TIMELINESS AND TRANSPARENCY:

Assessing the Review Process for HIV Drugs

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Prepared by

the Canadian AIDS Society,
the Canadian Treatment Action Council,
and the Canadian AIDS Treatment Information Exchange

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This paper was written by David Garmaise, Consultant. It is a revised version of a paper first produced in November 1998.

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Executive Summary

The overall regulatory environment is more responsive and more transparent today than it was in 1998, when the first version of this paper was produced. While these improvements are welcome, there is still a long way to go.

In the last 10-15 years, considerable progress has been made in the treatment of HIV infection as a result of the development of new classes of anti-viral drugs, the development of new drugs in each class, and the use of combination drug therapy. However, many people living with HIV/AIDS who are using combination therapy have experienced problems with resistance, diminished effectiveness and severe side effects. As a result, HIV-positive people need to be able to change the mix of their combination drug therapy. Given the still relatively limited number of anti-viral drugs currently on the market, it is critically important that new anti-viral drugs be developed and be made available in a timely fashion.

A major problem facing people living with HIV/AIDS in Canada is that new HIV anti-viral drugs are being approved in Canada considerably later than in the United States and many other countries. Generally speaking, this is due to two factors: (a) the length of time required by the Canada's Therapeutic Products Directorate to review new drug submissions; and (b) delays in filing a new drug submission in Canada. The analysis done for this paper suggests that the first factor – the time required to review new submissions – is much more significant an issue than the delays in filing.

The analysis also revealed a third critical issue: the lack of transparency surrounding the process of reviewing drug submissions in Canada. Although some progress has been made in this area in recent years, this lack of transparency makes it very difficult to identify and resolve the problems that lead to delays in approval.

To address these and other issues concerning the drug review process, the Canadian AIDS Society, the Canadian Treatment Action Council and the Community AIDS Treatment Information Exchange make the following recommendations:

1. **TPD should increase the resources devoted to the review of human prescription drugs.**

2. **TPD should convert its current review time targets into firm commitments and should establish an enforcement mechanism to ensure that the timelines are met.**

3. **TPD should adopt an open process for drug reviews, such as the one used by FDA.**

4. **TPD should establish a formal mechanism for consumer input into the drug review process.**

5. **TPD should ensure that consumers are represented on the various TPD expert advisory committees.**

6. **TPD should continue its efforts to increase transparency and should seek consumer input on this process. The efforts could include regular bilateral and multilateral meetings with consumer groups and other stakeholders.**

7. **TPD should implement the practice of rolling reviews for all drugs accorded priority review.**

8. **TPD should conduct more joint reviews with other regulatory agencies.**

9. **TPD should make more use of information sharing with other regulatory agencies.**

10. **TPD should obtain approval for changes to its accounting system that will allow it to carry over unspent fees from one fiscal year to the next.**

11. **TPD should investigate innovative solutions more aggressively – i.e., evaluate what countries like Australia and Sweden are doing to speed up the review process.**

12. **HPFB should institute an active consumer-centred post-marketing surveillance system and ensure that it is adequately resourced.**

Introduction

This paper has been prepared by the Canadian AIDS Society (CAS), the Canadian Treatment Action Council (CTAC), and the Community AIDS Treatment Information Exchange (CATIE). The purpose of the paper is to examine, from the perspective of people living with HIV/AIDS and HIV/AIDS community-based organizations, the issues involved in the licensing of therapeutic products used in the treatment of HIV/AIDS.

The paper focuses primarily on new pharmaceutical products that manufacturers are seeking to market in Canada. It does not deal with the licensing of complementary therapies, approval to conduct clinical trials, or approval for new indications for a pharmaceutical product already on the market.

Although this paper deals mainly with HIV anti-viral drugs, the problems identified and the solutions proposed in the paper apply to drugs for all chronic and life-threatening illnesses. CAS, CTAC and CATIE want to work in partnership with other consumer organizations to bring about improvements to the drug regulatory system that will help people in all disease groups.

The next section of this paper provides a brief overview of the drug review process in Canada. This is followed by a discussion of the issues that CAS, CTAC and CATIE have identified with respect to the drug review process. The paper also includes a section on potential solutions; this section contains a series of recommendations. Finally, there is a short concluding section and a bibliography.

