CANADIAN TREATMENT ACTION COUNCIL (CTAC)

Position Paper on

Compassionate and Expanded Access Programs

for Treatments in Development

May 23, 2008

Prepared for CTAC by:
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Executive Summary

The mandate of the Canadian Treatment Action Council (CTAC) is to secure and ensure access to therapies and treatments for people living with HIV/AIDS by working with the public, private and not-for-profit sectors.

CTAC....

• Informs research and public policy, and promotes public awareness;
• Provides mentoring and skills building in these areas to people living with HIV/AIDS;
• Encourages and facilitates the exchange of related information to stakeholders;
• Builds and works with coalitions to address broader health care issues impacting access to therapies and treatments.

Prescription drugs increasingly play a vital role in the healthcare of Canadians. New drugs have helped to improve the quality and length of life for many Canadians. Frequently, prescription drugs are used as a substitution for other treatments and medical interventions, including surgery. New discoveries have had a positive impact on a wide variety of illnesses, medical conditions and disabilities.

Individuals who are seriously ill need timely access to drugs in development. This is particularly true for those for whom no treatments are available or those for whom available treatments have failed or are intolerable. In many cases, the health of people waiting for access to new treatments deteriorates, and in some cases people die, while waiting for treatment access. Access to new treatments can mean the difference between life and death for some people.

HIV/AIDS is a very complex illness and results in a weakened immune system in those who are infected. Research has shown that the maximum benefit of HIV treatments is realized when the drugs are provided to patients in multiple drug combinations. HIV/AIDS treatments can have serious side effects and can often interact with other prescription drugs as well as non-prescription drugs. Side effects of currently available treatments can be just as serious as the illness being treated. In some cases side effects are so serious that the drug has to be stopped.

Drug resistance can develop in people taking HIV/AIDS treatments, which means the drugs no longer work in these people. Drug resistance can be further complicated by cross-resistance to other drugs, which means that when you develop resistance to one drug in class, it may also result in resistance to other drugs in that class. For people who have developed resistance, or for those for whom current treatments are unsuitable, access to drugs in development is often their only hope.

The Therapeutic Products Directorate (TPD) of Health Canada regulates prescription drugs in Canada. From the time a New Drug Submission (NDS) is submitted to the TPD until the drug is commercially available can take two years or more. The release of drug through compassionate/expanded access programs or other early access mechanisms has been an accepted and expected aspect of drug development in Canada.
Early access to drugs in development can normally be obtained either through Canada’s Special Access Program (SAP), or though compassionate and expanded access programs. Compassionate access programs are set up at the discretion of the drug sponsor and generally offer the drug to a very small number of people. Expanded access programs are also provided at the discretion of the sponsor in the form of an arm of a clinical trial. This means that the trial drug is provided to all participants in this trial. These open label programs are usually initiated late in the research process and provide early access to drugs to a larger number of people, however there are usually limitations and restrictions. All forms of early access to drugs in development require the support of a physician.

Since a variety of stakeholders are impacted by the implementation of early access programs for drugs in development, there are many perspectives on whether early access should be mandatory and then there are the accompanying legal, moral and ethical issues. The philosophy behind Canada’s drug legislation is to ensure that drugs available to Canadians are safe, effective and of high quality. Drugs, which have not gone through the complete review and approval process, have not been licensed by the Therapeutic Products Directorate (TPD), which is the regulatory authority at Health Canada.

The pharmaceutical industry makes huge profits from its products and takes advantage of favourable tax regulations and a sophisticated, publicly funded health care system in Canada. None of the profits enjoyed by the industry would be possible without the commitment of clinical trial participants. Therefore, it is incumbent upon the pharmaceutical companies who are bringing new drugs to market, to provide early access to these products, particularly for the catastrophically ill.

CTAC has, since its inception, worked with pharmaceutical companies, physicians, and governments towards improving early access to drugs in development. While most, if not all, pharmaceutical companies provide early access to the drugs they have in development, such access is not mandatory, and is completely at the discretion of the drug sponsor. CTAC supports the concept of mandatory compassionate and expanded access programs for drugs in development.

For purposes of this document, Compassionate Access is defined as the provision of emergency medical treatment to catastrophically ill patients. Catastrophic Illness is defined as a serious or life-threatening condition, for which no effective/tolerable treatments are currently available, and for which the prognosis is death or considerable deterioration of health in the next twenty-four months. CTAC believes in the right of patients who are catastrophically ill, in consultation with their physician, to access any treatment or treatment combination, which causes no direct harm to others, which the patient and doctor believe may have benefit. Expanded access is defined as access for people who are not necessarily meeting the criteria for a clinical trial but are in need of the experimental drug to create a viable regimen. Generally expanded access programs are administered as an arm of a clinical trial. CTAC takes the position that compassionate and expanded access programs should be designed so that the most seriously ill get first access to drugs.
In order to ensure that early access to drugs is provided in a manner that has minimal impact on the delivery of emergency or compassionate treatment, it is crucial that guidelines be developed with regard to a variety of aspects of early access. Health Canada has a responsibility to initiate a dialogue with stakeholders to develop guidelines for the implementation of mandatory compassionate and expanded access. Health Canada has a further responsibility to ensure that appropriate legislative measures are enacted to prohibit the sale of experimental drugs provided through all early access mechanisms.

CTAC holds firmly the beliefs that:
• compassionate and expanded access to drugs in development is crucial for the survival of many people living with HIV/AIDS,
• compassionate and expanded access programs can be administered in a way that does not interfere with ongoing research or the drug review and approval process, and
• all other challenges to successful implementation of compassionate and expanded access programs can be resolved
• Health Canada’s Special Access Program (SAP) should be made more readily accessible for patients to access drugs not approved for use in Canada.
Section 1 - Introduction

Prescription drugs have greatly enhanced the length and quality of life of millions of Canadians and increasingly play an important role in the treatment of many illnesses and conditions. In 2002, Commissioner Roy Romanow led the Royal Commission on the Future of Healthcare in Canada, which was a critical analysis of healthcare in the country. Its report, entitled “Building on Values: The Future of Healthcare in Canada”, was seen by many as the voice of Canadians on healthcare in Canada. The following quotes are taken from the Report:

# “The current and potential benefits of prescription drugs are undeniable.”¹
# “Prescription drugs are increasingly used as a substitution for other treatments and medical interventions, including surgery.”²
# “In 1980, $1.3 billion was spent on prescription drugs in Canada, about 5.8% of the total spending on healthcare in the country. By 2001, the percentage had doubled to 12% and the amount of money spent on prescription drugs had climbed dramatically to $12 billion.”³
# “Looking ahead, there is every reason to believe that we have only seen the tip of the iceberg, when it comes to the potential for new prescription drugs”.⁴

“Health Canada ’s Therapeutic Products Directorate (TPD) is the Canadian federal authority that regulates pharmaceutical drugs and medical devices for human use. Prior to being given market authorization, a manufacturer must present substantive scientific evidence of a product's safety, efficacy and quality as required by the Food and Drugs Act”.⁵

It generally takes 10 - 14 years from discovery of a compound to market access.⁶ During this time drugs are subject to a variety of research, first in the test tube, then in animals and finally in humans. Research in humans is conducted in clinical trials and there are four phases of the trials.

The following excerpt from the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, describes the four ‘Phases of Pharmaceutical Research’.⁷

Phase I clinical trials generally examine the acute, dose-related pharmacological toxicities of new pharmaceutical drugs; they are often conducted in healthy subjects, but may involve patients in studies with interventions that are known to be toxic.

Phase II clinical trials primarily examine the short-term pharmacological toxicities of - and, to a lesser extent, the efficacy of - new drugs; they are conducted in populations with specific diseases.

Phase III clinical trials primarily examine the pharmacological efficacy - and, to a lesser extent, the short term toxicities - of new drugs. Phase III and IV clinical trials are designed to increase the survival or quality of life of subjects suffering from a specific disease or condition.

Phase IV clinical trials, also known as post marketing surveillance studies, primarily examine the long-term efficacy and toxicity of already marketed drugs.
Although Health Canada is involved throughout all phases of research, it is only after Phase I, II and III trials have been completed that a new drug submission (NDS) is submitted by the manufacturer for review by Health Canada to determine whether the drug will be approved for sale in Canada.

Once drugs are authorized for sale in Canada they are subject to additional reviews to determine whether they will be listed on various federal and provincial/territorial prescription drug reimbursement plans or whether they will be covered under private insurance plans. When a drug manufacturer receives a patent for a drug and has set a price, the price is reviewed by the Patented Medicines Prices Review Board (PMPRB) to ensure that it is not excessive as defined in the PMPRB Regulations. A manufacturer need not wait for PMPRB approval before selling a drug, but may have to roll back the price if it is deemed to be too high.

The TPD target times for reviewing a normal New Drug Submission (NDS) and Abbreviated New Drug Submission (ANDS) is 300 calendar days and for priority reviews the target time is 180 days. The average number of days for non-priority approvals in 2004 was 876 calendar days and for priority reviews 217 calendar days. The target times for review by Common Drug Review range from 89-124 business days, which translates into approximately 124 - 174 calendar days. From the time a New Drug Submission is submitted to Health Canada at the end of Phase III clinical trials, until the drug is available on provincial/territorial drug plans or is covered by private insurance plans, can take 2 years or more.

For people who are ill, timely access to treatment is crucial. The need for access becomes paramount when currently available medications are ineffective or otherwise unsuitable or when no treatment exists. The provision of experimental drugs on a compassionate basis to those who cannot afford to wait for normal approval and marketing timelines has resulted in countless lives saved and immeasurable improvement to quality of life.

“Cooperation between players... can provide hope to the desperately ill through providing promising, if unproven, treatments in advance of licensure in a compassionate manner. This is more than passing a drowning man a straw at which to grasp. Not only does it offer hope to the afflicted, but the act of compassion offers comfort. Those three things - comfort, hope and real help - are all the rights and needs of the desperately ill.” - Dr. Bill Cameron, Ottawa General Hospital.

Compassionate Access Programs and Expanded Access Programs are implemented at the discretion of the drug sponsor. These programs vary in size (number of sites and number of patients per site) and accessibility. There is also variability from one company to another and from one drug to another even within the same company.

The issue of compassionate and expanded access to medications in development is not new. Powerful arguments have been presented on all sides of this debate and there are many ethical and moral issues that must be considered. This Paper will articulate CTAC’s views on a number of fundamental issues related to compassionate and expanded access.
The terms Compassionate Access Program and Expanded Access Program have been used to describe both patient/physician-initiated emergency treatment and industry-initiated programs that afford early access to drugs in development. The terms may have different meanings in different locations, or in some cases they mean the same thing and the terms are used interchangeably. Health Canada’s Special Access Program (SAP) is a separate and very different means of emergency access to drugs in development which is also sometimes called compassionate access.

To begin an examination of those CTAC positions, which will be articulated in this paper, it is necessary to look at some fundamental definitions. CTAC takes the position that the terms ‘compassionate’, ‘expanded’ and ‘special’ have distinct and different meanings in the context of access to drugs in development.

Note: CTAC positions on a variety of issues related to compassionate and expanded access programs for drugs in development are in **bold type** in this Paper so they are easier to locate at a glance.
Section 2 - Definitions

A) Compassionate Access Programs

Merriam-Webster defines compassion as: “sympathetic consciousness of others' distress together with a desire to alleviate it.” In our society the amount of compassion or sympathy appropriate to a given situation is usually proportionate to the degree of suffering or distress of another person or group. In other words, we feel greater sympathy for those who are suffering or distressed the most. The idea of granting or facilitating early access to experimental drugs, on a compassionate basis for individuals who are seriously ill, has long been accepted and is in fact expected in our society.

In 1990, Mr. John Dixon wrote about the concept of catastrophic rights in his book, “Catastrophic Rights, Experimental Drugs and AIDS”. Mr. Dixon, who is a past-President of the British Columbia Civil Liberties Association, also served as senior policy adviser to the Deputy Minister of Justice. The concept of catastrophic rights, which could also be described as the rights of the catastrophically ill, was widely recognized and accepted.

Mr. Dixon, in his testimony before the Sub-committee on HIV/AIDS said, “The “catastrophic right” spoken of in my book was the right of patients - catastrophically ill patients - to be free of the regulatory obstructions of government when it was clear that no other alternative remained to them and the scientific needs of our country were preserved.” In describing his frustrations in dealing with government departments, he said, “... finally it was understood that government ought not, out of purely paternalistic considerations, prevent catastrophically ill patients from having access to drugs.”

On the first day of five days of hearings held in 1995 and 1996, Mr. John O’Reilly, Chair of the Standing Committee on Health, Sub-committee on HIV/AIDS, gave a general definition of compassionate access. He said, “Let us recall that compassionate access refers to the delivery of a drug whose sale has not yet been approved by Health Canada for patients who, in consultation with their physician, feel that this treatment may offer them some hope of saving life, restoring health or alleviating pain.”

CTAC defines compassionate access as the provision of emergency medical treatment to catastrophically ill patients.

For purposes of this document, Catastrophic Illness is defined as a serious or life-threatening condition, for which no effective/tolerable treatments are currently available, and for which the prognosis is death or considerable deterioration of health in the next twenty-four months.

