Proposal for TGA actions in accelerating product development and review for critical life-saving medicines

August 2014

Executive summary

Health Authorities globally have recognised the need to provide a faster access for medicines with a high unmet clinical need for life-threatening conditions by establishing specific programs to accelerate the medicinal product development and/or the regulatory review process. Such programs have been established in USA, Europe, Canada, Japan and New Zealand. The US Food and Drug Administration (FDA) has invested significant resources in these programs with two programs for accelerating product development and two programs from expediting regulatory review. In particular, the 'Breakthrough' designation program is unique in that the FDA invests significant resources and time in numerous discussions with the Sponsor and close co-operation in the development of the clinical program.

In contrast, Australia currently has no formal expedited review process. The current TGA registration process prevents the expediting of evaluations faster than the standard registration process of 14-15 months and is prerequisite on a comprehensive suite of supporting data which limits opportunities for early applications based on early-phase clinical trials which further delays access to the medicine. For many Australians suffering life-threatening diseases who have run out of treatment options, this timeframe is simply too long.

In recognition of the high unmet clinical need and promising clinical data, some medicines are granted 'Breakthrough' designation by the FDA, and through close collaboration with the FDA, the marketing authorisation application for a medicine is accepted for evaluation by the FDA under 'Priority Review'. An approval announcement by the FDA would then be anticipated sometime within a six month timeframe. In contrast, despite the accelerated clinical development program undertaken by a sponsor at a global level, the earliest date with which a medicine in this situation would be registered in Australia would be 12-18 months after the FDA approval if all the comprehensive data requirements and standard evaluation timelines under the current TGA regulatory framework were followed. This delay denies broad access to Australians compared to overseas. Whilst limited patients may be able to obtain treatment through SAS schemes provided by the Sponsor, or through obtaining treatment from overseas; patients who are financially-constrained or in a poor state of health, may have succumbed to their disease and passed away in this time.

As such to ensure Australians have timely access to life-living medicines, it is proposed that firstly the TGA acknowledge the considerable resources invested by the FDA in granting a medicinal product 'Breakthrough' designation by recognising this FDA designation in the regulatory framework in Australia. Secondly, that the product development and registration review process for a medicine granted breakthrough designation by the FDA be expedited by the following actions:

1) Accept limited clinical data based on surrogate end-points, which demonstrate markedly positive benefit-risk,
2) Designate priority review with accelerated review timelines with a target approval date of 6 months from submission,
3) Grant conditional approval for applications assessed on limited clinical data, and/or
4) Allow for submission of additional data or rolling submission.

This will prevent Australians being denied timely access to critical life-saving medicines, which are already available in comparable countries overseas, by a one-size-fits-all and inflexible regulatory framework.

Introduction

Health Authorities globally have recognised the need to provide a faster access for medicines with a high unmet clinical need for life-threatening conditions through establishing the legal framework for the regulatory agency to work closely with sponsor during the development of the medicines and/or expediting registration of medicines based on early clinical data including the use of surrogate endpoints while confirmatory clinical studies are on-going. These authorities include those in the US (Federal Drug Administration), Canada, Europe (European Medical Agency), Japan and New Zealand.

In contrast, Australia currently has no formal expedited review process. The current TGA registration process adopts a prospective allocation of resources to evaluate applications at the pre-submission phase which prevents the expediting of evaluations faster than the standard registration process of 14-15 months. Furthermore, the current TGA registration process requires a comprehensive suite of supporting data in accordance with adopted EU-guidelines limiting opportunities for early applications for registration based of early-phase clinical trials, further delaying access to the medicine. For many Australians suffering life-threatening diseases who have run out of treatment options, this timeframe is simply too long.

FDA Programs to Expedite Drug Development and Review

FDA has established four pathways designed to expedite product development and/or the regulatory review and approval process for medicines that provide significant improvements in safety or efficacy in areas of high unmet clinical need.