Two of the tables in this paper contain explanatory footnotes. Letters of the alphabet have been used to identify these footnotes. References and additional explanations for some of the statements in the text have been included as endnotes; numbers have been used to identify the endnotes.

Methodologies

This is a revised version of a paper first produced in November 1998. The following methodologies were used in the preparation of the 1998 paper:

- review of relevant background documents;
- interviews with officials of Health Canada;
- interviews with representatives of the pharmaceutical industry in Canada; and
- interviews with treatment activists in community-based organizations.

In preparing this revised version, the author consulted with officials in the Health Products and Foods Branch of Health Canada; with representatives of the pharmaceutical industry; and with treatment activists at CTAC. The author also consulted relevant documents and websites.

Terminology

In most cases, the term “drug” is used to refer to a pharmaceutical product.

Pharmaceutical companies are referred to as “manufacturers.”

The term “new drug submission” is used to describe an application for approval to market a new drug. (This is the term commonly used in Canada, but other countries sometimes use a different term.)

The term “licence” is used to describe the official notice issued to allow a manufacturer to market a new drug. (Countries use different terms; in Canada, the licence is officially known as a “notice of compliance.”)

The time required to approve a new drug is expressed in days. (This is common practice in Canada; in the United States, the time is usually expressed in months.) The days are calendar days, not working days.

The term “priority review” is used to describe a process of fast-tracking the review of a new drug submission. (This is the term commonly used in Canada, but other countries use different terms.)

Limitations

The paper focuses primarily on HIV anti-viral drugs because the research and analysis done for the paper revealed that, for people living with HIV, this is where the major problems occur.

For the most part, in discussing the issues around the drug review process, the paper makes comparisons only between Canada and the United States because this is particularly relevant for Canadians living with HIV/AIDS.

The Drug Review Process in Canada

This section provides a brief description of the drug review process in Canada.

Before a new drug can licensed for sale in Canada, the manufacturer must file a New Drug Submission (NDS) with the Health Products and Food Branch (HPFB) of Health Canada. The NDS should demonstrate the safety, efficacy and quality of a product. The HPFB has regulations and guidance on what information is required and what format must be used. Since mid-2003, the Therapeutics Products Directorate (TPD), the unit in HPFB that reviews NDSs for pharmaceutical drugs, has required that NDSs be submitted in the Common Technical Document (CTD) format developed by the International Conference on Harmonization (ICH).

The CTD contains five modules. The modules are described in the following table.

Table I – CTD Modules

Module	Description
Module 1: Administrative Information and Prescribing Information	Module 1 contains administrative information concerning the application; information on the proposed labelling (e.g., product monograph); and some summary information.
Module 2: Common Technical Document Summaries	Module 2 contains summaries of the information found in Modules 3, 4 and 5; and provides a Table of Contents for the information in these modules.
Module 3: Quality	Module 3 contains information on the quality of the drug being submitted.
Module 4: Nonclinical Study Reports	Module 4 provides information on the non-clinical studies that have been conducted on this drug.
Module 5: Clinical Study Reports	Module 5 provides information on the clinical studies that have been conducted on this drug.

Submission Costs

HPFB levies fees to evaluate the documentation submitted by a manufacturer. For new HIV anti-viral drugs, the evaluation fees are in the range of $100,000 to $250,000, depending on the number of indications and dosage forms. According to the TPD, the current user fee structure, which was established in 1995, is outdated and does not address all of the relevant costs associated with the evaluation of a submission.

Submission Time Frames

The TPD has established a target (called a “performance standard”) of 45 calendar days to screen an NDS and 300 calendar days to review it. If deficiencies are found in the submission, the manufacturer is requested to respond to the deficiencies; this can extend the screening and review time frames. Table II illustrates the TPD targets in more detail.

Priority Review

Since 1992, the TPD has had a policy of Priority Review which covers some drugs intended for the treatment of a serious, life -threatening or severely debilitating disease or condition. Submissions granted Priority Review status are subject to the same quality, safety and efficacy requirements as non-priority submissions, but they have shorter review times.

The Priority Review policy was amended several times, the latest being in 2005.[1] The current policy applies to:

> a New Drug Submission (NDS) or Supplemental New Drug Submission (S/NDS) for a serious, life-threatening or severely debilitating illness or condition for which there is substantial evidence of clinical effectiveness that the drug provides:
>
> > effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada; or
> >
> > a significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada.