CTAC recognizes the concept of catastrophic rights or rights of the catastrophically ill.
CTAC takes the position that patients who are catastrophically ill, in consultation with their physician, have the right to access any treatment, which causes no direct harm to others, and which the patient and doctor believe may have benefit.

CTAC takes the position that compassionate access programs must be designed so that the most seriously ill get first access to drugs.

“In its simplest format, the compassionate release of medication for HIV or AIDS means that an individual has a mechanism to obtain and thus the ability to take any medication that he or she believes may improve or prolong life.”

- Dr. Christos Tsoukas, Montreal General Hospital.

Compassionate access to drugs in development can be through a patient/physician-initiated request to the manufacturer and regulator through the Special Access Program or through industry-initiated compassionate access programs which are set up as a clinical trial protocol.

CTAC takes the position that all stakeholders should strive to ensure adequate, timely and appropriate early access to drugs in development, on a compassionate basis, to the catastrophically ill and that such access should be at no cost to either the physician or the patient.

CTAC takes the position that compassionate access programs, designed to provide drug access to the catastrophically ill, should be mandatory.

CTAC takes the position that it is imperative that the size of compassionate access programs be in keeping with the needs of the catastrophically ill.

B) Expanded Access Programs

Expanded Access programs are a broadened or ‘expanded’ version of compassionate access programs.

\[
\text{CTAC takes the position that expanded access programs differ from compassionate access programs in that the participants do not have to be at death’s door to be eligible to participate, but immediately require the drug to create a viable regimen.}
\]

Expanded access programs can involve large numbers of patients and are an important aspect of drug development. Expanded access programs have traditionally occurred in the late stages of drug development. They are beneficial to the patient, the health care provider, the drug sponsor and the regulator. Expanded Access Programs have provided thousands of people with early access to treatments that went on to be approved for wider use.

Expanded Access Programs have the potential to provide considerable improvement in illness and/or quality of life to many people who, while not catastrophically ill, may no longer be able to
derive benefit from currently available therapies. Expanded Access Programs benefit the health care providers because it provides an opportunity for them to become familiar with using the new drug before it becomes widely available. Expanded Access Programs benefit the drug sponsor and the regulator by providing additional safety and efficacy data that would not otherwise be available.

**CTAC takes the position that, as with compassionate access, expanded access programs should be designed so that the most seriously ill get earliest access, regardless of where they live in Canada.**

**CTAC takes the position that all drug trial protocols must contain plans for an expanded access program as an additional arm to the trial.**

**CTAC takes the position that all people enrolled in compassionate/expanded access programs should continue to receive drugs until they are available to the trial participants on provincial/territorial/federal formularies and/or covered by private insurance.**

Historically, compassionate/expanded access programs in Canada for early access to anti-HIV drugs have ranged in size (number of patients) from less than a hundred to a few thousand patients. Canada is usually one of a number of countries where an experimental drug might be made available through early access programs. When early access programs are announced they are almost always announced in the U.S., the European Union and other locations as well as Canada but not always at the same time. The portion of the worldwide allocation that Canada typically receives is only a small percentage of the overall total.

In 1995, 3TC had the largest expanded access program ever, with the anti-HIV drug being provided to 45,000 people worldwide (3,000 in Canada)\(^{17}\). It is interesting that the same company which produced 3TC, also sponsored one of the smaller compassionate access programs in 1997 for its product Ziagen, which was provided to only 2500 people worldwide.\(^{18,19}\) Examples of the size of compassionate and expanded access programs for drugs and the number of worldwide patients provided drug access include:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>Patients</th>
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<tbody>
<tr>
<td>AZT 20</td>
<td>1987</td>
<td>5,000</td>
</tr>
<tr>
<td>DDI Didanosine</td>
<td>1989</td>
<td>35,000 (^{20});</td>
</tr>
<tr>
<td>DDC Zalcitabine</td>
<td>1991</td>
<td>5,000 (^{20});</td>
</tr>
<tr>
<td>D4T Stavudine</td>
<td>1992</td>
<td>12,000 (^{20});</td>
</tr>
<tr>
<td>3TC Lamivudine</td>
<td>1995</td>
<td>45,000 (^{17});</td>
</tr>
<tr>
<td>RTV Ritonavir</td>
<td>1995</td>
<td>2,000 (^{21});</td>
</tr>
<tr>
<td>IDV Indinavir</td>
<td>1995</td>
<td>1,400 (^{22});</td>
</tr>
<tr>
<td>SQV Saquinavir</td>
<td>1996</td>
<td>4,000 (^{23});</td>
</tr>
<tr>
<td>ABC Abacavir</td>
<td>1998</td>
<td>3,000 (^{24});</td>
</tr>
<tr>
<td>NFV Nelfinavir</td>
<td>1998</td>
<td>14,000 (^{25});</td>
</tr>
<tr>
<td>EFV Efavirenz</td>
<td>1999</td>
<td>14,000 (^{25});</td>
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The drug Tipranavir provides one example of how compassionate access programs are expanded to become expanded access programs. In September 2003 Boehringer Ingelheim (BI) announced a compassionate access program for up to 600 people worldwide. In June 2004 BI announced an expanded access program which provided several thousand treatment experienced patients access to tipranavir. Another example of difference between the size of compassionate access programs and expanded access programs was the drug tenofovir (Viread). Its manufacturer, Gilead Sciences, enrolled a compassionate access program in 2000 which provided drug access to approximately 300 people worldwide. In February, 2002 Gilead announced that the compassionate access program had expanded to 7700. The smallest trial on the list is for TMC114 which recently enrolled 500 people in a compassionate access program, of which 45 were available in Canada. As a portion of the overall total, 45 represents about 9% for Canada. Compassionate access programs for other drugs typically allot between 5% and 20% of the total spaces for Canada.

Many factors must be considered when trying to determine what would constitute reasonable expanded access including: the amount of potential benefit of the new drug based on preliminary research; the known and potential toxicities, the degree of difficulty in manufacturing the drug and ease or difficulty of administration. In addition to these, CTAC takes the position that it is imperative that the size of expanded access programs be in keeping with the needs of patients requiring the drug to create a viable regimen.

**C) Special Access Program**

Throughout the time that the Sub-committee on HIV/AIDS was conducting its hearings in 1995-1996, changes had already been proposed to Health Canada’s Emergency Drug Release Program (EDRP). In 1997 the Special Access Program (SAP) became a new means by which an individual could gain emergency access to drugs in development. SAP is usually used for access for a single patient or small number of patients, however recently SAP has been fraught with challenges. “Health Canada, through its Special Access Programme (SAP), allows doctors to gain access to non-marketed drugs and medical devices that have not yet been approved for sale in Canada. Practitioners treating patients with serious or life-threatening conditions request Special Access in cases where conventional therapies have failed, are unavailable or are unsuitable.”

Sections C.08.010 and C.08.011 of the Food and Drug Act Regulations provide for the release by
Under SAP, a physician must initiate the request with Health Canada on behalf of a patient. Once a physician receives approval to access a drug through SAP, (s)he then has to get approval from the drug company to release the drug. Pharmaceutical companies are under no obligation to release experimental drugs and are not required to explain reasons for refusing access to a drug in development. The Regulations that allow the manufacturer to provide the drug also permit the manufacturer to sell the drug. Many drug manufacturers who provide drugs through SAP do so at no cost to the patient or physician, however they are not required to do so. Drugs provided under this program are not monitored by post approval surveillance programs.

According to Health Canada’s web site, every effort is made to review SAP requests within twenty-four hours. A triage system helps ensure that requests from the most critically ill people get quick reviews. When physicians make requests under SAP for numerous patients, Health Canada has requested that the physician and/or the manufacturer submit a protocol for a clinical trial. This creates additional bureaucracy and lengthens considerably the time it takes to get emergency access to drugs in development.

For information on CTAC’s position on SAP see Section 6) E) xi).
Section 3 - About HIV/AIDS

HIV (Human Immunodeficiency Virus) is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). HIV disease is a very complex disease that destroys the body’s immune system. The virus replicates by infecting certain immune system cells (known as CD4 cells or T4 cells or T cells) thereby destroying the body’s ability to fight other infections. As these immune system cells are depleted, the host is susceptible to a wide range of opportunistic infections (OI’s) that may occur, or are worsened, as a result of a weakened immune system. There is no cure for HIV disease.

Current treatment consists of drug combinations used to suppress viral replication that can be selected from numerous classes of drugs including: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside/tide reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and fusion inhibitors (FIs). Fusion inhibitors are part of a class of drugs known as entry inhibitors. A new entry inhibitor has recently come to market. Maraviroc is a CCR5 attachment inhibitor which prevents the virus from attaching to one of the co-receptors on the CD4 cell. Also new to market and first in class is an integrase inhibitor, Isentress (Raltegravir), which shows promise. Each class of drugs inhibits HIV replication at a different point in the virus’ replication cycle. In addition to the five classes of drugs currently available, research is ongoing into new classes of drugs such as maturation inhibitor, gene based therapies and immune boosting agents.

All of the current treatments available to fight HIV are of limited benefit. Research has shown that even in the presence of undetectable viral load in circulating blood that there is ongoing low-level viral replication. 38 HIV resistance has been seen in vitro (in test tube) in all of the drugs used to treat HIV and has, inevitably, been translated into treatment failure for many people taking these drugs. There is also a significant amount of cross-resistance among drugs in each class of anti-HIV drugs.

“It is unlikely that a single drug will have a dramatic impact on HIV disease progression. The reasons for this likelihood are based on recent data suggesting that the average patient has approximately two billion HIV particles produced and destroyed in their body daily. A single drug would have to decrease this amount of virus by 99.999999% to be clinically effective in the long term.” 39 - Dr. Christos Tsoukas, Montreal General Hospital.

The highly treatment experienced patient generally requires a minimum of two additional active drugs (to which they are not resistant) in order to construct a viable regimen. It is, therefore, likely that catastrophically ill individuals may need access to more than one experimental drug.

A number of HIV-specific and non-HIV-specific drugs may be prescribed for the prevention and/or treatment of opportunistic infections. Many of the medications used to treat HIV and associated conditions are extremely toxic and can cause, or contribute to, a number of other illnesses and even death. For some people, these side effects or drug interactions prove to be as detrimental as the illness and result in discontinuation of the medication. Serious adverse events, both expected and unexpected, are possible with many of these drugs long after they have been
approved for use. When used in multiple drug combinations some of the available drugs interact with each other and dose adjustments to one or more drugs may be required. The presence or absence of food can impact the way some of the drugs are absorbed by the body. Because of a lack of research, very little is known about interactions with: other prescription drugs; non-prescription drugs (over-the-counter drugs); street drugs; complementary therapies such as herbal/natural remedies, and Aboriginal and other traditional healing practices.

HIV/AIDS is a very complex illness and continues to pose a significant challenge for humanity. Many people have developed resistance to, or cannot tolerate, available treatments. For many people, accessing medications in development is a matter of survival. Sadly, people die waiting for access to new treatments. 

\[40, 41\]
Section 4 - Current Situation

A) Canada

i) Standing Committee on Health Report

The debate over Compassionate and Expanded Access Programs has been going on for as long as there have been drugs in development. In the late eighties and early nineties, when limited treatment options were available for HIV/AIDS, the community rallied fervently for access to drugs in development. As a result, perhaps the most in-depth look at compassionate/expanded access ever to take place in Canada occurred in the mid-nineties.

The federal government’s Standing Committee on Health created a Sub-committee on HIV/AIDS in November 1994 to examine a number of issues related to HIV/AIDS and the government’s HIV/AIDS Strategy of the day. During the course of its work the Sub-committee recognized that access to experimental drugs was an important issue, not only for those living with HIV/AIDS, but also for anyone with a life-threatening illness. In order to more fully examine the complex issues associated with compassionate and expanded access the Sub-committee organized a series of five roundtable discussions from December, 1995 to May, 1996 and its report to Parliament was presented in October, 1996. The roundtable discussions included a broad array of stakeholders. The report contained eight recommendations, which are listed below.

Recommendation No. 1

The Sub-Committee recommends that the Governor in Council make whatever changes are necessary to the Regulations of the Food and Drugs Act in order to require that pre-investigational new drug submissions and investigational new drug submissions include a statement of the pharmaceutical manufacturer’s intention with respect to the compassionate provision of the investigational agent(s).

Recommendation No. 2

The Sub-Committee recommends that Health Canada in co-operation with the Pharmaceutical Manufacturers Association of Canada and treatment activist groups, develop compassionate access guidelines. These guidelines are to include, but not necessarily be limited to, criteria to judge whether a pharmaceutical manufacturer’s offer of compassionate access to an investigational therapy is fair and reasonable; and provisions to accommodate the flexible nature of consumer demand and the availability of an investigational therapy. These guidelines should be developed in all due haste and be available for decision-making purposes no later than 1 June 1997.

Recommendation No. 3
When a Pharmaceutical Manufacturer, in the absence of a clinical trial in Canada, establishes a compassionate access program to provide Canadian patients with an experimental therapy, the Sub-Committee recommends that the Drugs Directorate of Health Canada conduct the evaluation of the new drug submission for that therapy as expeditiously as possible.