Expedite Product Development	Expedite Registration
Fast Track Designation	Accelerated Approval
Breakthrough Therapy Designation	Priority Review

1. Fast Track Designation

Fast track is a process designed to facilitate the development, and expedite the review of medicines that fill an unmet medical need for serious conditions. The designation is requested by the sponsor any time during the drug development process and a decision made by the FDA within 60 days.

The FDA's Fast Track Designation has two mechanisms to help speed up access to important medicines:

- Early and frequent interactions between the FDA and sponsor ensures the most efficient development program. This includes working together on trial design to collect the data needed to support registration. Frequent communication between the sponsor and FDA assures that issues are resolved quickly, marketing applications are submitted earlier, and patients access important medicines sooner.
- A "rolling review" allows sponsor to submit sections of the marketing application for review by FDA as they are completed rather than waiting for all sections to be complete before regulatory review begins.

2. Breakthrough Therapy Designation

Breakthrough Therapy designation was created in 2012. Since that time, The FDA has received 186 requests for the designation and granted 48. Six breakthrough drugs have been approved for marketing: four for cancer, one for Hepatitis C, and one for cystic fibrosis. The most recent breakthrough approval was for Zykadia (ceritinib) for certain patients with late stage non-small cell lung cancer. The drug was approved less than three and a half years after the first patient entered a clinical trial and its safety and effectiveness were established in a clinical trial of only 163 patients.

Drugs granted breakthrough therapy designation receives:

- Intensive guidance by the FDA for an efficient drug development program, beginning as early as Phase 1. Because a breakthrough designation requires a drug to potentially demonstrate a large effect compared with available therapies, the development program may be considerably shortened. It is important to note that the compressed development program must still generate adequate data to meet the FDA's rigorous standards for safety and effectiveness.
- Organizational commitment involving senior managers. This high-level commitment begins when the designation is made and continues throughout the development and review program. The

Director of the Center for Drug Evaluation and Research at FDA has described Breakthrough Therapy designation as an "all hands on deck" approach to expedite the development of promising new drugs.

3. Accelerated Approval

The accelerated approval pathway has been enormously successful, speeding access for patients to targeted cancer drugs, like Gleevac for CML, Herceptin for breast cancer and Xalcori for lung cancer. More than 80 new products have been approved under accelerated approval since the program was established in 1992, about 75% of which were to treat cancer and HIV infection. HIV infected patients, thanks to many new medicines approved under this pathway, now look forward to a nearly normal lifespan.

Accelerated approval is a pathway that allows a drug to receive FDA marketing approval based on:

- An agreed-upon surrogate endpoint (such as a laboratory measure or x-ray) or an intermediate clinical endpoint (such as tumor shrinkage), rather than what are considered standard outcome measures, such as overall survival.
- Medicines approved under this pathway must undergo further clinical testing to confirm the predicted outcome; e.g., to confirm that tumor shrinkage actually predicts that a patient will live longer.

Marketing approval may be withdrawn or the labeled indication changed if the confirmatory trials fail to verify clinical benefit. FDA has withdrawn accelerated approval for only one of those, Avastin for metastatic breast cancer.

4. Priority Review

A Priority Review designation means FDA commits to take action on an application within 6 months after the application is filed. For standard applications (those not deemed to be priority), FDA's review time commitment is 10 months.

Priority review is determined at the time a marketing application is submitted to the FDA. It does not speed the drug development and testing process.

EMA Programs to Expedite Drug Development and Review

1. Conditional Marketing Authorisation

Commission Regulation (EC) 507/2006 provides the legal basis for conditional approval by the EMA as a means to expedite drug development. As outlined in the current EMA guidance document EMEA/509951/2006 an application for 'Conditional Marketing Authorisation' may be requested by the applicant or proposed by the Committee for Medicinal Products for Human Use (CHMP) provided the sponsor can justify that the medicinal product falls into at least one of the following categories:

- Medicinal product treats a seriously debilitating or life-threatening disease,
- Medicinal product to be used in emergency situations, or
- Orphan medicinal products

Products which fall into the above categories may be approved on the basis of surrogate markers and/or other less complete data than is normally the case but is subject to the following specific obligations:

- The supporting data demonstrates a positive risk-benefit balance,
- It is likely that the applicant will be able to provide comprehensive data after the granting of a conditional marketing authorisation,
- The product fulfills unmet medical need, and
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

A conditional marketing authorisation is valid for 1 year and may be renewed annually provided a positive benefit–risk is demonstrated at each renewal, which ensures Sponsor fulfill their post-marketing requirements.