The Priority Review policy states that the targets time frames for submissions granted Priority Review status are 25 calendar days for submission screening; and 180 calendar days for submission review. If deficiencies are found in the submission, the manufacturer is requested to respond to the deficiencies; this can extend the screening and review time frames. Table II illustrates the TPD targets in more detail.

Table II – TPD Submission Time Frames[a]

Activity	Regular Submissions	Priority Submissions
SCREENING	45 days	25 days
REVIEW	300 days	180 days
Total (if no deficiencies)	**345 days**	**205 days**
IF DEFICIENCIES, ADD:		
Time for sponsor to respond to notice[b]	up to 90 days[c]	up to 90 days[c]
Additional screening	45 days	25 days
Additional review	150 days	90 days
Total	**up to 630 days**	**up to 410 days**

Notes:

[a] All days shown in this table are calendar days (not working days). Also, these times include the time required for labelling review (which involves a final review of the product monograph and package/label information by a separate group within TPD).

[b] TPD may issue either a notice of deficiency (NOD) or a notice of non-compliance (NON). The NOD would be issued during the review process, while the NON would be issued at the end of the review process. TPD may also issue a request for clarification (called a "clarifax") at any time during the review. Sponsors have 15 days to respond to a clarifax. However, theoretically, the time involved in responding to a clarifax does not extend the times shown in the table above.

[c] Sponsors may respond more quickly than 90 days. In a survey conducted in 1996, R and D Canada (then the Pharmaceutical Manufacturing Association of Canada) found that the average time for sponsors to respond was 72 days for regular submissions and between zero and three days for priority submissions.

Conditional Licence

When authorizing the sale of a new drug in Canada, TPD may issue a Notice of Compliance with Conditions (NOC/c). Products approved under the NOC/c policy have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment – but Health Canada believes that additional studies are required to verify the clinical benefit of the drug.

Discussion of the Issues

This section examines two critical issues: (a) the timeliness of the drug review process; and (b) the transparency of the process.

Timeliness

The concerns about the timeliness of drug reviews for HIV/AIDS anti-viral drugs fall into two categories: (a) the length of time required to review new drug submissions; and (b) delays in filing the submissions.

Table III (see the next page) shows the filing dates and approval dates for all HIV anti-viral drugs approved by both TPD and the Federal Drug Administration (FDA) in the United States between 1995 and the present. The table also shows how many days were required for approval.

Table III – TPD and FDA Filing Dates, Approval Dates and Priority Status for Individual Anti-Viral Drugs Approved Since 1995[2]

Drug	Manufacturer	Regu-lator	Priority Status	Date of Filing of NDS	Date of Approval to Market	Time Required for Approval
Zerit (stavudine or d4T)	Bristol-Myers Squibb	TPD	NO	93-12-01	96-03-26	845 days
		FDA	YES	93-11-14	94-05-14	181 days
Epivir (lamuvidine or 3TC)	Shire	TPD	YES	95-07-17	95-12-08	144 days
		FDA	YES	95-06-29	95-11-20	144 days
Invirase (saquinavir)	Roche	TPD	YES	95-09-19	96-03-22	185 days
		FDA	YES	95-08-13	95-12-06	115 days
Norvir (ritonavir)	Abbott	TPD	YES	96-02-06	96-08-14	189 days
		FDA	YES	95-12-21	96-03-01	71 days
Crixivan (indinavir)	Merck Frosst	TPD	YES	96-02-03	96-09-13	222 days
		FDA	YES	96-01-31	96-03-13	42 days
Viramune (nevirapine)	Boehringer Ingleheim	TPD	NO[a]	96-06-12	98-10-04	809 days
		FDA	YES	96-02-23	96-06-21	119 days
Rescriptor (delavirdine)	Pharmacia & Upjohn	TPD	NO	96-12-13	98-07-22	586 days
		FDA	YES	96-07-15	97-04-04	263 days
Viracept (nelfinavir)	Agouron	TPD	NO	97-03-15[b]	98-08-11	514 days
		FDA	YES	96-12-26	97-03-14	78 days
Fortovase (saquinavir)[c]	Roche	TPD	NO	97-05-09	98-11-23	563 days
		FDA	YES	97-05-09	97-11-07	182 days
Combivir[d] (zidovudine and lamuvidine)	GlaxoSmithKline	TPD	NO	97-08-08	98-12-03	482 days
		FDA	YES	97-06-01	97-09-26	117 days
Ziagen (abacavir)	GlaxoSmithKline	TPD	YES	98-06-24	99-06-04	345 days
		FDA	YES	98-06-24	98-12-17	176 days
Sustiva (efavirenz)	DuPont Pharma	TPD	YES	98-06-30[b]	99-03-19	262 days
		FDA	YES	98-05-29[b]	98-09-17	111 days

(Table III continues on the next page.)