**Recommendation No. 4**

The Sub-Committee recommends that the Governor in Council amend the regulations of the *Food and Drugs Act* that pertain to the Emergency Drug Release Program to give Health Canada the authority to require pharmaceutical manufacturers to account for a refusal to provide compassionate access to a therapy not approved in Canada.

**Recommendation No. 5**

The Sub-Committee recommends that Health Canada review and strengthen the mandate of the National Council on Bioethics in Human Research to clearly establish the objective of promoting harmonized national standards of ethics in research involving humans.

**Recommendation No. 6**

The Sub-Committee recommends that Health Canada move with all due haste to put into effect, no later than 1 June 1997, a conditional approval process for drugs designed to treat life-threatening illnesses.

**Recommendation No. 7**

The Sub-Committee recommends that the Government of Canada study the future direction of drug regulation in Canada. This study should investigate, but not necessarily be limited to, the cost-benefits of the present system, the advisability of phasing out the Canadian system, the efficiency and effectiveness of the new drug evaluation system in the European Community, and the possibility of applying this model to NAFTA partners.

**Recommendation No. 8**

The Sub-Committee recommends that the federal Minister of Health propose to the Conference of Ministers of Health the establishment of a consultative mechanism to facilitate the timely adoption of new drugs on provincial formularies.
ii) Current Regulation

In March of 1997, the then Health Minister, David Dingwall, tabled the government’s response to the Sub-committee report. The response spoke in general terms about early access through clinical trials and the federal government’s then Emergency Drug Release Program (EDRP), now Special Access Program (SAP). There were no specific measures in the response to improve access to investigational therapies.

In Canada prescription drugs are regulated under the Food and Drugs Act and Food and Drugs Act Regulations. Since the report of the Sub-committee on HIV/AIDS in 1996 some changes have been made to both the Regulations as well as to operating procedures within Health Canada.

As noted above in Section 2, Definitions, Health Canada’s Special Access Program (SAP) was created in 1997 in an effort to expedite emergency access to drugs in development.

The issue of conditional approval was addressed by government regulators when, on May 28, 1998, the former Therapeutic Products Programme issued the policy statement Notice of Compliance with Conditions (NOC/c).

In August 1998 the three national, federally funded research Councils in Canada released a policy statement on ethics in research. The three Councils were, the Medical Research Council (MRC) of Canada, the Natural Sciences and Engineering Research Council (NSERC) of Canada and the Social Sciences and Humanities Research Council (SSHRC) of Canada. The document was titled, “Tri-Council Policy Statement; Ethical Conduct for Research Involving Humans”. The Mandate of the Councils reads, “The people of Canada, through Acts of Parliament have created and funded the MRC, NSERC and SSHRC, to promote, assist and undertake research in the domains indicated by their names. In discharging our mandates, the Councils wish to promote research that is conducted according to the highest ethical standards. The Councils have therefore adopted this policy as our standard of ethical conduct for research involving human subjects. As a condition of funding, we require, as a minimum, that researchers and their institutions apply the ethical principles and the articles of this policy.” This was a significant step forward in terms of enhancing and protecting the rights of research participants in Canada.

Recommendation 8 of the report of the Sub-committee speaks to the need for “...a consultative mechanism to facilitate the timely adoption of new drugs on provincial formularies.” Under the auspices of the Canadian Coordinating Office of Health Technology Assessment (CCOHTA), the Common Drug Review (CDR) process was implemented in September, 2003. Although the original intent was to streamline the review process for listing drugs on provincial/territorial formularies, the result has been added bureaucracy and an additional 5-6 months for drugs to be listed. One province (Quebec) never joined CDR and at least one province, Alberta, has opted out of the CDR process with regard to new HIV therapies, which means that there is inconsistency in terms of formulary access across Canada.

In addition to the changes noted above, there have also been changes to the drug review process.
The changes include: increased funding for drug reviews, improved internal processes, and enhanced international regulatory cooperation/harmonization. Canada has participated in the “International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use”, which is an organization of regulatory authorities in Europe, Japan and the U.S. On Nov. 18, 2003 a memorandum of understanding (MOU) was signed “...that will further enhance cooperation between Health Canada and the U.S. Food and Drug Administration.” In April, 2004 a “Memorandum of Understanding between the Health Products and Food Branch, Health Canada and the Therapeutic Goods Administration, Department of Health and Aging of Australia, regarding Therapeutic Products”, was signed. The purpose of the MOU is to establish an arrangement between the two regulatory agencies that will facilitate the exchange of information and documentation, and encourage the development of collaborative activities relating to therapeutic products.

**iii) Current Practice in Canada**

There are six ways in which drugs may be available for use in Canada. They are:

1. **Prescription** - Drugs approved for use in Canada by the TPD may be prescribed by any physician authorized to write prescriptions in Canada. There are two types of approvals issued by the TPD: the first is a Notice of Compliance (NOC), which means that the manufacturer is permitted to market the drug without any restrictions, and the second is a Notice of Compliance with Conditions (NOC/C), which means that the manufacturer has authorization to market the product but must agree to produce additional research to verify the effectiveness of the drug, or there may be restrictions on the use of the drug. Any drug which has received a NOC or a NOC/C can be prescribed for use.

2. **Clinical Trials** - New drugs, not approved for sale, may be accessible through clinical trials. In a clinical trial, an experimental drug is tested against either a control drug or, if no effective treatment is available, a placebo. In most clinical trials, patients are randomly assigned to receive either the experimental drug or the control drug/placebo. There are many different types of clinical trials in all phases of research. Trials can be single blinded where the patient does not know whether (s)he is receiving the experimental drug, or they can be double-blinded where neither the patient nor the doctor knows whether the patient is receiving the experimental drug or the control drug/placebo. Clinical trials have inclusion and exclusion criteria. This means that there are certain conditions a patient must meet in order to be allowed to participate in the trial.

   This type of drug access has serious limitations, especially for those for whom currently available treatments have failed or are intolerable. Generally speaking, participants enter clinical trials for purely altruistic reasons, i.e., the advancement of science and should not enter a trial for any other reason. While new drugs may be available through clinical trials, such access is not a viable means of obtaining new drugs.

3. **Compassionate Access Programs** - Programs that are set up at the discretion of the drug manufacturer during the clinical testing stages, usually sometime after safe dosage has been determined and before the drug receives regulatory approval. Compassionate access
refers to providing a drug to a person who has no other clinical options and who is expected to die without the drug. Often, adding the drug is only adding monotherapy to a failing regimen, but it may keep the person going until new drugs come along. (Monotherapy is the practice of treating with only one drug. In the early years of HIV patients had limited drug treatment options and frequently used one HIV treatment and when it failed they switched to another treatment.) In patients who have treatment options available, switching/adding a single drug is not recommended by most doctors, however for patients with no options, switching/adding a single drug can be a life-saving measure. Access to drugs through compassionate access programs is decided on a case-by-case basis. Compassionate access programs are not designed to further scientific knowledge but rather are intended as emergency treatment, therefore normal data collection does not occur, however healthcare providers, drug manufacturers and Health Canada closely monitor safety issues related to experimental drugs.

4. Expanded Access Programs - Programs that are set up at the discretion of the drug manufacturer, usually sometime in the later half of Phase III trials and before the drug receives regulatory approval. These programs are set up for patients who need access to the drug to create a viable treatment regimen. In contrast to compassionate access, expanded access programs may be established as a separate and additional protocol of a clinical trial where the trial drug is made available to all participants. These clinical trials can vary quite significantly in terms of number of participants and eligibility criteria. In this type of study safety and efficacy data are collected. Everyone in the expanded access program gets the experimental drug. While many drug manufacturers offer expanded access programs, and/or other forms of early access, there is no requirement for them to do so, and some don’t offer these types of access to experimental drugs.

5. Special Access Program (SAP) - Health Canada’s SAP provides emergency access to unapproved drugs. The request must be initiated by a physician on behalf of a patient or patients. SAP also requires the consent of the drug manufacturer since provision of emergency access to unapproved drugs is completely voluntary. For more information on SAP see Section 2, Definitions and Section 6.)

6. Importation for personal use from other countries - According to Health Canada, “The Food and Drugs Act and Regulations (the Regulations) do not regulate the importation of drugs for personal use unless the drugs sought to be imported are listed in Schedule F to the Regulations (prescription drugs). The Controlled Drugs and Substances Act regulates the importation of substances or drugs classified as controlled, narcotic or restricted. It has been the policy of the Health Products and Food Branch Inspectorate (HPFBI) to permit individuals to import a three-month supply of a drug for their own personal use unless prohibited by law. This policy is comparable to policies in other countries.”

B) Other Jurisdictions

i) United Kingdom

In the U.K., access to drugs is generally the same as in Canada. The five ways in which drugs
may be obtained in the U.K. are:

1) Drugs on Prescription - [A] “doctor can prescribe any drug listed in the British National Formulary, the guide to drugs licensed for use in the UK.”

2) Clinical Trials - “Clinical trials of experimental therapies are taking place at centres all over the country. Some are large ‘multi-centre’ trials coordinated by the Medical Research Council; others are smaller studies taking place at only one or a few individual treatment centres.”

3) Compassionate Access - “Sometimes drug companies set up more formal arrangements to permit access to experimental drugs before they are licensed. Such schemes must be approved by the Medicines Control Agency, and technically speaking, are a form of trial, because the company uses the scheme to collect information about the safety of the drug. Compassionate release schemes are a means of providing experimental drugs to individuals who have exhausted other treatment options, either because they cannot tolerate other licensed drugs, or because they have ceased to benefit from those drugs.”

4) Named-patient Basis - “Named patient basis prescribing is a scheme which allows a doctor to prescribe an unlicensed drug to a particular ‘named patient’. It is only an option for drugs whose manufacturer is prepared to release it on this basis, and has to be arranged by the doctor on an individual basis. Some companies are unwilling to release unapproved drugs in this way.”

5) Importing Drugs from Abroad - “There are two ways of importing drugs from abroad before they are licensed in the UK, or if they are unavailable in [the U.K.]. One is to use a buyer’s club; the other is to use an international pharmacy.”

ii) United States

Access to drugs in the U.S. is similar to access in Canada and the U.K., however there are some differences.

1) Drugs that are approved for use by the U.S. Food and Drug Administration (FDA) are available by prescription.

2) Clinical Trials - Access to drugs through clinical trials in the U.S. is very similar to access to trials in other industrialized countries. They all require regulatory approval and ethics approval.

3) Special Exception/Compassionate Exemption - “If the eligibility criteria in a study protocol are not suitable for a particular patient, it may still be possible to be treated
according to the study protocol as a **special exception** (sometimes called compassionate exemption). Treating a patient as an exception is at the discretion of the investigator and sponsor..."\(^{56}\)

4) Emergency Investigational New Drug (IND) - “Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.”\(^{57}\)

5) Treatment IND - “Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.”\(^{58}\)

6) Parallel Track Program - “Another mechanism to permit wider availability of experimental agents is the "parallel track" policy ([Federal Register of May 21, 1990](https://www.federalregister.gov/documents/1990/05/21/1990-09374/)) developed by the U.S. Public Health Service in response to AIDS. Under this policy, patients with AIDS whose condition prevents them from participating in controlled clinical trials can receive investigational drugs shown in preliminary studies to be promising.”\(^{58}\) There have been discussions about the suitability and practicality of implementing a similar system in Canada.

7) Compassionate/Expanded Access Programs - Usually, the U.S. is one of the first countries to have a particular drug available through compassionate/expanded access programs (it should also be noted that the U.S. is usually the first country in which clinical trials are conducted). As with many other countries, compassionate/expanded access programs in the U.S. are presented as a separate open arm of a clinical trial. They are administered by industry and approved by the regulator.

### iii) Australia

In Australia, drug access is very similar to that of other industrialized countries. The ways in which drugs can be accessible are:

1) Prescription - Prescription drugs are regulated under the Therapeutic Goods Administration (TGA) and the process for approval is similar to that of other industrialized countries. Any physician can prescribe drugs which have received approval from the TGA and are listed on the Australian Register of Therapeutic Goods (ARTG). “The legislation provides the following mechanisms that allow individuals to gain limited access to therapeutic goods not on the ARTG (Australian Register of Therapeutic Goods):

- Special Access Scheme (SAS) (Categories A & B);
- Clinical Trials (CTN & CTX Schemes);
- Authorized Prescribers; and
- Importation for Personal Use.”\(^{59}\)
2) Special Access Scheme (SAS) (Categories A & B) - “SAS refers to arrangements which provide for the import and/or supply of an unapproved therapeutic good for a single patient, on a case by case basis. Category A is defined in the Regulations and Medical Device Regulations as persons who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of treatment; and Category B is defined as all other patients.”[^60] The Australian SAS is similar to Canada’s SAP and the U.K.’s Named-Patient Basis.

