of drugs, is less clear. The level of research and evaluation of the effectiveness of drugs appear to vary among provinces, depending on the interest and availability of skilled clinical, basic, epidemiologic, social and health services researchers.

### *5. Post-approval surveillance is not a priority within TPP. There are insufficient resources devoted to post-approval surveillance.*

The failure to recognize the importance of post-approval surveillance means that historically this activity has not received its fair share of resources or attention.

### *6. It is not clear whether a portion of the Drug Information Number (DIN) fees are being assigned to post-approval surveillance.*

Each new drug has at least one DIN number assigned to it. A portion of the fees charged for the assignment of DIN numbers is supposed to help defray the costs of post-approval surveillance. However, TPP has not provided any accounting to show that this is happening.

### *7. There is a lack of coordination of resources within TPP.*

Historically, the officials in TPP working on post-approval surveillance have been scattered among several divisions. It is not clear whether the recent reorganization of TPP has addressed this problem.

### *8. There is a lack of information-sharing.*

There is little information sharing between officials of TPP working on pre-approval issues and those working on post-approval issues.

### *9. There are problems with the database that is being used to record reports of drug reactions.*

There are limits to the types of reports that can be obtained from the Canadian Adverse Drug Reaction Database. As well, there are concerns that the database may not be able to handle the increases in volumes if the number of reports grows significantly in the coming years. CADRMP is looking at the possibility of combining its database with the one being used by the Federal Drug Administration in the United States in an effort to enhance the use of the data.

## Programmatic Problems

### *1. Pre-marketing clinical trials fail to identify many adverse reactions.*

Most of the clinical trials for HIV/AIDS drugs are of short duration. They do not capture all populations, and they do not reflect real life in terms of adherence and other variables. For all of these reasons, clinical trials are not very effective at identifying adverse reactions.

### *2. Few Phase IV clinical trials are being conducted.*

The exact number of Phase IV clinical trials is not known, but it likely to be small (or none). TPP has very little information on how often Phase IV clinical trials on HIV/AIDS drugs are conducted, or how often these trials are required or requested by officials making decisions on the approval of new drugs. Unfortunately, the Regulations do not require the reporting of Phase IV trials.

### *3. For those adverse drug reactions that are reported to CADRMP, there is no system in place to disseminate information on them to HIV/AIDS consumers and the organizations that represent them.*

The predominate route of dissemination of information on adverse drug reactions is to health professionals. Unfortunately, due to the volume of evolving medical information in HIV/AIDS, many health care professionals do not pay much attention to the publications on adverse effects in the Canadian Medical Association Journal or the Canadian Adverse Drug Reaction Newsletter. This means that many health professionals are not passing this information on to consumers.

### *4. There is a lack of information coming from other countries.*

There is no system in place in Canada to collect or receive information from other countries on serious adverse drug reactions and adverse drug reactions. Nor has there been any attempt to collect or analyze information at an international level. A more global focus should enable us to spot trends and identify problems faster.

# Section VI
# Conclusions and Recommendations

The current system of post-approval surveillance does not meet the needs of consumers, including persons living with HIV/AIDS. The previous section described many of the problems with the system. In this Section, we provide recommendations for improving the system and making it more responsive.

## Guiding Principles

The post-surveillance system should be based on the following guiding principles:

1. It should be **consumer-centred**.

2. It should be **easily accessible**.

3. It should **meet Canadian needs** – i.e., it should use a Canadian database and Canadian strategies for data collection.

4. It should be **open and transparent**.

5. It should **respect individual confidentiality**.

## General Recommendations

To strengthen the current system, the following general strategies are recommended:

1. The Therapeutics Products Programme (TPP) should develop a comprehensive strategy for post-approval surveillance of HIV/AIDS drugs. The strategy should include (a) measures to promote and facilitate the reporting of adverse reactions by manufacturers, health care professionals and consumers; (b) improved analysis of the adverse reaction data to spot trends and problem areas; (c) the commissioning of research on the causes of adverse reactions; (d) improved dissemination of the data, the analysis of the data and the results of the research; and (e) making Phase IV trials a condition of licensing of the drug. This strategy could serve as a blueprint for the post-approval surveillance of all drugs licensed for sale in Canada.

2. TPP should establish clear goals and objectives for its post-approval surveillance system.

3. Federal and provincial/territorial levels of governments should agree on their respective roles in a national post-approval surveillance system.

4. TPP should establish an advisory body whose membership includes a broad spectrum of stakeholders, including community representation. The role of the advisory body should be to advise TPP on the post-approval surveillance system.

5. TPP should keep the Federal-Provincial-Territorial Pharmaceutical Issues Committee abreast of developments with respect to the post-approval surveillance system, and should encourage joint activities, where appropriate.

6. TPP should provide an accounting of the annual Drug Information Number (DIN) renewal fees it receives, and should ensure that an appropriate percentage of these fees is allocated to the post-approval surveillance system (as per original and ongoing agreements).

7. Information on the post-approval surveillance system should be included in medical schools and programmes for continuing education (for physicians and other health care professionals).