Table III (cont'd)

Drug	Manufacturer	Regu-lator	Priority Status	Date of Filing of NDS	Date of Approval to Market	Time Required for Approval
Agenerase[e] (amprenavir)	GlaxoSmithKline	TPD	YES	98-10-14	01-03-02	869 days
		FDA	YES	98-10-05	99-04-15	192 days
Trizivir (AZT, 3TC, abacavir)	GlaxoSmithKline	TPD	NO	99-12-15	01-10-17	672 days
		FDA	YES	99-12-16	00-11-14	334 days
Videx EC (didanosine or ddI) (enteric coated)	Bristol-Myers Squibb	TPD	NO	00-04-15[b]	01-10-15	555 days
		FDA	YES	00-01-15[b]	00-10-31	290 days
Kaletra (lopinavir + ritonavir)	Abbott	TPD	YES	00-06-29	01-03-09	253 days
		FDA	YES	00-06-15[b]	00-09-15	92 days
Viread (tenofovir)	Gilead Sciences	TPD	YES	02-02-15[b]	03-03-18	408 days
		FDA	YES	01-05-15[b]	01-10-26	164 days
Fuzeon (enfuvirtide or T-20)	Roche	TPD	YES	02-09-26	03-07-14	329 days
		FDA	YES	02-09-17	03-03-13	176 days
Reyataz) (atazanavir)	Bristol-Myers Squibb	TPD	YES	03-03-15[b]	03-12-05	270 days
		FDA	YES	02-12-20	03-06-20	182 days
Lexiva (fosamprenavir)	GlaxoSmithKline	TPD	NO	03-05-21	04-12-10	569 days
		FDA	NO	02-12-20	03-10-20	304 days
Emtriva (emtricitabine or FTC)	Gilead Sciences	TPD	NO	04-09-17	05-11-21	431 days
		FDA	NO	02-09-03	03-07-02	302 days
Truvada (emtricitabine + tenofovir)	Gilead Sciences	TPD	NO	04-12-17	06-01-06	387 days
		FDA	NO	04-03-11	04-08-02	144 days

[a] Viramune was initially accorded priority status, but the status was later revoked.
[b] The day of the month is approximate.
[c] Same ingredients as Invirase, but in a different form which is more bio-available.
[d] Combivir is a combination of zidovudine and lamuvidine, which is easier for patients to take than the two drugs separately.
[e] This drug was in review for the second time.

Length of Time Required by TPD to Review New Drug Submissions

Although the situation has improved a little in recent years, at least with respect to HIV drugs,[3] TPD still takes considerably more time to review new drug submissions than many other countries, particularly the United States.

With respect to HIV anti-viral drugs, an analysis of the information in Table III reveals that the average time required for approval is considerably longer at TPD than it is at FDA. The average approval times for HIV antiviral drugs approved by both TPD and FDA since 1995 were 450 days at TPD and 172 days at FDA. Thus, for drugs approved during this period, TPD took significantly more than twice as long as FDA to process the submissions. Table IV shows the average approval times for TPD and FDA for each two-year period between 1995 and 2006.

Table IV – TPD and FDA Average Approval Times for Antiviral Drugs Broken Out by Two-Year Periods

Calendar Years When Drugs Approved by TPD	TPD (no. of days)	FDA (no. of days)
1995-1996	317	111
1997-1998	591	152
1999-2000	304	144
2001-2002	587	227
2003-2004	394	207
2005-2006	409	223
Average over the full 12 years	450	172

It is worth noting that the performance of TPD improved somewhat in the 2003-2004 and 2005-2006 periods as compared to the 2001-2002 period.

