Introduction

Thank you for the opportunity to comment on the proposed Provisional Approval pathway for prescription medicines that is being developed by the Therapeutic Goods Administration (TGA). To quote from the consultation paper, “The objective of the Provisional Approval pathway is to allow certain promising new medicines to reach patients with unmet clinical needs earlier than might otherwise be the case, while ensuring appropriate measures are in place to manage the risks inherent in the fact that additional data are still required.”

Before a policy is brought in, there is always uncertainty about whether it will fulfill its intended purpose. One way to help in determining the effects of a policy is to study a similar one that has been used in another jurisdiction. Canada was chosen as a comparator country for the purposes of this brief because the two countries possess a similar level of economic development, medical systems, population size and limited resources for regulatory oversight compared with the United States or the European Union. This brief will draw upon Canada’s experience with similar expedited review policies, specifically its Notice of Compliance with conditions (similar to the proposed provisional approval pathway) and its priority approval pathway. As this brief will demonstrate, Health Canada’s experience with these pathways raises significant concerns about whether the proposals for Australia will meet their objectives and whether the health of the Australian population will be adequately protected.

Specifically, the brief will examine four aspects of expedited approval pathways:

1. Ability to predict therapeutic innovation;
2. Safety of products once they are on the market;
3. Availability of information regarding the progress of products through the Notice of Compliance with conditions pathway;
4. Fulfillment of postmarket conditions required of products approved through the Notice of Compliance with conditions pathway.

Expedited approval pathways in Canada

In an effort to ensure that promising therapies for serious illnesses can reach Canadians in a timely manner Health Canada has developed two other pathways for approving new active substances (NAS, a molecule never marketed before in Canada in any form). The first of these is the priority review of drug submissions intended “for a serious, life-threatening or severely debilitating disease 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” (1). The company seeking approval still has to submit a complete new drug submission but the review period is reduced to 180 days.

The second mechanism is the Notice of Compliance with conditions. The goal of this policy is to “provide patients suffering from serious, life threatening or severely debilitating diseases or conditions with earlier access to promising new drugs” where surrogate markers suggest that these new products offer “effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada or significantly improved efficacy or significantly diminished risk over existing therapies” (2). In the case of cancer,
example, a surrogate outcome might be a shrinkage in tumor size or a longer time until the cancer recurs.

Besides data based only on trials with surrogate markers, other instances where a Notice of Compliance with conditions might be used are for NAS with Phase II trials that require confirmation with Phase III trials or NAS with a single small to moderately sized Phase III trial that requires confirmation of either the efficacy or safety of the agent under question (3). In return for Notice of Compliance with conditions status, companies sign a Letter of Undertaking to complete confirmatory clinical studies, that is studies that definitively establish efficacy, and submit the results of these to Health Canada, although typically there is no timeline given for completing these studies. Should these postmarket trials not provide sufficient evidence of clinical benefit the Notice of Compliance with conditions could be revoked and the product removed from the market (4). If companies apply for Notice of Compliance with conditions status when they file a new drug submission and Health Canada agrees to the NOC/c application then drugs are reviewed in 200 days. If companies do not initially apply for Notice of Compliance with conditions status then drugs are reviewed in either 180 or 300 days, and Health Canada retains the option to grant Notice of Compliance with conditions status at the end of the review even in the absence of a manufacturer’s application for this type of review.

1. Ability to predict therapeutic innovation

   a. Drugs reviewed through the priority approval pathway

A total of 426 drugs were approved by Health Canada between 1997 and 2012. Therapeutic evaluation was determined by consulting the evaluations of 345 of these drugs that were undertaken by the Canadian Patented Medicine Prices Review Board (PMPRB) and/or the independent French drug bulletin Prescrire International. The latter is included as an independent international assessment of the product’s contribution to therapy. It has the advantage of being primarily focused on clinical individual patient care decisions. This is highly relevant to any consideration of whether priority approval pathways meet the regulatory goal of providing more rapid patient access to therapies that contribute to an improvement in therapy and ultimately to better health. The therapeutic evaluation of one or both of these organizations was compared to that of Health Canada as determined by its granting these products a priority review. If either PMPRB or Prescrire or both organisations considered a drug to be innovative, it was classified as innovative (5).