3) Clinical Trials (CTN & CTX Schemes) - CTN (Clinical Trial Notification) Scheme - “Under the CTN Scheme, all material related to the proposed trial, including the trial protocol is submitted directly to the HREC (Human Research Ethics Committee) by the researcher at the request of the sponsor. The TGA does not review any data relating to the clinical trial. The HREC is responsible for assessing the scientific validity of the trial design, the safety and efficacy of the medicine or device and the ethical acceptability of the trial process, and the approval of the trial protocol. In some institutions a scientific review or drug sub-committee may review the proposal before consideration by the HREC. The institution or organization at which the trial will be conducted, referred to as the ‘Approving Authority’, gives the final approval for the conduct of the trial at the site, having due regard for the advice of the HREC.”[^61]

CTX (Clinical Trials Exception) Scheme - “Under the CTX Scheme, a sponsor submits an application to conduct clinical trials to the TGA (Therapeutic Goods Authority) for approval.”[^61]

4) Authorized Prescribers - “The Authorised Prescriber provisions of the legislation allows doctors to supply individual patients with unapproved therapeutic goods under a range of circumstances [...]. The classes of patients who may access unapproved therapeutic goods prescribed by an Authorised Prescriber are those suffering from a life-threatening or otherwise serious illness or condition ...”[^62]

5) Importation for Personal Use - Subject to regulations, “Individuals may import medicines and other therapeutic goods without the goods being listed on the ARTG (Australian Register of Therapeutic Goods)...”[^63]

6) Compassionate and Expanded Access Programs - In Australia, as is the case with many other countries, compassionate and expanded access programs are set up as an open arm of a clinical trial. These programs are sponsored and delivered by industry, and approved by the regulatory authority. This is consistent with processes in other industrialized countries including Canada.

iv) New Zealand

As with other industrialized countries, New Zealand has a number of mechanisms by which drugs can be obtained. The New Zealand Medicines and Medical Devices Safety Authority
describes measures to provide access to unapproved drugs.

1) Prescription - “Medsafe is the New Zealand Medicines and Medical Devices Safety Authority. It is a business unit of the Ministry of Health and is the authority responsible for the regulation of therapeutic products in New Zealand.”

2) Clinical Trials - Clinical trials must be approved by Medsafe and are generally very similar to trials in other countries. As with many other industrialized countries, New Zealand requires that clinical trials meet rigorous standards for ethical conduct of trials.

3) Compassionate and Expanded Access Programs - When administered as an arm of a clinical trial, compassionate/expanded access programs are available for many new drugs.

Unlike many other countries, New Zealand does not have specific programs or other discrete mechanisms to allow for access to unapproved medicines. Rather, the Medicines Act confers considerable authority on medical professionals. According to Medsafe, “...the need to provide for access to unapproved medicines was recognised when the Medicines Act was formulated. Section 25 of the Act permits registered medical practitioners, dentists and midwives (hereafter referred to collectively as "practitioners") to procure, administer and arrange the administration of an unapproved medicine. Section 29 permits an authorised supplier or a medical practitioner to supply or sell an unapproved medicine to a medical practitioner provided the Director-General of Health is notified.”

The Medicines Act provides authority for doctors to access treatments from a broad array of sources. “The terms of section 25 are inclusive and permissive, allowing the practitioner to "procure the sale or supply of any medicine" for a particular patient in his or her care. "Any medicine" includes approved and unapproved medicines.”

The Medicines Act does not allow individuals to import drugs but it does provide for doctors to import drugs on behalf of a patient. “"Procure the sale or supply" refers to obtaining the medicine through the usual channels such as a pharmacy or a pharmaceutical company, and it also permits the practitioner to use other means of obtaining a medicine such as importation.”

v) Australia-New Zealand Therapeutic Products Authority

Australia and New Zealand have agreed to implement a system of joint reviews for drug reviews. According to the Trans-Tasman Therapeutic Products Agency web site, “In December 2003, the Australian and New Zealand Governments agreed to establish a joint agency and regulatory scheme for therapeutic products (prescription and over-the-counter medicines, complementary medicines, medical devices, blood and tissues). The new agency is to be called the Australia New Zealand Therapeutic Products Authority (ANZTPA).” “ANZTPA will be a joint, trans-Tasman agency with responsibility for regulating therapeutic products across both countries. When established, it will replace Australia’s Therapeutic Goods Administration (TGA) and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe).” The details of how the new Agency will work are expected to be refined throughout 2006/2007.
vi) European Medicines (Evaluation) Agency (EMEA)

According to its web site the “European Medicines Agency (EMEA) is a decentralised body of the European Union with headquarters in London. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. The EMEA coordinates the evaluation and supervision of medicinal products throughout the European Union. The Agency brings together the scientific resources of the 25 EU Member States in a network of 42 national competent authorities.”

The EMEA web site also describes how drugs are approved in Europe. “The new European system offers two routes for authorising medicinal products:

• a “centralised” procedure with applications made directly to the European Agency for the Evaluation of Medicinal Products (commonly known as the European Medicines Evaluation Agency leading to the grant of a European marketing authorisation by the Commission. Use of this procedure is compulsory for products derived from biotechnology, and optimal for other innovative medicinal products.

• a “mutual recognition” procedure which is applicable to the majority of conventional medicinal products. Applications are made to the member states selected by the application and the procedure operates by mutual recognition of marketing authorisations. Where this is not possible the EMEA is called upon to prepare a binding arbitration.”

The EMEA press office, in a news release in Dec., 2005 said “Two thousand and six will be the first full year of implementation of major new provisions in the EU pharmaceutical legislation, which entered into force 20 November, 2005.” “Owing to the new legislation, the Agency will assume full responsibility for evaluating medicines intended for the treatment of HIV/AIDS, cancer, diabetes and neurodegenerative disorders which must now be authorised through the centralised procedure. New regulatory procedures aimed at increasing access to medicines, including accelerated assessment, conditional-marketing-authorisation and compassionate-use procedures will also be applied.”

Note: All countries of the EU retain their respective regulatory authority and approval processes and each country can approve a drug, which is then subject to the mutual recognition provisions of the legislation.

vii) International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

“The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.” The six parties to ICH consist of representation from both industry and government regulators in each of the three regions. Canada, the WTO and the European Federation of Pharmaceutical Industries and Associations (EFPIA), which is currently represented by Switzerland, hold observer status in
ICH. Canada has been participating in ICH for some time and has adopted the ICH Guidelines.
Section 5 - CTAC Positions on Compassionate and Expanded Access Programs for Medications in Development

A) The Debate - Compassionate/Expanded Access

As noted previously, the hearings of the Sub-committee on HIV/AIDS of the Standing Committee on Health in 1995/1996 represented an in-depth examination of compassionate/expanded access to drugs in development. A wide variety of arguments were articulated by the many stakeholders represented at the hearings. The five days of hearings produced approximately 260 pages of evidence. It would be impossible to capture all of the various viewpoints on all issues in a small sampling. The following 14 quotes, which have been taken from the record of Evidence for the hearings, are provided as a brief look at the range of issues and the diversity of views.

“[...] it is possible to define conditions under which it is ethical to provide a non-validated therapy to a patient with a catastrophic illness.”73 - Dr. Bill Cameron, University of Ottawa at the Ottawa General Hospital.

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“While the deterrent aspect of liability claims might prevent some harm, appropriate protection requires a more priori approach, especially when health is at stake. This is particularly true, I would say, for vulnerable populations who could easily be convinced to use a drug whatever the side effects and potential harm. People have a right to the best available treatment, but they also have to be protected against harm.”74 - Mr. Trudo Lemmens - Member, McGill Centre for Medicine, Ethics and the Law.

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“Manufacturers have shown, through the consistent implementation of early access programs in Canada, that the provision of expanded access is a priority and a recognized responsibility, and that companies have and will continue to shoulder this responsibility.”75 - Dr. Sophia Fourie, Pharmaceutical Manufacturers' Association of Canada (PMAC),

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“One should never underestimate not only the dangers, but also the potential lack of ethics in providing medication in the absence of rigorous scientific evidence related to its use in humans.”76 - Dr. Michel Denis, Scientific Officer, Medical Research Council of Canada
“I believe compassionate access should be considered an arm or branch of the controlled clinical trial. [...] we do give hope, and it's very difficult for us to measure either quantitatively or qualitatively the effect of this hope. [...] “I think if we're going to develop compassionate access programs to a greater extent, we need some clear guidelines on how we use these drugs, how we can evaluate if they're doing some good, and how to be sure we're not just doing harm.”

- Dr. Sharon Walmsley, Toronto

“[Compassionate Access] raises additional concerns and risks about providing products that may never be approved to physicians and patients, whether under a mandatory or voluntary control. If you provide a product through a compassionate release program, there are no guarantees that you're ever going to see the product approved or reimbursed in Canada.”

- Mr. William D. Milligan, Vice-President, Pharmaceutical Manufacturers' Association of Canada.

“It is dangerous to assume that serious illness renders people incapable of rationally considering benefits and risks. People who are ill are no more or less likely to behave irrationally than people who are not. [...] Resist the temptation to assume that people fighting catastrophic illnesses do not know what is best for them and must therefore be protected from making their own decisions. Drug manufacturers do not have a monopoly on truth, people who earn their living by studying ethics do not have a monopoly on morality, and patients do not have a monopoly on virtue. [...] The threshold test should be whether it is possible to protect the drug research system and the needs of the general public without sacrificing people who are already ill.”

- Ms. Susan Conrad, Human Rights Lawyer - lives with MS.

“AIDS is teaching us that drug therapy is a very important part of health care. Yet in our overall health care system we treat physician care and hospital care under the Canada Health Act while drug care and other important parts of health care are treated separately.”

- Mr. Charles Black, Senior Adviser, Insurance Operations, Canadian Life and Health Insurance Association
“To compel a manufacturer to distribute a drug would require amending the Food and Drugs Act. Such an amendment would completely change the philosophy of this legislation. The Food and Drugs Act comes under the criminal law powers of the federal Parliament since it aims at prohibiting the sale of products considered to be dangerous and establishes a regulatory scheme for controlling distribution of these products. This is part of criminal law.”

82 - Mr. Mario Simard, Senior Legal Counsel, Justice Canada

“[...] a middle ground can be found where there is an incentive for these companies to have clinical trials within Canada with compassionate arms as well, and in such a way as to be positive for both the people living in the country and the pharmaceuticals participating in those trials. I think a good example of that is the Clinical Trials Network.”

83 - Mr. James Kreppner, Canadian Hemophilia Society

“...the issue of compassionate access to medications often implies choice and independence, with the individual having the ability to choose between no therapy and proven or unproven treatments. The individual thus attains a feeling of empowerment and control. These feelings are usually quite powerful and may result in additional and sustained patient efforts to fight this illness. Thus compassionate access therapies may contribute to an improvement in the patient's clinical status, despite the potential access and use of a marginally effective medication.”

84 - Dr. Christos Tsoukas, Montreal General Hospital

“The current system is based on informed consent and signing informed consent forms. (...) there may be insufficient information to provide to the patient for the patient indeed to give informed consent. Informed consent even under optimum conditions does not provide protection from lawsuits for a physician or a manufacturer.”

85 - Dr. Sophia Fourie; Vice-President, Medical and Regulatory Affairs, Pharmcia Uphohn Inc., Pharmaceutical Manufacturers' Association of Canada

“...compassionate access to experimental drugs is an issue that falls between medical treatment and research. While the nature of the intervention is research, the patient requesting an experimental drug and the physician seeking to satisfy the request share a therapeutic intent to provide benefit.”

86 - Mr. Derek Jones, National Council on Bioethics in Human Research

B) Rights of the Catastrophically Ill
According to historians, the first declaration of human rights was inscribed on a clay barrel, known as Cyrus’ Inscription Barrel, or Cyrus’ Inscription Cylinder, in 539 B.C. \(^87, 88\) Human rights are fundamental to a free and democratic society. Throughout history there have been many other documents which articulate the rights of individuals and society. Some of the older fundamental human rights declarations form the basis for many of the modern-day declarations:

1. **Magna Carta** - In 1215, the first draft of the Magna Carta was created. While the document was primarily intended to ensure that the laws applied to all, including the monarchy, it did speak of the rights of individuals and society. Paragraph 1. says, in part, “... by this our present charter confirmed for us and our heirs forever that the English Church shall be free, and shall have her rights entire, and her liberties inviolate ...”\(^89\)

2. **English Bill of Rights, 1689** - Like the Magna Carta, the English Bill of Rights was not solely a citizens’ rights document. It does, however proclaim the rights of society and individuals. It says, “... it may be declared and enacted that all and singular the rights and liberties asserted and claimed in the said declaration are the true, ancient and indubitable rights and liberties of the people of this kingdom...”\(^90\) [http://www.yale.edu/lawweb/avalon/england.htm](http://www.yale.edu/lawweb/avalon/england.htm)

3. **U.S. Bill of Rights** - In 1787, the U.S. Bill of Rights, which consists of ten amendments to the U.S. Constitution, was enacted. Amendment V, among other things, says, “No person shall [...] be deprived of life, liberty, or property, without due process of law; ...”\(^91\)

4. **Declaration of the Rights of Man and the Citizen, (August 1789, France)**\(^92\) - Two years after the enactment of the U.S. Bill of Rights in 1787, the ‘Declaration of the Rights of Man and the Citizen’ was adopted by France for its citizens in 1789. Articles 1-5, as noted below, speak of the rights to freedom, security and liberty. Articles 4 and 5 are particularly relevant in terms of compassionate/expanded access to drugs in development. Articles:
   1. Men are born free and remain free and equal in rights. Social distinctions can be based only on public utility.
   2. The aim of every political association is the preservation of the natural and imprescriptible rights of man. These rights are liberty, property, security, and resistance to oppression.
   3. The sources of all sovereignty reside essentially in the nation; no body, no individual can exercise authority that does not proceed from it in plain terms.
   4. Liberty consists in the power to do anything that does not injure others; accordingly, the exercise of the rights of each man has no limits except those that secure the enjoyment of these same rights to the other members of society. These limits can be determined only by law.
   5. The law has only the rights to forbid such actions as are injurious to society. Nothing can be forbidden that is not interdicted by the law, and no one can be constrained to do that which it does not order.