As noted earlier, TPD has established time targets for the review of new drug submissions. These targets are not enforceable in any way. (The FDA has review timelines which are similar to those of TPD.[4] However, while the TPD time frames are targets, the FDA time frames are firm commitments made to the US Congress in exchange for the right to implement a user fee system.)

Factors Contributing to the Delays at TPD

What factors contribute to the delays in approving new drug submissions at TPD? Several possible explanations were advanced by the representatives of the pharmaceutical industry and community-based organizations interviewed during the course of the research for this paper:

- There are insufficient resources at TPD devoted to the review of new drug submissions. TPD has approximately 550 person years. The equivalent unit at FDA had approximately 1,800 employees at the end of 2004[5] (a ratio of less than one to three). One person year is equal to one position funded for one full year.
- There is a lack of experienced reviewers. Many of the more experienced reviewers have moved on to other positions at HPFB, resulting in a loss of knowledge of the products and files in TPD. This requires additional training for newer staff, which is difficult to do

with limited resources.

- Unlike the FDA, TPD does not permit rolling reviews. A rolling review means that the manufacturer can submit partial data in advance of the formal filing date of a new drug submission. Usually, this data is submitted as it becomes available. The reviewing agency is thus able to get a head start on the review.
- TPD does not do many joint reviews with other regulatory agencies. Several of the people interviewed for this paper suggested that TPD has not been able to negotiate more joint reviews because other regulatory agencies find that working with TPD slows them down.

Delays in Filing a New Drug Submission in Canada

From the information in Table III, it is possible to compare when submissions for new HIV anti-viral drugs were filed at FDA and TPD. Table VI presents a summary of the relevant information.

Table VI – Filing Dates for HIV Anti-Viral Drugs: Comparison between FDA and TPD

Drug	Date Filed at FDA	Date Filed at TPD	Gap
Zerit (stavudine or d4T)	93-11-14	93-12-01	17 days
Epivir (lamuvidine or 3TC)	95-06-29	95-06-29	0 days
Invirase (saquinavir)	95-08-13	95-09-19	37 days
Norvir (ritonavir	95-12-21	96-02-06	47 days
Crixivan (indinavir)	96-01-31	96-02-23	23 days
Viramune (nevirapine)	96-02-23	96-06-12	110 days
Rescriptor (delavirdine)	96-07-15	96-12-13	151 days
Viracept (nelfinavir)	96-12-26	97-03-15	79 days
Fortovase (saquinavir)	97-05-09	97-05-09	0 days
Combivir (zidovudine and lamuvidine)	97-06-01	97-08-08	68 days
Ziagen (abacavir)	98-06-24	98-06-24	0 days
Sustiva (efavirenz)	98-05-29	98-06-30	32 days
Agenerase (amprenavir)	98-10-05	98-10-14	9 days
Trizivir (AZT, 3TC, abacavir)	99-12-16	99-12-15	0 days
Videx EC (didanosine or ddI) (enteric coated)	00-01-15	00-04-15	91 days
Kaletra (lopinavir + ritonavir)	00-06-15	00-06-29	14 days
Viread (tenofovir)	01-05-15	02-02-15	396 days
Fuzeon (enfuvirtide or T-20)	02-09-17	02-09-26	9 days
Reyataz) (atazanavir)	02-12-20	03-03-15	85 days
Lexiva (fosamprenavir)	02-12-20	03-05-21	152 days
Emtriva (emtricitabine or FTC)	02-09-03	04-09-17	744 days
Truvada (emtricitabine + tenofovir)	04-03-11	04-12-17	281 days

The delay in filing at TPD ranged from 0 to 744 days, with the average being 107 days.

One of the reasons for the delays in filing at TPD may be the fact that Canada is a small market compared to the US and the manufacturers, therefore, do not move as quickly as they might to file in Canada. In recent years, a more likely explanation for the delays can be traced to the cross-border issues created by US residents importing drugs from Canada. In many cases, the drug manufacturers wait for the price of the new drug to be set in the US before filing an NDS is Canada.

Conditional Licences

On May 28, 1998, TPD issued a new policy on conditional licences. The policy has been updated several times, most recently in 2005.[6] The purpose of the policy is to:

a. Provide patients suffering from serious, life-threatening or severely debilitating diseases or conditions with earlier access to promising new drugs.

b. Create a mechanism to ensure that a manufacturer that has a drug approved under this policy conducts confirmatory studies to verify the clinical benefit of the drug and further establish the safety profile.