8. TPP should analyze incoming reports of drug reactions on a timely basis, and prepare synopses based on these analyses.

9. TPP should develop and implement mechanisms to ensure timely, broad and effective dissemination of adverse drug reaction synopses to all stakeholders. The synopses should be provided to one or more community-run newsletters as well as peer-reviewed scientific journals.

10. TPP should promote the development of a system for the international collection, analysis and sharing of information on serious adverse drug reactions and adverse drug reactions.

11. TPP should standardize the terminology it uses for the monitoring of adverse reactions.

12. TPP should ensure that its post-approval surveillance activities are centralized in one or two divisions within the Bureau of Licensed Product Assessment and are well-coordinated.

13. TPP should ensure that information is shared between the officials involved in pre-marketing approval of drugs and those involved in post-approval surveillance.

## Recommendations Specific to Gathering Data on Adverse Reactions

To improve the gathering of data on adverse reactions, the following strategies are recommended:

1. The Regulations should be altered to require drug manufacturers to report adverse drugs reactions as well as serious adverse drug reactions.

2. The post-approval surveillance system should include effective mechanisms for consumers, health care professionals and other stakeholders to report drug reactions and drug reactions.

3. TPP should develop local, regional and national strategies to solicit reports of drug reactions from health care professionals.

4. TPP should develop local, regional and national strategies to solicit reports of drug reactions from consumers and organizations that represent consumers.

5. TPP should ensure that its strategies for soliciting reports of drug reactions address issues specific to women (e.g., menstrual, menopause, hormonal, pregnancy) and other population groups.

6. A comprehensive education programme should be developed for people reporting drug reactions.

7. TPP should ensure that its database systems are upgraded to accommodate increasing number of reports of drug reactions and to facilitate analysis of the data.

8. TPP should ensure that the reports of drug reactions continue to be entered on its database system on a timely basis.

9. TPP should embark on more pilot projects to test various methods of gathering data on drug reactions.

10. TPP should endeavour to obtain information on drug reactions on a regular basis from other countries.

## Final Word

Reform of the system along the lines outlined above will make it more responsive to the needs of consumers and help to improve the health of persons living with HIV/AIDS as well as all Canadians.

# Endnotes

[1] Food and Drugs Act: Food and Drug Regulations (Schedule No. 844), November 7, 1995.

[2] Ibid.

[3] Ibid.

[4] Amery, W., Pharmacovigilance: What is it? Why does it exist?, International Journal of Risk and Safety in Medicine. 5, 1994: 77-84.

[5] Walop, W., *Commentary:* Postmarketing surveillance: its meaning, Post-marketing surveillance. 6, 1993: 155-158.

[6] Piantadosi, S., Clinical Trials: A Methodologic Perspective, A Wiley-Interscience Publication. 1997.

[7] Hlynka J.N. Developing a National Postmarketing Pharmaceutical Surveillance Program (PPSP). June 1991.

[8] Strategic Priorities Project (Discussion Paper), Project C-3, Canadian Adverse Drug Reaction Advisory Committee (CADRAC). Internal Report, Drugs Directorate, Health Protection Branch, Health Canada. March 26, 1996.

[9] Ibid.

[10] International Committee on Harmonization. Guideline E9: Statistical Principles for Clinical Trials.

[11] CIOM Working Group IV. Benefit-risk balance for marketed drugs: evaluation safety signals. 1998: 83-84.

[12] Webster's New World Dictionary, Third College Edition, Victoria Newfeldt (editor). 1988.

[13] The Wordsmyth English Dictionary-Thesaurus. Internet: <http://www.lightlink.com/bobp/wedt/wedt-artfl.html>.

[14] Last, J.M., A Dictionary of Epidemiology, 2nd edition, Oxford University Press. 1988.

[15] Webster's, supra at 13.

[16] Food, supra at 1.

[17] Canadian Adverse Drug Reaction (ADR) Monitoring Program Fact Sheet, Therapeutic Products Program, Health Canada.

[18] Ibid.

[19] Ibid.

[20] Canadian Adverse Drug Reaction Newsletter, Therapeutic Products Programme, Health Canada, Vol. 8, No. 4. October 1998.

[21] Letter dated July 11, 2000 to David Garmaise from Robert G. Peterson, A/Director General, Therapeutic Products Programme.

[22] Ibid.

[23] Canadian Adverse Drug Reaction Newsletter, Therapeutic Products Programme, Health Canada, Vol. 7, No. 3. July 1997.

[24] Ibid.

[25] Letter, supra at 21.

[26] Hlynka, supra at 7.

[27] Ibid.

[28] Ibid.

[29] Ibid.

[30] Gagnon, et al. Working in Partnerships...Drug Review l 3629e Future, Review of629e Canadian Drug Approval System. July 1992.

[31] Ibid.

[32] Ibid.

[33] Product Licensing Framework III (DRAFT), Therapeutic Products Programme, Health Canada. June 1988.

[34] Health protection Branch Policy on Conditional Licences, Therapeutic Products Programme, Health Canada. May 28, 1998.

[35] Ibid.