5. **Universal Declaration of Human Rights** - The atrocities of the Second World War served
as the catalyst for the development and adoption of the declaration. The Preamble begins, “Whereas recognition of the inherent dignity and of the equal and inalienable rights of all members of the human family is the foundation of freedom, justice and peace in the world, ...” The Universal Declaration of Human Rights was adopted by the United Nations in 1948. Article 1. of the declaration guarantees that the rights articulated in the declaration are applicable to all human beings. It says, “All human beings are born free and equal in dignity and rights.” Article 3. says that, “Everyone has the right to life, liberty and security of person.” Article 25 says that, “Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services [...].”

Canadian Charter of Rights and Freedoms is an important document in defining the rights of Canadians. Paragraph 1 speaks to the guarantee of rights and freedoms. “1. The Canadian Charter of Rights and Freedoms guarantees the rights and freedoms set out in it subject only to such reasonable limits prescribed by law as can be demonstrably justified in a free and democratic society.”

Paragraph 7 of the Canadian Charter of Rights and Freedoms is the section that deals with the right to life. “7. Everyone has the right to life, liberty and security of the person and the right not to be deprived thereof except in accordance with the principles of fundamental justice.”

Quebec Charter of Human Rights and Freedoms affords many rights including fundamental rights and freedoms. Paragraph 1. reads, “Every human being has the right to life, and to personal security, inviolability and freedom.” Paragraph 2. Reads, “Every human being whose life is in peril has a right to assistance.”

The Universal Declaration of Human Rights, the Canadian Charter of Rights and Freedoms and the Quebec Charter of Human Rights and Freedoms all specifically proclaim the right to life, liberty and security of person. By definition, individuals who are catastrophically ill are at risk of losing their personal security (at a minimum) and are ultimately at risk of losing their lives. Surely, the right to life and personal security provisions of these Declarations is triggered in such circumstances. These documents collectively provide the foundation for conclusions about the Rights of the Catastrophically Ill, which are reached in this paper.

CTAC takes the position that the fundamental right of individuals to access to potentially life-saving medications flows from the cumulative effect of centuries of expounding and expanding the rights of human beings.

CTAC takes the position that the Universal Declaration of Human Rights, the Canadian Charter of Rights and Freedoms and the Quebec Charter of Human Rights and Freedoms secure an individual’s right to life and personal security. Therefore, CTAC takes the position that provision of experimental drugs in Canada through compassionate and expanded access programs should be mandatory for drug sponsors.
CTAC recognizes that all stakeholders have interests and rights related to the provision of compassionate and expanded access programs. Doctors have a right to “do no harm”. Pharmaceutical manufacturers have a right to take precautions to ensure sound business decisions are made. Regulators have a right to establish procedures for access to drugs in development. Researchers have a right to conduct rigorous scientific research. And, catastrophically ill individuals have a right to preserve their own lives. As well, CTAC recognizes that other stakeholders may have additional and diverse rights and interests with regard to early access to drugs in development.

**CTAC takes the position that in the case of conflicting rights, the right to preserve one’s life is paramount and takes precedence over all other rights.**

**C) Compassionate Access and Expanded Access Establishment Criteria**

Individuals suffering from catastrophic illness have died and others have experienced significant and irreversible deterioration of health while waiting for the normal course of drug development to provide access to new treatments. The time from submission of a new drug submission (NDS) at the end of Phase III trials to approval on provincial formularies can often take two years which is time that seriously ill people simply do not have.

**CTAC takes the position that all clinical trials protocols submitted for review and approval in Canada must include plans for both a compassionate and expanded access program.**

**CTAC takes the position that Compassionate Access Programs should be implemented for experimental drugs as soon as the safe dosage has been determined and when preliminary data indicates some potential benefit.**

Provision of new drugs through compassionate access programs would mean that very sick people would have access to potentially life-saving treatment when they need it the most - before their time runs out.

**CTAC takes the position that Compassionate Access Programs should be ‘Expanded’ to become a formal part of the protocol when optimal dose has been determined and additional safety data has been gathered. This should normally be at the beginning of Phase III studies.**

CTAC has historically called on pharmaceutical companies to coordinate their research in Canada with research in the U.S. so that trials in both countries begin simultaneously. This would allow for submission to regulators at the same time in both countries. In keeping with this concept of equitable access, **CTAC takes the position that Canadian and U.S. compassionate and expanded access programs should be launched simultaneously to ensure equitable access to new treatments.**

In some compassionate and expanded access programs, a limited supply of drug or other limited access combined with high patient need, has resulted in many more people wanting access to the
drug than could be met by the supply. In an effort to try to ensure ‘fairness’, lotteries have been held where individuals were selected randomly and indiscriminately. **CTAC takes the position that lotteries are unfair and CTAC does not support this practice as a selection process for access to experimental treatments.**

Since new treatments started appearing for HIV/AIDS in the mid-nineties, many pharmaceutical companies have provided compassionate access to their respective new discoveries. However, under our current regulatory system, provision of compassionate access programs is completely voluntary and in some cases pharmaceutical companies have decided to not provide drug access in this way. In other cases compassionate and expanded access has been offered but the size of the program has been insufficient to meet the needs of the catastrophically ill. Community and physicians have had to devote considerable time and resources to make the case, often unsuccessfully, for greater access.

**CTAC supports the recommendations of the Sub-committee on HIV/AIDS of the Standing Committee on Health Report, “Compassionate Access to Investigational Therapies”, which are listed on page(s) 5-6 of this document. Of particular note is recommendation no. 1 which recommends that compassionate access be made mandatory through changes to legislation.**

**CTAC takes the position that expanded access programs should be made mandatory by Health Canada as a condition of approving a clinical trial.**

Since the first HIV/AIDS treatments were introduced in the mid-late eighties, community groups and individuals have worked with industry, physicians, governments and other stakeholders to ensure that HIV/AIDS drugs were available in Canada to those who desperately needed them. Community participation has resulted in countless lives saved and immeasurable improvement to quality of life for thousands of people.

**CTAC takes the position that community must be involved in the development and implementation of all compassionate access programs and expanded access programs in Canada.**

In many cases, compassionate/expanded access programs are designed by industry to try to provide for equal access by evenly spreading available spots across the country. Frequently, compassionate/expanded access programs provide access to drugs in development to patients in larger cities but access for people in rural/remote areas can be very difficult, if not impossible.

**CTAC takes the position that compassionate access programs and expanded access programs should be designed so that the catastrophically ill get first priority in terms of access to drugs in development, regardless of where they live in Canada. When the supply of experimental drug is insufficient to meet the needs of the catastrophically ill, then the drug should be made available first to those most in need. Criteria must be developed with input from all stakeholders to determine which individuals are most in need of access to experimental drugs.**
D) Compassionate and Expanded Access Program Characteristics

i) Ethics Review

Ethics review of clinical trials is currently mandatory in Canada under the Food and Drugs Act and Regulations. Section C.05.001 of the Regulations says, in part, that “research ethics board’ means a body that is not affiliated with the sponsor; and a) the principle mandate of which is to approve the initiation of, and conduct periodic reviews of, biomedical research involving human subjects in order to ensure protection of their rights, safety and well-being.”

The end of the Second World War brought about many changes. As noted earlier, the Universal Declaration of Human Rights was adopted by the United Nations in 1948. There was also a significant change in the way research on humans was conducted when the Nuremberg Code was established in 1949. The document is short and contains ten ‘Directives for Human Experimentation’. Since that time, a plethora of documents have been released worldwide, which collectively are the foundations of all credible research conducted in the world today.

CTAC takes the position that ethics review of all clinical trials is essential to ensure that 1) participants are protected and 2) the trials meet minimum ethical standards.

The implementation of compassionate/expanded access programs is usually done as a separate open arm of a clinical trial. In such circumstances, compassionate/expanded access trial protocols are subject to the same review as any other clinical trial. Normal ethics review for clinical trials is usually conducted at each clinical trial site by local research ethics boards (REBs). Ethics review, conducted by local REBs, for clinical trial protocols for compassionate/expanded access presents a number of problems. It is worth noting that drugs accessed through Health Canada’s Special Access Program (SAP) are not subject to any formal ethics review at all.

CTAC takes the position that Compassionate Access Programs should not be subject to ethics review. Compassionate Access is about treatment, not research.

Local ethics review for national expanded access protocols provided by local REBs can be problematic. During his testimony before the Sub-committee on HIV/ADS, Dr. Benjamin Freedman of McGill University in Montreal said, “In terms of the definitional interface between research and treatment, we want to re-emphasize the need for clarity in understanding the role of research ethics boards and compassionate/expanded access programs. This difficulty arises in part because REBs are generally responsible for reviewing the ethics of research protocols. Other institutional or hospital ethics committees - clinical bioethics committees, for example - have more typically been involved in the ethics of clinical treatment decisions. The possibility of confusion of roles arises when a therapeutic undertaking, such as compassionate/expanded access to experimental therapies, contains elements of both research and treatment.”

As with normal clinical trials, CTAC takes the position that some ethics review is required for all clinical trial protocols for Expanded Access Programs. However, ethics review for
expanded access protocols should not be conducted by local REBs because: 1) the ethical procedure appropriate to research (which is the mandate of local REBs) is not suitable for a situation which is primarily treatment, and 2) The urgency for access to drugs in expanded access programs would be better served through a central/national ethics review process.

In the case of compassionate and expanded access programs for HIV/AIDS, the Canadian HIV Trials Network (CTN) has had a long and successful history of conducting clinical trials and its National Ethics Review Committee (NERC) has been instrumental in providing national ethics review for expanded access protocols. For other disease/disability conditions, there may be similar national organizations that can provide appropriate disease-specific ethics review.

ii) Free and Informed Consent

The Tri-Council Policy Statement - Ethical Conduct for Research Involving Humans uses the term “free and informed consent” to describe the “decision made by the potential research subjects on whether to participate in research.” “Free and informed consent" was decided upon for a number of reasons: it states the requirement for voluntariness and information; it was felt to include the idea that consent is the act of deciding, perhaps as a result of balancing a number of choices; it retains the traditional word "consent"; and the phrase has unambiguous meaning in the law.”

Free and informed consent is seen as a keystone underpinning for all research in humans. During his testimony before the Sub-Committee in 1995, Mr. William D. Milligan, Vice-President of the Pharmaceutical Manufacturers' Association of Canada said, “The legal issues [related to compassionate access] hinge on the ability or inability to achieve true informed consent. On drugs where very little data are established and/or proven, the risk-benefit assessment is not possible. If the drug is at an early stage of development, decisions in releasing the drug for use in individuals would default to ethical decisions. There, research on human subject guidelines and decisions relating to the physician's commitment to do no harm also impact.”

The Nuremberg Code - Directives for Human Experimentation, addresses informed consent in Directive 1. “The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision.”

The term, “free and informed consent” is particularly appropriate for use in compassionate access. In the case of compassionate and expanded access, an individual may have to make a choice without having all of the information which might ordinarily be available. This does not render the consent any less valid as long as it was made with the subject having all available and relevant information at the time, and as long as the decision was made free of interference or influence.
Ms. Susan Conrad, a human rights lawyer, during her testimony before the Sub-Committee said, “Based on my professional experience, I can state that there is nothing that physicians, or anyone else for that matter, can do to insulate themselves against the possibility of being sued. Patients reserve the right to file suits at any time, both before and after a drug is formally licensed. The best protection physicians have against the possibility of being sued is to obtain genuinely informed consent.”

CTAC takes the position that individuals have the right to give free and informed consent, and further asserts the validity of such consent, even if the consent is given when less than optimal levels of information exist.

iii) Inclusion/Exclusion Criteria

Under normal clinical trials, it is necessary to ensure that each arm of a trial has certain consistencies. All clinical trials have inclusion/exclusion criteria. This term generally refers to the rules about who can or cannot enter a certain trial. Inclusion criteria mean that there are certain conditions that must be met before an individual can be ‘included’ in a trial. Exclusion criteria mean that there are certain conditions which, if met, ‘exclude’ people from participating. For the sponsor of a drug, clinical trials represent a means to gain further information about how the drug performs.

Examples of inclusion criteria include: having a CD4 count or viral load measurement in a certain range and having failed or developed intolerance to, certain other medications. Exclusion criteria includes things like: being pregnant, having certain medical conditions which might put the participant at greater risk for side-effects or drug interactions, or having used certain other drugs which lower the potency of the study drug or vice versa.