The policy says that

> [a]pproval under the NOC/c policy may be granted for a drug product with promising clinical benefit, providing it possesses an acceptable safety profile based on a benefit/risk assessment, and is found to be of high quality.

The policy defines "promising clinical [benefit]" as

> evidence based on well-controlled and well-conducted clinical trials establishing that the drug product has an effect on a surrogate or clinical endpoint that is reasonably likely to predict clinical benefit.

The policy also says that before the issuance of a conditional licence the sponsor must undertake in writing to design and carry out confirmatory studies to verify the clinical benefit of the drug.

The FDA has a similar policy as part of its system of priority review.[7]

The TPD's NOC/c policy appears to be designed to allow manufacturers to file a drug submission earlier than they could if this policy were not in effect. It seems to suggest that TPD will be able to issue a conditional licence based on a submission which contains only surrogate marker data (as long as confirmatory studies conducted after the issuance of a conditional licence provide positive clinical endpoint data), whereas surrogate marker data alone is not sufficient to obtain a regular licence.

It is not clear exactly how this new policy will help bring HIV anti-viral drugs to market faster. For one thing, the policy claims that manufacturers will be able to file their submissions earlier. Yet, as the analysis in this paper has shown, delays in filing are an insignificant problem when compared to the length of time it takes HPB to conduct its reviews.

Rescriptor was the first HIV anti-viral drug to be accorded a conditional licence under this new policy. However, it should be noted that the policy was not in place until some time after the submission for approval of Rescriptor was filed.

Since the start of 1999, 14 drugs have received conditional licences, only one of which was an HIV drug (Viread). At the time of writing, the conditions were successfully met for two of the 14 drugs, Viread and Activase. Viread received its NOC/c on 18 March 2003; the conditions were met 16 months later on 20 July 2005. With respect to Activase, the NOC/c was granted on 16 February 1999; the conditions were not met until 26 January 2005, almost six years later.

Of the other 12 drugs that received an NOC/c, one was subsequently suspended. According to Health Canada's website, the conditions have not yet been met for the remaining 11 drugs.[8] The earliest of the 11 drugs was awarded an NOC/c in February 1999 and the latest in December 2005. Although none of these were HIV drugs, this information is included here because the conditional licences could in future play an important role in the review and approval of new HIV drugs. In preparing this paper, no attempt has been made to analyze the conditions that have been imposed or to assess why it sometimes takes many years for the conditions to be met.

Transparency

Historically, it has been very difficult to get at the root of the problems with the drug approvals process because of the lack of transparency at TPD.

TPD has said that all information related to a review of a new drug submission is confidential and that this is to protect the privacy rights of the manufacturer. For this reason, TPD has been reluctant to discuss the details of a particular new drug submission with any third party. This has frustrating for representatives of community-based organizations. Even the representatives of the pharmaceutical industry have complained about TPD's lack of transparency when it comes to getting information about the status of their own submissions.

In contrast, FDA conducts public hearings of all new drug submissions where the public is not only granted an opportunity for input, but where the review, deliberation and assessment of the drug (including comments of individual panel members) become a matter of public record. Most of the data reviewed in these public hearings is already in the public domain. Where unpublished data is embargoed, summaries of that data are reviewed instead.[9]

In the last few years, there has been some improvement at TPD with respect to transparency. For example:

- TPD has held public meetings during the review of two non-HIV drugs or devices (COX-II inhibitors and breast implants);
- TPD has posted online summaries of the basis of its decisions on new drug approvals;
- consumers are one of the stakeholder groups represented on the Advisory Committee on Management, a forum for obtaining advice on management issues relevant to TPD;

- TPD conducted a series of stakeholder workshops in June 2005 on the registration and disclosure of clinical trial information; and
- TPD has announced plans to launch a new online database that will provide more information on all drugs licensed in Canada since 1994.

However, consumer organizations still find it difficult to obtain information on where NDSs are at in the review process. As well, there are many advisory committees at TPD still lacking consumer representation.

Potential Solutions and Recommendations

This section discusses potential solutions to the issues identified in the previous section, and presents a series of recommendations.