Conditional marketing authorisation as a route to approval has expedited patient access for numerous life-saving medicinal products, such as Xalkori (Crizotinib) for non-small cell lung cancer, and Tyverb (lapatinib) for HER2 positive breast cancer.

2. Accelerated Assessment

Commission Regulation (EC) 725/2004 provides the legal basis for accelerated assessment by the EMA as a means to expedite drug review, in which it is stated under Recital 33 that "in order to meet, in particular the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, accelerated assessment procedures should be set up, reserved for medicinal products of major therapeutic interest, and procedures for obtaining temporary authorisation subject to certain annually reviewable conditions". As outlined in the current EMA guidance document EMEA/419127/05 applications accepted for 'Accelerated Assessment', the time limit is reduced from the standard 210 days to 150 days. The decision by the CHMP to grant a medicinal product accelerated assessment is based on the applicant providing adequate justification that the product meets an unmet clinical need or provides significant improvement over existing therapy; as well as consideration of the recommendations of the rapporteurs.

Other Programs to Expedite Drug Development and Review World-wide

Canada

In recognition of the need to providing expedited review of critical new drugs and breakthrough therapies, Health Canada has established the regulatory framework for granting medicinal products a 'Priority Review' status. Priority review status allows for the submission review target to be shortened from the standard 215 days to 180 days

In order to qualify for priority review, the medicinal product must address a serious/life-threatening or severely debilitating disease. Applicants requesting for priority review for a medicinal product must demonstrate that it is:

- An 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.

"Substantial clinical evidence" of clinical effectiveness must be provided to support the above qualifying criteria. In general, Health Canada requires at least two adequate and well controlled clinical studies, each convincing on its own to establish effectiveness of the drug involved. However in

some instances, Health Canada may deem clinical evidence consisting of a single, large-scale, adequate and well controlled study or one pivotal trial; or “promising” clinical evidence including the use of non-validated surrogate markers, or Phase II studies to be “substantial clinical evidence”.

Japan

In Japan, to expedite review, the Ministry of Health, Labour and Welfare (MHLW) have established a priority review system for medicinal products designated as orphan drugs and other drugs considered especially important from a medical standpoint. Granting of priority review to a medicinal product is based on the assessment of the criteria:

A. Seriousness of indicated diseases
   i) Diseases with important effects on patient’s survival (fatal diseases)
   ii) Progressive and irreversible diseases with marked effects on daily life
   iii) Others

B. Overall assessment of therapeutic usefulness
   i) There is no existing method of treatment.
   ii) Therapeutic usefulness with respect to existing treatment
      a) Standpoint of efficacy
      b) Standpoint of safety
      c) Reduction of physical and mental burden on the patient

Products for priority review are given priority at each stage of the review process as much as possible.

In addition, to expedite drug development, the MHLW has also established the framework for medicinal products to be designated ‘priority face-to-face advice’ at the development stage. Products are designated on the basis of an overall evaluation of the seriousness of indicated disease and clinical usefulness. Under this designation, the MHLW provides face-to-advice and other items concerning the medicinal products. To qualify for this designation, applicants are requested to submit results of clinical studies up to late Phase II as an estimate of clinical usefulness, and the designation is decided after input of expert opinion in the field.

New Zealand

In New Zealand, Medsafe have adopted policy for Priority Assessment as well as Provisional consent.