The clinical trial protocols for expanded access programs are frequently set up like regular clinical trials. This process presents a number of challenges for individuals who are catastrophically ill. As a research tool, clinical trials provide valuable information about experimental drugs and, as such, rigid inclusion/exclusion criteria help ensure the validity of the trial results. As an expanded access program, the inclusion/exclusion criteria of a clinical trial arm need to be flexible to accommodate the needs and rights of participants.

In some cases, pharmaceutical companies are reluctant to provide access to the most catastrophically ill for a variety of reasons including: providing drugs to very ill people may not provide as much benefit as it might to someone less ill and providing drugs to very ill people may increase the risk of side-effects or other complications, both of which might reflect negatively on the product being provided and its sponsor. For this reason, compassionate access should be considered on an individual basis. Unlike expanded access, which is an arm of a clinical trial, compassionate access should be just for the very sick when the request is supported by a physician.

CTAC takes the position that the primary inclusion criteria for compassionate access
programs should be simple: a) be catastrophically ill, as defined by one’s physician; b) have the support and participation of one’s physician, c) other available therapies have failed or are unsuitable and d) patient is able and willing to give consent.

CTAC takes the position that expanded access programs should be a separate arm of a clinical trial with open criteria when the patient and physician agree that the patient need the drug to create a viable regimen.

CTAC takes the position that all informed consent forms for participation in clinical trials should contain a commitment by the drug sponsor to continue the participant on the trial drug until the drug has been approved for sale and is covered by the participant’s public or private plan.

iv) Cost of Access to Experimental Drugs

One very important issue that is raised in discussions about compassionate and expanded access programs is the issue of the costs associated with accessing drugs in development. These costs include the costs of the drug itself, cost of administration related to compassionate and expanded access programs for the drug sponsor, the physician and the regulator, and the cost of associated health care such as follow-ups with physicians, blood work and/or other diagnostic tests (which fall mainly under provincial health care plans).

Dr. Bill Cameron, in response to discussion about costs associated with compassionate and expanded access at the Sub-committee on HIV hearings in 1995 said, “Who pays for this? That is like asking which budget this goes on. The answer is that we all pay for it. Whatever budget it goes on, we all pay for it.”\textsuperscript{105} This is an undeniable truth and the question perhaps should really be, ‘what is the best way to deal with the costs’?

In addition to the discussions about direct and indirect costs associated with compassionate and expanded access, there have also been discussions about the financial benefits of early access to drugs in development. Dr. Mark Wainberg, during his testimony before the Sub-committee on HIV/AIDS in 1995, said, “If the expectations that we have of 3TC prove correct, Canadian taxpayers may save tens of millions of dollars during the next decade through reduced hospitalization costs. What better proof that investments in research can pay big dividends?”\textsuperscript{106}

Another consideration is the potential benefit to the drug sponsor of providing early access to drugs in development. Mr. William Milligan, representing the Pharmaceutical Manufacturers Association of Canada at the hearings in 1995 said, “I think ... that when you look at compassionate access programs from the industry perspective [...] there is an advantage for pharmaceutical companies in providing drugs for compassionate access programs. It allows patients and physicians to get experience. It puts an immense amount of pressure on provincial agencies to come up with reimbursement for these drugs when the period of that compassionate access provision runs out. There are a lot of advantages and benefits to pharmaceutical companies providing compassionate access products when they expect they're going to go to market.”\textsuperscript{103}
Dr. Benjamin Freedman, on the cost of access to experimental drugs, wrote in 1996 that, “It is fair to say that drug research in Canada involves a partnership between drug companies and research subjects; without the willingness of persons to submit themselves to a research protocol, companies would be out of business. Many REBs have taken the position that to satisfy this partnership, companies must agree to supply those research subjects who had been assigned to placebo with the test drug if the trial's results are positive. Drug research involves a further partnership as well, with the Canadian public and government. Drug companies take advantage of a favourable tax and financial climate, and a sophisticated health-care infrastructure, supported by the taxpayer. Reciprocity and equity suggest that companies be made to understand that open-label supply of experimental drugs in conformity with policy and ethics is part of the cost of doing business in Canada.”

The Food and Drugs Act Regulations normally prohibit the sale of new drugs until they are approved, however the provision of the Regulations that deals with providing new drugs through the Special Access Program (SAP), also allows a manufacturer to sell an unapproved new drug.

While the vast majority of drugs, provided through early access mechanisms (including clinical trials, SAP and compassionate/expanded access), are provided by the drug sponsor at no cost, the fact that the Regulations provide for sale of unapproved drugs raises the prospect of two classes of patients - those who can afford to buy the drug and those who can not afford to buy the drug. Since neither private insurance nor provincial/territorial/federal prescription drug plans will cover the cost of unapproved drugs, any costs which are attached to early access to drugs will severely limit the number of people who will have access.

CTAC recognizes that there are costs associated with compassionate and expanded access programs, however when the savings to the healthcare system and the benefits to the industry are factored in, the net cost may be minimal. It may be possible that providing drugs through early access mechanisms will result in a decrease in overall costs to Canadians. **CTAC takes the position that research on the implications of all aspects of early access to drugs, including costs, is required.**

**CTAC takes the position that it should be mandatory that all drugs, supplied through early access mechanisms including SAP and compassionate and expanded access, should be provided at no cost to the patient or the physician.**

**CTAC takes the position that the Food and Drugs Act Regulations should be amended to completely ban the sale of drugs before they are approved for use and sale by Health Canada.**

**CTAC takes the position that the issue of cost of early access to drugs warrants further discussion and believes that Health Canada should take a lead role in initiating a multi-stakeholder consultation where costs and other important issues related to early access to drugs in development can be explored and addressed.**
E) Additional Issues Considered in Formation of this Paper

i) Safety

Throughout the process of drug development, safety of the research participants is paramount. Stringent guidelines for the conduct of all research in Canada are outlined in the Food and Drugs Act and the Food and Drugs Act Regulations. As well Canada is a party to numerous international treaties and other agreements/commitments. Some of these international agreements/commitments, all of which hold the safety of the research participant as the highest priority, include: Tri-Council Policy Statement, International Conference on Harmonization (ICH) Guidelines and the World Medical Association Declaration of Helsinki.

When drugs are provided through early access mechanisms, the safety of the drug has not been fully established. That is, in fact, one of the issues to be determined by ongoing research. There are risks involved in taking any drug before its safety can be fully assessed. Dr. Benjamin Freedman, in an article in the Canadian HIV/AIDS Policy & Law Newsletter, said, “... Patients who are desperately ill sometimes consent to research with the idea that they have nothing to lose. This is a mistake. No disease is so dreadful and imminent that it cannot be made worse by the inapt application of an experimental treatment.”[109] For the catastrophically ill person, the level of acceptable risk may well be much greater than would normally be the case.

Since compassionate and expanded access programs are primarily treatment, the person requesting access to experimental drugs in this way provides free and informed consent and acknowledges that, because there has been insufficient research, there are unknown risks to taking experimental drugs. The consent provided for access to treatment, also provides an implied consent to be excluded from provisions of ethical guidelines, when such guidelines restrict access to treatment.

CTAC takes the position that the human rights of catastrophically ill individuals to security of person, which are outlined in several human rights documents noted in this Paper, supersedes any ethical requirements that apply as a result of the treatment intervention being classified as research.

CTAC takes the position that when a catastrophically ill person has the support of his/her physician, and has been adequately informed of the risks, decisions on the level of acceptable safety ultimately reside with the person who has to take the drug, even though the level of information available about safety may be less than optimal.

ii) Impact of Access to the Experimental Drug on Ongoing Research

Some people have argued that large compassionate and expanded access programs can have a negative impact on clinical trials which are happening at the same time. The argument is that the potential trial participants are opting to enter the compassionate and expanded access program in order to ensure that they receive the new drug rather than enter a clinical trial where they may be
randomized to receive either the new drug or another drug (possibly a placebo when no standard treatment has been developed). In these circumstances there may not be sufficient enrolment to carry out the clinical trial which ultimately holds up approval of the drug and holds up access for the majority of the population.

During the Sub-committee hearings in 1995, this issue received considerable discussion and there was a general consensus that compassionate/expanded access must not interfere with on-going research. A number of doctors made specific and notable comments on this issue. Dr. Ken Logue and Dr. Mark Wainberg both expressed concern about the potential impact of early access to drugs on on-going research. Dr. Logue said, “Facilitating the enrolment of large numbers of people in compassionate access programs without the concomitant conduct of sound clinical trials should not be considered a primary goal. Indeed, without ongoing trials conducted in a sound scientific fashion, the future availability of drugs to patients at all stages of illness, whether immediately life-threatening or not, will obviously be compromised.”

Dr. Wainberg testified that, “While I understand the delicate balances this committee needs to understand in rendering judgment about the proper compassionate release procedure for drugs in Canada, I think that process cannot be one that limits the ability of Canadian clinicians and academics to direct and participate in properly randomized clinical trials. I make this statement both personally and as president of the Canadian Association for HIV Research, with the backing of the organization's membership.”

CTAC takes the position that on-going clinical trials are crucial to the process of developing new drugs. Compassionate and expanded access programs must not interfere with the conduct of sound scientific research on new drugs.

CTAC does not believe that it has to be an either/or situation - that is, either research or compassionate and expanded access. CTAC takes the position that compassionate and expanded access programs can be delivered in manner that does not interfere with the conduct of sound scientific research on new drugs.

iii) Impact of Access to the Experimental Drugs on Drug Review Processes

One of the reasons why compassionate and expanded access to drugs in development is necessary is because of the lengthy process for drug reviews in Canada. As described earlier in this document, Health Canada’s target times for drug reviews can take a year (frequently the actual time for drug reviews exceeds the target times). After the drug is approved by Health Canada, it is then subject to further review to determine whether provincial/territorial/federal drug plans will cover the drug.

According to Dr. Bill Cameron, “The most ethical pursuit to bring the best treatment to the most people is rapid drug development. Nothing must interfere with this process. Speed is like justice - delay is denial of treatment. Nothing must interfere with the rapidity of drug development.”

Dr. Bill Cameron, Ottawa General Hospital.

CTAC has worked extensively with a wide variety of stakeholders to try to improve the review
times for new drugs in Canada and some improvements have occurred. **CTAC takes the position that timely and effective drug review processes are essential to ensure equitable and timely access to safe new drugs and that no irrelevant factors should interfere with the speediest completion of drug reviews and approvals.**

**CTAC takes the position that compassionate and expanded access programs can be delivered in a manner that does not interfere with the speediest completion of drug reviews and approvals.**

When drugs are provided through compassionate and expanded access programs, patients and health care providers insist that the sponsor of the drug commit to providing the drug until it is approved for reimbursement under public/private drug plans. Drug sponsors have suggested that compassionate and expanded access programs may slow down reviews by provincial/territorial/federal drug plans. **CTAC takes the position that provincial/territorial/federal drug reimbursement plans should be mandated to provide speedy reviews of drugs regardless of whether the drug is already available through any early access mechanism.**

**iv) Impact of Experimental Drug Access on Administrative Requirements**

In Canada, access to unapproved drugs is generally available through either clinical trials, the Special Access Program or through compassionate and expanded access programs. All of these early access mechanisms require records and controls. There are administrative requirements for the doctor who initiates the request for access, the pharmaceutical company which provides the drug and Health Canada. In clinics where large numbers of HIV + patients are treated, the administrative requirements for early access to drugs can be enormous.