RESOURCES DEVOTED TO THE REVIEW OF HUMAN PRESCRIPTION DRUGS

TPD has less than a third of the resources of FDA, yet the workload of the agencies is roughly comparable. An increase in resources at TPD should lead to faster reviews, providing the additional personnel are qualified to do the work required.

Recommendation 1: TPD should increase the resources devoted to the review of human prescription drugs.

REVIEW TARGETS

TPD has established time targets for the review of regular and priority new drug submissions, but the targets appear to be seldom met. The FDA and other regulatory agencies have converted these target into firm commitments.

Recommendation 2: TPD should convert its current review time targets into firm commitments and should establish an enforcement mechanism to ensure that the timelines are met.

TRANSPARENCY

More transparency at TPD would help people better understand the problems with the drug review process and would lead to greater accountability.

TPD should sit down with the consumer organizations and engage in an open and frank dialogue on the reasons for the delays in approving new HIV anti-viral drugs in Canada. This dialogue should extend to exploring ways to resolve the problems. One possibility is a consensus conference involving government officials, manufacturers and consumer organizations. However, such a conference should proceed only if there is a clear statement of will on the part of Health Canada to address the issues and only if there is adequate advance preparation (probably through the formation of a working group or task force).

It would also be helpful if TPD were to establish a mechanism for ongoing consumer input into the drug review process.

TPD should organize more bilateral and multilateral meetings with consumer organizations and other stakeholders.

While having consumer representation on TPD's Advisory Committee on management is a

positive development, consumers should also be represented on other expert advisory committees at TPD.

Recommendation 3: TPD should adopt an open process for drug reviews, such as the one used by FDA.

Recommendation 4: TPD should establish a formal mechanism for consumer input into the drug review process.

Recommendation 5: TPD should ensure that consumers are represented on the various TPD expert advisory committees.

Recommendation 6: TPD should continue its efforts to increase transparency and should seek consumer input on this process. The efforts could include regular bilateral and multilateral meetings with consumer groups and other stakeholders.

ROLLING REVIEWS

Rolling reviews have been shown to cut down the time it takes to get a drug to market in the United States. Logically, such a policy would be beneficial in Canada as well. It is possible that TPD's failure to adopt a policy of rolling review is tied to the issue of the insufficiency of resources at TPD.

Recommendation 7: TPD should implement the practice of rolling reviews for all drugs accorded priority review.

JOINT REVIEWS WITH OTHER REGULATORY AGENCIES

A joint review is where two regulatory agencies review a submission together, dividing up the work between them. TPD and FDA have conducted some joint reviews in the past. The HIV anti-viral drug ddI was reviewed jointly and was approved in both countries in 1991 within a day of each other. The HIV drug Mepron was also reviewed jointly. More joint reviews ought to speed up the process at TPD. It is possible, however, that other drug regulatory agencies will not consider joint reviews until TPD streamlines its bureaucracy and/or augments its resources.

Recommendation 8: TPD should conduct more joint reviews with other regulatory agencies.

SHARING INFORMATION WITH OTHER REGULATORY AGENCIES

There is evidence that TPD already shares some information (such as evaluation reports of a subset of the data included in the new drug submission) with other regulatory agencies during the course of reviewing a new drug submission. More information sharing would be beneficial. Foreign reviews could be used to identify specific issues raised by other review agencies and the responses provided by the manufacturers.

Recommendation 9: TPD should make more use of information sharing with other regulatory agencies.

ACCOUNTING PROCEDURES

Currently, any unspent fees received in one fiscal year cannot be carried over into the next fiscal year. A change in the accounting procedures to permit such carryover would increase the resources at TPD's disposal.

Recommendation 10: TPD should obtain approval for changes to its accounting system that will allow it to carry over unspent fees from one fiscal year to the next.

OTHER INNOVATIVE SOLUTIONS

If TPD really wants to improve its review times, it should examine what other countries are doing. Two examples:

- The regulatory agency in Australia, the Therapeutics Goods Administration (TGA), has compiled a list of seven large industrial countries; if a drug which has been submitted to TGA has already been approved by any two countries on this list, TGA reduces its target review time for that drug by 50 per cent.[10]
- The regulatory agency in Sweden is smaller than TPD and yet it approves new drugs in about half the time that TPD takes.[11]

Recommendation 11: TPD should investigate innovative solutions more aggressively – i.e., evaluate what countries like Australia and Sweden are doing to speed up the review process.