The PMPRB is a federal agency that is responsible for calculating the maximum introductory price for all new patented medications introduced into the Canadian market. It is important to note that the PMPRB is not a payer and therefore its decisions about therapeutic value are not influenced by the product’s price. As a precondition to decisions concerning a product’s allowable price in Canada, the PMPRB’s independent Human Drug Advisory Panel (HDAP) determines the therapeutic value of each product it reviews and these evaluations are published in its annual reports available on-line from 2003 to 2012 at <http://www.pmprb-cepmb.gc.ca/english/View.asp?x=91> and for previous years by directly contacting the PMPRB at <pmprb@pmprb-cepmb.gc.ca>. HDAP determines the ratings for the drugs before the maximum price is established. For the purpose of this study, products that were deemed breakthrough and substantial improvement were termed “innovative” and products in other categories were termed “not innovative”.
In deciding on the level of therapeutic innovation HDAP considers two primary factors:
- increased efficacy, and
- reduction in incidence or grade of important adverse reactions.

It also considers nine secondary factors:
- route of administration,
- patient convenience,
- compliance improvements leading to improved therapeutic efficacy,
- caregiver convenience,
- time required to achieve the optimal therapeutic effect,
- duration of usual treatment course, success rate,
- percentage of affected population treated effectively, and
- disability avoidance/savings.

The primary factors are given the greatest weight, followed by an assessment of any additional improvement as a result of the secondary factors (6).

Prescrire assesses the therapeutic value of medicines through a multistep process. First, it “examines the condition or clinical setting for which the drug is proposed; then the natural course of the disease, the efficacy and safety of existing treatments, and the most relevant outcome measures. This is followed by a systematic search for clinical data on the efficacy and adverse effects of the new drug, and an assessment of the level of evidence. Based on [its] independent analysis of clinical data, [it] form[s] a judgement as to whether or not the new drug is beneficial for patients or whether or not its harmful effects outweigh the benefit” (7). Based on its analysis, it rates products using the following seven category scale:
- bravo (major therapeutic innovation in an area where previously no treatment was available);
- a real advance (important therapeutic innovation but has limitations);
- offers an advantage (some value but does not fundamentally change the present therapeutic practice);
- possibly helpful (minimal additional value and should not change prescribing habits except in rare circumstances);
- nothing new (may be new molecule but is superfluous because does not add to clinical possibilities offered by previously available products);
- not acceptable (without evident benefit but with potential or real disadvantages);
- judgment reserved (decision postponed until better data and more thorough evaluation) (8).

The first 3 Prescrire categories were defined as innovative and the other Prescrire categories (except judgment reserved) were defined as not innovative. (Prescrire ratings were not considered when it reserved judgment.)

PMPRB and/or Prescrire rated 52 (15.1%, 95% CI 11.68, 19.23) of the 345 drugs as innovative. Health Canada gave a priority review to 91 of these 345 drugs (26.4%, 95% CI 22.01, 31.27). There was a statistically significant difference between the PMPRB/Prescrire ratings and the Health Canada decision at p = 0.0003.

Yearly Kappa values, a measure of inter-rater agreement, comparing Health Canada and the PMPRB/Prescrire on an individual drug level ranged from a low of -0.091 (95% CI -0.180, -
0.002) in 1998 to a high of 1.000 (95% CI 1.000, 1.000) in 2010. Kappa values were at or below 0.400 in 9 of the 16 years meaning a level of agreement of fair or less in those years. The overall Kappa for the 16 years was 0.334 (95% CI 0.220, 0.447) or fair.

Based on a drug-by-drug comparison for all drugs evaluated by the PMPRB/Prescrire, the positive predictive value of Health Canada’s ratings was 36.3% (95% CI 26.6, 47.1) meaning that it gave a priority review to 91 drugs but only 33 were subsequently evaluated as innovative. The negative predictive value of Health Canada’s ratings was 92.5% (95% CI 88.4, 95.3) meaning that it gave a standard review to 254 drugs while 235 were assessed as not innovative.

b. Drugs reviewed through the Notice of Compliance with conditions pathway

A separate analysis looked at a total of 378 drugs approved from the start of the NOC/c policy on January 1, 1998 until March 31, 2013. The therapeutic innovativeness as determined by Health Canada in granting approval through this pathway was compared to the evaluations of the PMPRB and/or Prescrire (9).