**CTAC takes the position that administrative requirements for compassionate access to drugs should be consistent with the requirements of provision of any emergency medical treatment.**

CTAC recognizes that drugs provided through expanded access programs can provide important safety data about new treatments and that some level of administration is unavoidable. **CTAC takes the position that expanded access programs should be conducted as open arms of clinical trials.** However, since expanded access has an urgency associated with it, **CTAC takes the position that the administrative demands of expanded access programs should be pared down, streamlined and standardized so as to ensure minimal impact on delivery of treatment.**

CTAC recognizes that many doctors make substantial contributions, for which they are not usually compensated, in terms of administration required to conduct compassionate and expanded access programs. **CTAC supports the concept of compensation for administration of early access programs for doctors/healthcare providers who are not otherwise compensated for these services.** Further discussion is required, among all stakeholders, on how to deal with the costs of administration related to early access to drugs. **CTAC takes the**
position that administrative costs to the pharmaceutical industry and to Health Canada should be absorbed by these entities.

v) Quality of Research Data - Compassionate and Expanded Access

Programs

It is important to remember that the primary purpose of compassionate and expanded access is to satisfy the emergency treatment needs of catastrophically ill individuals. **CTAC takes the position that compassionate access is emergency medical treatment and as such cannot and should not be subject to the type of data collection used in clinical trials.**

Expanded access programs of clinical trials can provide important safety information, and to some degree efficacy information. In a regular clinical trial, an experimental drug is compared to either a current standard treatment or a placebo. When an expanded access program is added, every one in that arm gets the experimental drug so it is not being compared to another drug, although the data from such programs can be compared to a placebo arm or a standard-of-care arm of the trial. Pharmaceutical companies argue that the data collected from expanded access programs cannot be used to satisfy the research demands required to get a drug approved, and therefore the data collected from expanded access has little value. **CTAC recognizes the need for properly conducted, randomized clinical trials that produce data which can be used to secure regulatory approval for, and ultimately access for all to, new drugs.**

Frequently, expanded access programs are designed to more closely resemble regular clinical trials and some have fairly stringent criteria for accessing the experimental drug. Such limitations on access result in access being denied to some of those who are most in need. **CTAC recognizes that the catastrophically ill are not an homogenous group and that entry criteria for access to expanded access programs of clinical trials must be flexible enough to meet the needs of the catastrophically ill.**

**CTAC takes the position that safety data produced in expanded access programs is helpful for the physician, the manufacturer and Health Canada and can provide valuable information which can enhance our understanding about the safety of new drugs.** Since everyone in the compassionate/expanded access program is getting the experimental drug, there is an opportunity to collect additional safety data and, to some degree, efficacy data. In some cases there is data collected in compassionate/expanded protocols of clinical trials that would simply not be available in regular clinical trials. In compassionate/expanded access programs there are frequently people participating who would not qualify for access to regular clinical trials. Seeing how the drugs work in a wider population can provide important information. An example might be: how the drugs work in seriously ill patients with very low CD4 counts. In normal clinical trials, individuals with very low CD4 counts may be excluded and therefore normal clinical trials would not provide any data on how the drug works in this population.

vi) Impact of Compassionate and Expanded Access on Small Companies

As noted earlier, **CTAC supports the Sub-committee on HIV/AIDS recommendations (on**
pages 5 - 6 of this document), which include a recommendation that compassionate access be made mandatory. CTAC takes the position that expanded access programs should also be mandatory. Some opponents of mandatory provision of compassionate and expanded access have argued that early access could cripple small companies with a promising new product coming to market. This clearly then was not the case for the tiny Canadian company BioChem Pharma which partnered with Glaxo Wellcome to create the largest compassionate/expanded access program ever when it made its anti-HIV drug 3TC available to more than 45,000 people in 1995.17

During her testimony before the Sub-Committee in 1995, Dr. Sophia Fourie who was representing the Pharmaceutical Manufacturers Association of Canada said, “I can...make a general statement: usually small companies would tend to partner and team up with bigger companies. In this day and age of joint ventures and of mergers, I do not see that being a small company with a really exciting and advanced potential treatment.... You would be stuck and not able to do research.”113

vii) Misconceptions About Currently Available Treatments

Some opponents of compassionate and expanded access to drugs in development claim that the need for compassionate access has diminished as more and more new treatments have been developed. Some of the new treatments that have been approved for use in recent years are simply reformulated versions of existing drugs or combinations of existing drugs. Many of the genuinely new discoveries that have been approved in recent years share resistance patterns (cross-resistance) with previously available treatments. Other new drugs that have come to market have proven intolerable for some people. The bottom line is that, despite the new treatments that have been approved, many Canadians cannot construct a viable treatment regimen with currently available therapies as was discussed in Section 4. Sadly each year people continue to die while waiting for new treatments.

viii) When Drug Development is Terminated

By far, the vast number of drugs provided through early access programs go on to be approved for sale, and successfully marketed, in Canada. However, in rare cases clinical trials have been stopped by either the manufacturer or by Health Canada because of safety or lack of efficacy issues. Of course, even if the trials are allowed to come to completion, it does not guarantee that the drug will be approved.

CTAC takes the position that, for individuals who are accessing drugs through early access mechanisms, if the development of the drug is terminated, provisions must be made to ensure that the termination of supply is not abrupt and that sufficient time is provided for an orderly transfer to an alternate regimen.

(ix) Is Compassionate Access Research or Treatment?

Compassionate access, as defined and articulated in this Paper, refers to the provision of
emergency medical treatment to catastrophically ill patients. The patient population that requires the type of emergency medical treatment afforded by compassionate access is certainly not the usual population from which clinical trial participants are selected. It would not be fair to the patient, the drug or the drug sponsor to use data gathered from compassionate access to further research objectives. **CTAC takes the position that compassionate access is treatment, not research.**

**x) Is Expanded Access Research or Treatment?**

The question of whether expanded access should be considered as treatment or research has been debated extensively. Some argue that when drugs are in clinical trials they are considered research, just because you access them early through expanded access programs does not change anything - it is still research. Others argue that the primary purpose for accessing drugs in development is to treat an individual(s) and therefore it should be considered as treatment. The answer to this question of whether access to drugs in development should be considered research or treatment is important because it has implications on the way these programs are delivered including the type and amount of data which should be collected, the type and scope of ethics review required and the entry criteria for early access to drugs.

Dr. Benjamin Freedman, of McGill University wrote about ethics and compassionate access in an article in the October/96 issue of the Canadian HIV/AIDS Policy and Law Newsletter. He said, “When a catastrophic right is defined as "the right of a catastrophically ill adult to elect, in consultation with a physician, any therapy whatsoever that does not cause direct harm to others," the ethical procedure appropriate to treatment, rather than research, is chosen. [...] The treatment model relies upon a doctor supplying a patient with a well-grounded treatment recommendation, based on the sole interest of the patient, who then may choose to accept it after being adequately informed.”

Providing experimental drugs through expanded access programs can provide research data, however such programs must be viewed primarily as treatment and secondarily as research. Under these circumstances expanded access programs for medications in development, are an essential component of emergency care. Access to medications in development is frequently the only hope for persons with AIDS who no longer benefit from, or are intolerant of, currently available treatments.

**CTAC takes the position that expanded access, while administered as a separate open arm of a clinical trial, is primarily treatment and secondarily research.**

**(xi) Health Canada’s Special Access Programme (SAP)**

**Mandate of the Special Access Programme:** “The Special Access Programme (SAP) provides access to non-marketed drugs for practitioners treating patients with serious or life-threatening conditions when conventional therapies have failed, are unsuitable, or unavailable. The SAP authorizes a manufacturer to sell a drug that cannot otherwise be sold or distributed in Canada. Drugs considered for release by the SAP include pharmaceutical, biologic, and
Health Canada’s SAP has been operating since 1997 when it replaced the previous Emergency Drug Release Program (EDRP). At the time of its implementation, SAP was being touted by the Health Canada as a significant improvement over the EDRP. There are many who would argue that it has not proven to be much of an improvement at all. Now, after almost a decade, SAP appears to be a barrier, in some cases, to treatment access rather than a facilitator of access. In a recent case in B.C., SAP refused access to experimental drugs for six patients and it took nine months to get the Health Canada decision reversed. Health Canada did not approve the drugs for use as requested but came up with a compromise - a special clinical trial - but not before one of the patients requesting early access to the drugs died.

Dr. Julio Montaner and Dr. Timothy Christie wrote of their experience accessing drugs through SAP in the February/06 edition of ‘forecast’, the Journal of the B.C. Center for Excellence in HIV/AIDS. The following excerpts from the article highlight some serious concerns with regard to access to experimental drugs through SAP.

“The B.C. Center for Excellence in HIV/AIDS is relieved that five of our patients now have access to the experimental drugs TMC114 and TMC125. It is also promising that early blood results indicate that the health of our patients is improving under their new regimen. However, it is extremely worrisome that the drugs have only been made available after navigating a road fraught with numerous Health Canada roadblocks. Unfortunately, one of our patients died while waiting for access to these experimental drugs.”

“Health Canada only reversed their decision due to public pressure. With their lives at stake, some of our patients were compelled to take their stories to the media. In the wake of negative publicity and a federal election nearing, Health Canada came up with a new last minute option - a Compassionate Use Protocol, or a special clinical trial. In essence we were asked to redress our request under the pretense of “research”. The same group of patients, the same drugs, the same doctors - but under a different name.”

“The lengthy delay until Health Canada’s reversal, especially in light of one patient dying while waiting, should be of serious concern to all Canadians. One must ask why it is OK for these patients to accept the unknown risks of experimental drugs within the confines of a special clinical trial, but not within the parameters of SAP.” “The consequence of this absurdity is that these patients have been denied treatment for up to nine months and their conditions had substantially worsened.”

“SAP, in its current form, is poorly governed and renders arbitrary decisions. The program is inconsistent with the principles of “emergency” and/or “compassionate” access. A fully revamped SAP is urgently needed. A transparent decision-making process and full accountability are mandatory. SAP should be a viable option for future patients with life-threatening conditions.”
The B.C. case of catastrophically ill people being denied access to treatment had the worst possible outcome - a person died.

Another troubling event that happened at SAP recently was the denial of a cancer patient to early treatment access, and the reversal of the decision. In an article posted to GlobeandMail.com on April 1, 2006, Lisa Priest wrote, “A 73-year-old multiple myeloma patient who was denied access to a free drug because a $35,000 licensed alternative was available will be able to obtain Thalomid to treat his cancer after all.” The article went on to say that the problem was a clerical error.

Summary of Issues/Concerns Related to SAP
- Lack of transparency in decision making
- Inconsistent decisions
- Lack of accountability to patients, physicians and other stakeholders
- SAP pressure to provide early access to drugs in development in a research setting rather than as ‘emergency’ or ‘compassionate’ treatment
- Lack of appeal processes
- Lack of community/other stakeholder input/participation in decisions
- Food and Drugs Act permits the experimental drug to be sold for patients accessing through SAP
- Drugs can only be sent to a physicians office or in-patient pharmacy (cannot be sent to patients or regular pharmacies)
- Lack of safety/efficacy tracking of drugs approved for SAP
- SAP should be available to access drugs not approved for sale in Canada
F) CTAC Position Summary

“To understand that drug access, even without confidence of concrete help, is compassionate, it is necessary to take a passport to Susan Sontag's “Kingdom of the Sick” in *Illness as Metaphor*. From there we can see the benefit of comfort and hope separately from effective treatment. The road to cure provides us with the opportunity to comfort, through the provision of hope to the desperate. This is our real mission.”¹¹² - Dr. Bill Cameron, University of Ottawa at the Ottawa General Hospital.

It is true that compassionate and expanded access to drugs in development can positively affect the overall health of catastrophically ill people, even when such access is to a potentially ineffective or only marginally effective medication. Access, in and of itself, can provide comfort and hope. However, it is clear that early access to drugs in development can provide more than psychological benefits. Dr. Mark Wainberg, during his testimony before the Sub-committee in 1995, concluded his remarks by saying, “I can have no greater satisfaction than the knowledge that work done in my laboratory in collaboration with Biochem Pharma and Glaxo Wellcome has contributed to the development of a drug that has already enabled tens of thousands of people to live longer and higher-quality lives than would otherwise have been the case. This is in part a reflection of the availability of 3TC and other drugs through compassionate release programs.”¹¹⁷

The pharmaceutical industry makes enormous profits from its products. According to Marcia Angell*, “The main point about excess in the pharmaceutical industry is how much there is of it.”

In an article in the Canadian Medical Association Journal (CMAJ) entitled ‘Over and above - Excess in the pharmaceutical industry’, Ms. Angell put the pharmaceutical industry’s profits in perspective. She wrote, “Although the pharmaceutical industry claims to be a high-risk business, year after year drug companies enjoy higher profits than any other industry. In 2002, for example, the top 10 drug companies in the United States had a median profit margin of 17%, compared with only 3.1% for all the other industries on the Fortune 500 list. Indeed, subtracting losses from gains, those 10 companies made more in profits that year than the other 490 companies put together. Pfizer, the world's number-one drug company, had a profit margin of 26% of sales. In 2003, for the first time in over 2 decades, the pharmaceutical industry fell slightly from its number-one spot to third, but this was explained by special circumstances, including Pfizer's purchase of another drug giant, Pharmacia, which cut into its profits for the year. The industry's profits were still an extraordinary 14% of sales, well above the median of 4.6% for other industries. A business that is consistently so profitable can hardly be considered risky.”¹¹⁸

* Marcia Angell is Senior Lecturer in Social Medicine, Harvard Medical School, Cambridge, Mass., and the author of *The Truth About the Drug Companies: How They Deceive Us and What To Do About It* (2004).

In 2002, the top ten pharmaceutical companies made a total of over $35 billion in profit,¹¹⁹ none of which would be possible without the participation of sick people in clinical trials. In the bigger scheme of things, with such substantial profits, the cost of conducting
compassionate/expanded access is negligible. Canadians, who have participated in clinical trials, have taken the risks involved with experimental therapies. They have done so for primarily altruistic reasons. Clinical trial participants have also generously given of their time. Generally speaking the motive for participation in clinical trials is the hope that the data collected may help benefit others.

Representatives from the pharmaceutical industry have acknowledged that the industry has a moral responsibility to provide compassionate and expanded access programs. Health Canada has acknowledged that there is a need for early access to drugs in development and has acknowledged its moral duty to participate. It has done so through administration of the EDRP up to 1997 and SAP since 1997. It has also approved dozens and perhaps hundreds of compassionate and expanded access protocols. Physicians generally support early access to drugs in development. Given that there is a general consensus that compassionate and expanded access programs are necessary and the right thing to do, the next step is to determine the best way forward.