POST-APPROVAL SURVEILLANCE

A more efficient and effective system for the approval of new drugs should be accompanied by appropriate requirements for post-marketing studies and surveillance. The components of active, consumer-centred post-marketing surveillance system should include:

- the ongoing, systematic collection, analysis and interpretation of adverse effects, toxicity, drug interactions and the long-term effectiveness of HIV drugs following market approval;
- the use of this data for decisions about a drug's safety and clinical indications;
- timely dissemination of the data to all stakeholders;
- prescribed reporting systems; and
- the involvement of the community, persons living with HIV, researchers, the pharmaceutical industry, health care providers and TPD in all of the above components.

One of the ways to contribute to effective post-marketing surveillance would be to pro-actively monitor individuals who are taking the new drugs (instead of relying on the current, passive practice of filing adverse reaction reports). This would require an investment of resources.

The decision in 2005 to increase the number of regional centres receiving adverse drug reaction reports from five to seven is a step in the right direction, but much more needs to be done.

> **Recommendation 12: HPFB should institute an active consumer-centred post-marketing surveillance system and ensure that it is adequately resourced.**

Conclusion

The analysis in this paper has established quite clearly that there is a major problem with respect to the length of time required by TPD to review submissions for new HIV anti-viral drugs. There is also a problem, though it is much less significant, with respect to the delays in filing new drug submissions in Canada. It seems clear that the cause of both of these problems lies with TPD and not with the manufacturers of the drugs.

This paper has also described the need for Health Canada to take additional measures to improve the transparency of the drug approval system.

Advocacy on these issues should therefore focus on Health Canada (including TPD and the office of the Minister of Health) and other appropriate government departments and agencies (including the Department of Finance). CAS, CTAC and CATIE are prepared to sit down with Health Canada to explore potential solutions.

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The following is a list of publications and documents consulted during the preparation of this paper.

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ENDNOTES

See bibliography for complete references to the documents cited and for website addresses where copies of the documents can be obtained.

[1] Health Canada. *Priority Review of Drug Submissions.*

[2] This information was obtained from the website of the FDA and from discussions with representatives of pharmaceutical companies.

[3] For all drugs, Health Canada says that the review backlog of pharmaceutical submissions has been reduced by 89 percent between April 2003 and March 2005; and that 25 percent of regulatory decisions were made within time targets in 2004, up from 13 percent in 2003. Source: Health Canada. *Regulatory Review of Pharmaceuticals, Biologics and Medical Devices.* Note, however, that R and D Canada says that in 2004, TPD approved a total of 17 NDSs sponsored by member companies in an average of 918 days versus 639 days in 2003; and that this average figure constitutes an increase of 44 percent. However, R and D Canada adds: "In reviewing the information, there is no reason to believe that – at this point in time – this increase is a trend. In fact, data from previous years demonstrate that there was a good trend of decreases in average approval times." Source: R and D Canada. *NOC Survey – 2004.*

[4] The FDA timelines for regular submissions are two months for screening and 12 months for first action. "First action" can mean one of three things: (a)an approval letter indicating the drug is approved for sale; (b) an approvable letter indicating the scientific information is satisfactory, but that labelling still has to be negotiated. The gap between an approvable letter and an approval letter can be as high as 180 days; and (c) a notice concerning deficiencies. It is not clear whether the two months for screening is part of the 12 months for first action, or in addition to the 12 months for first action. For priority submissions, the timelines are 1.5 months for screening and six months for first action. Again, it is not clear whether the 1.5 months for screening is part of the six months for first action, or in addition to the six months for first action.

[5] Food and Drug Administration (FDA). *CDER 2004 Report to the Nation: Improving Public Health Through Human Drugs.*

[6] Health Canada. Notice of Compliance with Conditions (NOC/c).

[7] Federal Drug Administration (FDA), U.S. Department of Health and Human Services, *Food and Drug Modernization Act of 1997*. The FDA policy on priority review is part of the Act. A copy of the Act can be found on the FDA website at www.fda.gov/cder/guidance/s830.enr.pdf .

[8] See http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index_e.html.

[9] This information was obtained from interviews with several representatives of the pharmaceutical industry.

[10] This information was obtained from an interview with one of the representatives of the pharmaceutical industry.

[11] Ibid.