Twenty-seven of the 378 drugs approved during the time period were approved through the NOC/c. Ten of the 27 drugs were for cancer, 6 for HIV/AIDS, 3 for various hematological disorders and one each for: acute graft versus host disease, Alzheimer disease, amyotrophic lateral sclerosis, congestive heart failure, cystic fibrosis, Fabry disease, Friedreich’s ataxia and influenza. The PMPRB evaluated the therapeutic value of 24 out of 27 of the drugs and rated 19 as no therapeutic advance and 5 (21%) as representing a therapeutic advance. One of the remaining three was rated as “no therapeutic advance” by Prescrire and neither organization assessed the other two.

c. First-in-class drugs

A third analysis examined the therapeutic innovativeness of first-in-class drugs, ones that use a new and unique mechanism of action for treating a medical condition, approved by Health Canada, again by using the ratings given to these products by the PMPRB and/or Prescrire (10).

A total of 426 drugs were approved by Health Canada between 1997 and 2012 and 345 of these drugs were evaluated by PMPRB/Prescrire. Data on first in class status was available for 292 of these 345 drugs and the analyses were based on this group of 292. Ninety-eight drugs were first in class and only 16 of these (16.3%, 95% CI 10.3, 24.9) were therapeutically innovative. However, of the 16 first in class drugs that were given a priority approval, 14 proved to be therapeutically innovative (10).

Implications for the TGA

The October 2016 TGA consultation paper on expedited pathways for prescription medicines proposed the following criteria in deciding whether to allow products into the provisional approval and priority pathways:

1. The medicine is indicated for the treatment, prevention or diagnosis of a life threatening or seriously debilitating disease or condition.
2. The medicine addresses an unmet clinical need in Australian consumers.
3. **For Priority Review:** there is *substantial evidence demonstrating* that the medicine provides a major therapeutic advantage in efficacy and/or safety over existing treatments that are fully registered in Australia

4. **For Provisional Approval:** there is *promising evidence from early data* indicating that the medicine is likely to provide a major therapeutic advantage in efficacy and/or safety over existing treatments that are fully registered in Australia

These criteria are very similar to the ones used by Health Canada, but based on the Health Canada experience they are not sufficient for being able to predict whether a product will be a significant therapeutic advance. Use of an expedited pathway is resource intensive and creates an expectation among clinicians and patients that these products will bring major benefits. As demonstrated above, the Canadian experience indicates that in over \( \frac{3}{4} \) of cases, post-market evaluates indication that this expectation is not warranted.

**Recommendations**

1. The TGA should only grant approval through an expedited pathway to drugs that have a high likelihood of bringing about significant benefits. Based on the experience of Health Canada initially priority approval should only be given to drugs that are first in class.

2. If a provisional registration pathway is adopted, the TGA should adopt more intense monitoring of products that enter this pathway, to assess the extent to which this pathway is meeting regulatory goals to prioritise advances in therapy, and continue to refine the criteria that it uses based on the results of this ongoing evaluation;

3. Any provisional registration pathway must be accompanied by clear timelines for required efficacy studies and pre-established minimal efficacy thresholds that would allow a medicine to remain on the market.

**2. Safety of products once they are on the market**

   a. **Drugs reviewed through the priority approval pathway**

   Health Canada approved 434 drugs from January 1, 1995 to December 31, 2010. Eighty-four of these (19.4%) had a serious safety issue as operationally defined as a warning being in either bold print and/or in a black box. The probability of a drug acquiring a serious safety issue was 23.7% (95% CI 19.1, 28.3). 321 (74.4%) of these products had a standard review and 112 (25.6%) a priority review. (The approval status of one product could not be determined.) For products with a standard review there was a 19.8% (95% CI 14.8, 24.8) estimate of acquiring a serious safety issue compared to a 34.2% (95% CI 24.3, 44.2) estimate for a New Active Substance with a priority review (\( p = 0.005 \), Log-rank test). The chance of a product acquiring a serious safety warning did not appear to be related to either the disease it was meant to treat or its mechanism of action (11).