Under all current processes for early access to experimental drugs, the drug manufacturer has the final say. While it is true that the vast majority of drugs, which have been brought to market, have had compassionate and expanded access programs, the fact that it is not mandatory means that a manufacturer can choose to not offer any early access to its drugs. In cases where compassionate and expanded access are offered by the drug sponsor, there are frequently serious and multiple concerns. The size (number of people who can receive the drug) of the programs, the eligibility criteria and the and the time of initiation of compassionate/expanded access programs are just some of the issues with which the community is in a constant tug-of-war with the pharmaceutical industry.

CTAC takes the position that compassionate and expanded access programs should be mandatory, that the drugs provided should be provided at no cost, and that the pharmaceutical industry should consider early access to drugs in development as an essential component of the drug development process in Canada.

There are currently no provisions in Canadian legislation to make compassionate and expanded access mandatory and there are currently no public plans to change the legislation. Given the current reality, CTAC takes the position that pharmaceutical companies should be encouraged to continue to voluntarily commit to providing reasonable compassionate and expanded access to all drugs they have in development, and to commit to meaningful engagement with all stakeholders. In return for providing early access, there could be incentives for pharmaceutical companies. Such incentives could include: expedited review/fast-tracking of the NDS, tax breaks or other incentives.

CTAC takes the position that compassionate and expanded access programs must be patient-centered and firmly holds an individual’s ‘right to choose’ as absolute and irrefutable.

An increase in the contribution of the government of Canada to research is essential. Research on
the impacts of early access to drugs in development is required. The Food and Drugs Act Regulations must be amended to prohibit the sale of any drugs prior to approval by the Therapeutic Products Directorate of Health Canada - this would include drugs provided through SAP, clinical trials and compassionate and expanded access.

**CTAC takes the position that Health Canada’s Special Access Program (SAP), as it currently operates, does not adequately meet the needs of catastrophically ill Canadians and requires changes/improvements. CTAC recommends that Health Canada be mandated to collect safety data on drugs administered through SAP.**

The development of guidelines to ensure that 1) proposed early access to drugs in development is reasonable and 2) early access programs are administered in manner that provides the greatest benefit to the most seriously ill people must be led by Health Canada.

The U.S. Parallel Track system needs to be further explored with a view to establishing a similar system for early drug access in Canada. **CTAC supports the concept of greater autonomy for doctors, as is the case in New Zealand.**

Improvements to both the federal drug review and Common Drug Review (CDR) processes are required to ensure that new drugs are available to the greatest number of people in the shortest period of time. Greater cooperation with regulatory agencies in other countries would help to expedite drug reviews. Health Canada’s Special Access Program (SAP), as it currently operates, is not responsive to the needs of critically ill Canadians and changes to policies and/or procedures are required.

**CTAC holds firmly the positions that:**

- compassionate and expanded access to drugs in development is crucial for the survival of many people living with HIV/AIDS,
- compassionate and expanded access programs can be administered in a way that does not interfere with ongoing research or the drug review and approval process, and
- all other challenges to successful implementation of compassionate/expanded access programs can be resolved.
APPENDICES
Appendix 1

About the Canadian Treatment Action Council (CTAC)

CTAC is a national, not-for-profit organization serving the needs of people living with HIV/AIDS. CTAC is federally incorporated and operates in both official languages. CTAC promotes informed public policy, public education, and awareness on issues that impact on access to treatment and health care for people living with HIV/AIDS. CTAC works with governments, the pharmaceutical industry and other stakeholders to ensure research and development of safe and effective HIV/AIDS treatments and timely, equitable and affordable access to all HIV treatments. Treatment is a broad concept, which includes traditional as well as complementary and alternative medicine.

A) Organization and Governance

A nine-member Board of Directors manages the affairs of CTAC. The Directors are elected by the membership. The officers of the corporation (Chair, Vice-Chair, Secretary and Treasurer) make up the Board's Executive Committee. CTAC’s structure also provides for a Council which (1) acts as an advisory body to the Board and 2) whose members participate in CTAC committees, events and initiatives. The Council provides for representation from the provinces and territories, N-G-Os and large PWA-driven HIV/AIDS organizations in Canada as well as specific populations including women, Aboriginals, youth, illicit drug users and Black Canadians.

B) CTAC Advocacy History with Compassionate Access & Expanded Access Programs

CTAC was formed in 1997 for 2 reasons: 1) to address the many and complex treatment access issues that arose as a result of the introduction of new treatments, some in a new treatment class, and 2) to serve as a liaison between community and the various pharmaceutical companies who were developing these new treatments. Many of the treatment access issues addressed by CTAC have been issues that are non disease-specific. CTAC has worked with relevant stakeholders, including industry, governments, and health care providers, towards the establishment of compassionate and expanded access programs for many HIV/AIDS treatments which have since received approval for marketing. CTAC has also worked on a case-by-case basis with drug companies and government regulators to ensure that such programs were designed with the interest of consumers, particularly the catastrophically ill, as the primary focus.
Appendix 2

Guiding Principles

1. All clinical trials in Canada must provide for reasonable compassionate and expanded access.

2. Compassionate access programs must be first available to the catastrophically ill and then to those in the next greatest need. Expanded access should also be available to the most seriously ill first.

3. Catastrophic Illness is defined as a serious or life-threatening condition, for which no effective/tolerable treatments are currently available, and for which the prognosis is death or considerable deterioration of health in the next twenty-four months.

4. Expanded access programs should be delivered as a separate open arm of a clinical trial.

5. Ethics review is required by a central national body. In the case of compassionate/expanded access for HIV/AIDS drugs, ethics review should be conducted by the National Ethics Review Committee of the Canadian HIV Trials Network.

6. Informed consent must be given only after full disclosure by all parties involved in the delivery of the experimental drug including the patient, the health care provider, the regulator and the drug sponsor.

7. Community must be involved in the development and implementation of all compassionate/expanded access programs in Canada.

8. Compassionate and expanded access programs should be implemented in Canada and the U.S. simultaneously.

9. Compassionate and expanded access is primarily treatment and secondarily research.

10. Geography should not be a barrier to early access to drugs in development.

11. Drugs supplied through early access mechanisms including the Special Access Program and compassionate and expanded access programs, should be provided by the sponsor at no cost to the patient or the health care provider.

12. All people receiving drugs through compassionate and expanded access programs must continue to receive drugs until they are available on provincial/territorial formularies and private insurance plans.
13. It is imperative that compassionate access programs be large enough to accommodate all those patients who need the drug to stay alive and expanded access programs be large enough to accommodate all those patients who need the drug to create a viable regimen.
Appendix 3

Roles/Responsibilities of Stakeholders

This section lists CTAC’s positions on the main roles/responsibilities of the various stakeholders involved in the development/delivery of compassionate and expanded access programs.

A) Pharmaceutical Industry

- Provide Funding for research
- Conduct research
- Provide information before, during and after trials about experimental drugs to all stakeholders
- Ensure that compassionate and expanded access protocols are designed to minimize administrative requirements for physicians which can be a barrier to access for participants
- Provide early access to drugs through compassionate and expanded access programs and/or other early access mechanisms
- Continue to provide experimental drugs at no cost for all early access to drugs in development
- Ensure that the needs of the catastrophically ill are taken into consideration when determining the size of compassionate and expanded access programs
- Assist community in providing education aimed at reducing unnecessary or inappropriate access to drugs in development
- Ensure that all trials have an expanded access arm and a compassionate access program

B) Federal Government

- Ensure adequate and appropriate legislation, regulations and policies on all aspects of drug development and approval
- Ensure appropriate post approval surveillance of all drugs
- Approval of clinical trial protocols, including compassionate and expanded access programs
- Ensure that catastrophically ill people have the means by which to access drugs in development. This would include individual access through a re-vamped SAP or other mechanism for early access, and multiple-person access through compassionate/expanded access
- Establish, in consultation with stakeholders, guidelines for early access to drugs including guidelines that establish what would constitute reasonable compassionate and expanded access
- Establish guidelines to ensure appropriate mechanism to deal with the costs associated with early access to drugs in development
- Fund research
• Responsible for improvements to the drug review processes at both the TPD and
  Common Drug Review (CDR) to provide earlier access through commercial means for
  everyone, thus reducing the demand for compassionate/expanded access
• Act as liaison between physicians and pharmaceutical companies for drug access through
  the Special Access Program
• Responsible for initiating multi-stakeholder consultations on the best way(s) to
  implement compassionate and expanded access programs and other early access
  processes
• Ensure Federal Government reimbursement plans are consistent and effective
• Set up a National Ethics Review Committee
• Cost of administration of compassionate and expanded access programs for physicians
  and Health Canada should be cost-shared by the provincial/territorial and federal
  governments
• Implement Health Canada’s proposed Progressive Licensing Framework - a life cycle
  approach to drug management

C) Provincial/Territorial Governments

• Determine which drugs will be covered under provincial/territorial drug plans (CTAC has
  advocated for continued coverage under compassionate/expanded access programs until
  drugs are covered by provincial/territorial drug plans). When compassionate and
  expanded access programs terminate, the financial burden for drug access transfers to the
  provinces/territories and/or private insurance. Provinces and territories must ensure
  timely review processing and uninterrupted drug access
• Ensure availability of appropriate and timely access to diagnostic tests, blood work and
  follow-up visits with physicians
• Cost of administration of compassionate and expanded access programs for physicians
  and Health Canada should be cost-shared by the provincial/territorial and federal
  governments
• Ensure that provincial/territorial review processes are completed as expeditiously as
  possible in order to make new drugs available to the most people in the shortest time
• Ensure appropriate post approval surveillance of all drugs
• Dismantle Common Drug Review (CDR) or overhaul it to be effective and efficient

D) Health Care Providers

  i) Researchers

• In collaboration with relevant stakeholders including HN and community, conduct good
  quality research
• Ensure that clinical trials adhere to the highest ethical standards emphasizing respect for
  the rights of the participant, including the right to provide informed consent, even under
  less than optimal conditions
• Advocate with sponsors of clinical trials for compassionate and expanded access
  programs
• Administer compassionate and expanded access programs
• Advocate for post approval surveillance of drugs to ensure ongoing monitoring

ii) Canadian HIV Trials Network

• Continue to conduct and coordinate a wide variety of clinical trials on HIV/AIDS and related treatments
• Continue to provide national ethics review for compassionate and expanded access programs for HIV/AIDS treatments through the National Ethics Review Committee (NERC)
• Expand role of CTN to ensure linkages throughout Canada that will enable the most seriously ill to access experimental HIV/AIDS drugs through compassionate and expanded access programs regardless of where they live in Canada

iii) Clinicians

• Ensure that patients have all available information
• Monitor patients progress (in cooperation with researcher in cases where the researcher and the clinician are not the same person)
• Ensure appropriate medical interventions, when necessary, including genotyping and medical history review
• Ensure that patients are not exposed to sequential monotherapy and that every effort is made to secure at least two new active drugs for patients who are failing their current regimen
• Report adverse events consistently

iv) Professional Associations, e.g., Canadian Medical Association (CMA), Canadian Association for HIV Research (CAHR), Universities.

• Education of respective memberships on importance compassionate and expanded access
• Help to bridge the gap between physicians who have considerable experience accessing drugs in development and physicians who operate in rural areas and/or physicians who are not knowledgeable about early access to drugs in development
• Support the conduct of ongoing, sound scientific research
• Work with patients and other relevant stakeholders to ensure that governments and industry meet their responsibilities

v) Health Care Institutions - e.g., hospitals, clinics, others

• Ensure that research conducted meets highest standards
• Ensure HIV/AIDS-specific ethics review board in each institution
• Ensure that every effort is made to make early access programs available to the respective institution’s patients (this would include arranging, through satellite mechanisms or in other ways, access in cases where a hospital or institution is not selected as a trial site for early access programs)
Ensure that appropriate support is in place for the conduct of clinical trials, including compassionate/expanded access

**vi) Local Research Ethics Boards (REBs)**

- Continue to conduct ethics review of research trials based on thorough knowledge of diseases for which drugs are being reviewed
- Continue to apply the highest ethical standards to the conduct of research trials
- Support and inform a national process for ethics review for treatment undertakings such as compassionate and expanded access programs
- Ensure disease-specific patient/community representation on local REBs
- Ensure that REBs are multi-stakeholder in composition including patients with diseases for which drugs are being reviewed, ethicists and researchers

**E) Patient/Consumer Groups**

- Provide education to consumers on the proper usage of compassionate and expanded access programs - compassionate/expanded access is not a suitable option for everyone, and for some their health could be further jeopardized
- Ensure adequate and appropriate expertise is provided to industry and/or Health Canada through participation in advisory committees or other advisory capacities, where such participation opportunities exist
- Initiate/maintain dialogue with pharmaceutical companies regarding the progress of drugs in development
- Inform public policy at all levels of government regarding clinical trials including compassionate and expanded access programs, drug review processes and post approval surveillance

**F) Patients**

- Educate yourself and get as much information as possible to help you become a better participant in your own health care
- Ensure that they have provided all known details about their medical condition to physicians so that the physician can make the most appropriate treatment recommendation
- Ensure that all issues/questions are satisfactorily resolved before signing free and informed consent
- Participate in follow-up care with a physician to closely monitor the effects of the experimental drug
- Responsibility to avoid activities/behaviours that are known or suspected to cause harm
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