   b. **Drugs reviewed through the Notice of Compliance with conditions (NOC/c) pathway**

   Health Canada approved a total of 378 NAS from January 1, 1998 until March 31, 2013. Twenty-seven received a NOC/c and 265 a standard review. (The other 86 had a priority review.) Eleven of the 27 (40.7%, 95% CI 28.9, 52.8) with a NOC/c received a safety warning only (9, 33%) or were withdrawn because of safety concerns (2, 7.4%). Out of the 265 with a standard review, 50 (18.9%, 95% CI 12.9, 24.9) received a safety warning only
Kaplan-Meier curves were used to compare the likelihood of drugs approved under the NOC/c policy acquiring a serious safety warning compared to those approved through a standard review. There was a statistically significant difference between the two curves (p = 0.0113, Log rank (Mantel-Cox) test) with drugs approved through the former policy more likely to acquire a serious safety warning.

In other words, this analysis shows that drugs that received the equivalent of Australia’s proposed provisional approval were more to receive a serious safety warning or be withdrawn from the market compared to drugs with a standard review (40.7% versus 18.9%).

**Implications for the TGA**

The March 2017 consultation document from the TGA proposes to review an application through the priority review pathway within 150 days. Evidence from Canada indicates that shorter approval times lead to more safety problems once a drug is on the market and that the higher likelihood that there will be safety issues with these drugs is not due to either the mechanism of action of the drugs or the disease that they are meant to treat. The only other significant factor is the time taken to review the evidence regarding safety and efficacy.

**Recommendations**

1. Any drug approved through an expedited approval pathway needs to be intensively monitored for safety.
2. The TGA should adopt a precautionary principle approach to safety of drugs approved under an expedited approval pathway and, even in the absence of definitive scientific evidence of a safety problem, should move quickly to restrict access or withdraw products from the market. Specifically, the TGA should establish a standard for the time from which it receives safety information until it makes a decision about action on that information. This time frame should be publicly available and when the TGA makes a decision the information behind the decision should also be publicly available.
3. Product information, including Consumer Medicines Information, and packaging of all drugs approved under either type of expedited approval process (provisional approval or priority approval) should include a warning, accompanied by a black triangle or similar symbol, to inform clinicians and patients of the limited assessment of both efficacy and safety and the need to be alert to the possibility that a new serious health problem that develops on therapy could be due to the drug.

3. **Availability of information regarding the progress of products through the Notice of Compliance with conditions pathway**

Health Canada currently lists products approved through its Notice of Compliance with conditions on a website - [http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php). The website includes information about the additional studies required to move from provisional to full approval in the form of a Qualifying Notice. However, the information about these additional studies is highly variable ranging from minimal e.g., “final results of the pivotal Phase 3 study” to very detailed e.g., “A randomised, double-blind, comparative, parallel-group, multicentre trial to evaluate the safety and efficacy of abacavir versus placebo in combination with background antiretroviral therapy in HIV-1..."
infected antiretroviral therapy experienced subjects with CD4+ cell counts >100 cells/mm3 and plasma viral load between 400 copies/mL and 50,000 copies/mL”. There was only a single instance where a clinicaltrials.gov identification number was given for a required postmarket study and only one Qualifying Notice out of 63 listed a completion date for the studies (12). A separate document on the website “Dear Health Care Professional Letter” gives a summary of the clinical reasons why a Notice of Compliance with conditions was granted. Once conditions are fulfilled this is indicated on the Health Canada website but no further information is provided about the nature of the information used to fulfill the conditions. Health Canada does not specifically notify either healthcare professionals or patients about fulfillment of the conditions and it does not indicate if the necessary postmarket studies have been published nor does it require the company to do so (12). Health Canada also does not indicate the status of the required studies on any website or in any document.

Implications for the TGA

The March 2017 consultation document from the TGA states: “It is proposed that the TGA website will include a dedicated webpage for the publication of provisionally registered medicines and/or indications, similar to the current webpage that publishes orphan drug designations. This webpage could include general messaging about what provisional registration is and the implications of early registration without full clinical data. It could also provide details such as why the medicine was granted provisional registration status, the clinical trials to be undertaken and other conditions of registration.” This level of information does not appear to differ significantly from what is on the Health Canada website. The planned TGA provisions, similarly to those currently in place in Canada, are likely to lead to incomplete information in many cases concerning the characteristics of planned studies or the outcomes they aim to assess, differences in information quality between manufacturers, and inadequate access to the full reports of postmarket studies.

Recommendations

1. Information about drugs granted provisional registration should include complete information about any required postmarket studies including clinicaltrials.gov identification numbers (if available) and the expected date of study completion.
2. The TGA should post updates about the status of required studies on a regular basis, perhaps every 6 months.
3. Once a product has moved to full registration, the TGA should inform clinicians and patients about this change and the nature of the evidence used including a detailed summary of the studies.
4. Publication of results of these postmarket studies should be a requirement of provisional approval, whether this publication occurs in a medical journal or in a clinical trial registry. When the studies have been published, either the TGA or the company involved should be required to mail a copy of the studies to healthcare professionals.
5. The TGA should conduct research to ensure that its communications regarding products granted provisional approval is being read and understood by healthcare professionals and patients.

4. Fulfillment of postmarket conditions required of products approved through the Notice of Compliance with conditions pathway
Up until September 30, 2014 there were a total of 63 NOC/c for 46 new drugs or new indications for existing drugs and 34 NOC/c were fulfilled for 26 products – 19 with a NOC/c for a single indication, 6 with 2 indications and 1 with 3 indications. The average time to completion was 1390 days (3.8 years) (12). A more recent analysis found that there are 9 products on the Canadian market for more than 6 years without their conditions being fulfilled, with 3 of these available for greater than 10 years (data unpublished).

In at least one case, Health Canada did not suspend the sale and allowed a drug to stay on the market despite not fulfilling its conditions. Iressa (gefitinib) was approved under this policy as a third-line treatment for non-small cell lung cancer (NSCLC) on the condition that the company submit a study showing that it improved survival (13). When the study results were submitted to Health Canada they showed no survival benefit for gefitinib compared to placebo (14). Health Canada recognized that the conditions had not been fulfilled, but rather than removing gefitinib from the market, in February 2005 it elected to allow it to continue to be sold on the rationale that “1. There is no alternative therapy available for treatment of Canadian NSCLC patients who failed two lines of therapy; 2. Iressa® shrinks tumours, which may lead to less shortness of breath, less pain and less cough; [and] 3. The safety profile of Iressa® is more acceptable than that of any other chemotherapy which may be considered in this situation” (13) (p. 2). (In 2009, the drug was deemed to have met its conditions after a new study showed non-inferiority, i.e., survival after taking it was no worse compared to another chemotherapy drug (15).)

Had Health Canada enforced its Notice of Compliance with conditions policy, it should have removed gefitinib from the market after it received the results of the study showing no survival benefit. Gefitinib could have been reconsidered after the 2009 study was completed and evaluated.

**Implications for TGA**

The TGA March 2017 consultation document states that provisional registration will be granted for a 2-year period with a further period of 1 to 2 years, with a maximum of two extensions and “in order for an extension to be granted, the sponsor will be required to make an application to the TGA before the provisional registration period lapses. It is proposed that the extension application will include an interim report on the clinical data that has been generated within the provisional registration period and will outline any modifications to the completion dates for ongoing clinical trials.” Based on the Health Canada experience it seems that most products will require at least a 1 year extension.

The consultation document also states that “the TGA will need sufficient regulatory powers to allow a provisionally registered medicine to be suspended or cancelled if there is evidence that the benefit-risk balance of the product has changed (e.g. where a confirmatory trial does not verify efficacy).”

**Recommendations**

1. Any extensions that the TGA grants to the provisional registration period need to be made public and the rationale for the extension similarly needs to be made public.
2. Criteria for acceptance of an extension should be determined *a priori* to ensure fair and consistent application across products and manufacturers, and to avoid meaningless rubber stamping that would allow for long delays in study completion.
3. The TGA should consider imposing financial penalties if conditions are not met in a
   timely manner. Currently, both the Food and Drug Administration and the European
   Medicines Agency have the authority to levy such penalties (16).

4. The TGA needs to have a public timeline for acting on evidence that a product is either
   ineffective or unsafe and promptly withdraw registration.

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References