Medsafe will grant priority status to a medicinal product (upon application) on the basis of significant clinical advantage or significant potential cost savings for the tax payer; with the principle being to shorten the time to consent and hence realise the potential of these new medicines. Medsafe uses internal processes to ensure that evaluation is commenced in a timely manner. Granting of priority assessment status is conditional on applicants responding to a Medsafe request for information within 28 days. In cases where the sponsor cannot obtain the information requested within the 28 day timeframe, it can still be provided after this deadline but the priority status of the application will be revoked.

Section 23 of the Medicines Act 1981 also provides the legal basis for Medsafe to grant 'provisional consent' to the sale/supply/use of a new medicine if the minister is of the opinion that is desirable that the medicine be sold/supplied/used on a restricted basis for the treatment of a limited number of basis.

Medsafe has utilised this ability to grant provisional consent to provide faster access in situations where there is a clinical need for the medicine and when the available data set, though less comprehensive than that required for full approval, demonstrates that the risk: benefit profile of the medicine is acceptable. Provisional consent is valid for two years, but can be renewed, or converted to a full consent provided that the sponsor provides additional data justifying this approach. It is also possible to place conditions or restrictions on the use or supply of a medicine that is given provisional consent. Provisional consent allows a product to be used in the community at an earlier stage than would be possible if it was necessary to wait until further data were available to satisfy the data requirements for full consent and is therefore a useful tool to allow early access to a treatment where other options are limited, or absent, such as a vaccine to manage an epidemic.

The success in expediting access to life-saving medicine is demonstrated in the timeline of actions during the approval process for the meningococcal B vaccine (MeNZB) application published on the Medsafe website, where by discussions between the sponsor and Medsafe in February 2003 lead to an agreement that Medsafe would accept that additional data in a 'rolling fashion'. The New Medicine Application was received on June 2003 and 'provisional consent' was granted on April 2004.

Historically a number of products such as the HIV/AIDS medications were first approved under provisional consent when they initially became available, and have since obtained full consent as even more data demonstrating safety and efficacy became available. More recently, in 2006, by granting provisional consent, Medsafe has allowed New Zealanders to be the first country in the world to access to Herceptin (Trastuzumab) for the treatment of HER2 postive breast cancer.

How Australia Can Expedite Drug Development and Review

Several short and long term actions that is considered and implemented by the TGA will expedite access to life-saving medicine.

Long-term TGA reform – Adopting FDA 'Breakthrough' Designation

Over the longer term, through reforming current regulatory framework, the TGA can benefit from the time and resources invested into expedited review programs for medicinal products in recognised health authorities overseas, especially the FDA. A range of expedited product development and review programs have been resourced and made available by the FDA to ensure access to promising medicinal products in a timely manner. In particular, the 'Breakthrough' designation is a unique program in that the FDA invests significant resources and time in numerous discussions with the Sponsor and close co-operation in the development of the clinical program.

It would take significant resources for the TGA to establish a similar 'Breakthrough' designation program in Australia. However, Australia can benefit for the work put in by the FDA by:

- Recognizing and adopting the 'Breakthrough' designation granted by the FDA, and
- Expediting drug development and review by adopting the actions proposed below for medicinal products granted a 'Breakthrough' designation

Short-term actions for current and future products granted 'Breakthrough' designation

For medicines which treat seriously debilitating or life-threatening disease, or are used in emergency situations, which are not adequately managed by a drug marketed in Australia, and future products granted Breakthrough designation, the TGA can:

1. Accept limited clinical data based on surrogate end-points, which demonstrate markedly positive benefit-risk,

2. Designate priority review with accelerated review timelines with a target approval date of 6 months from submission,
3. Grant conditional approval for applications assessed on limited clinical data, and/or
4. Allow for submission of additional data or rolling submission.

The above proposed actions are not without precedence. Prior to the implementation of the new Streamlined Submission Process, priority review, conditional approval based on limited data and the provision of addition data during evaluation was possible and was utilised by the TGA in the evaluation of multiple products. The application to register Isentress (Raltegravir) 400mg tablets, (AUST R 140238) for the treatment of adults infected with HIV-1 in 22 May 2007 was:

- Accepted for review with limited supporting clinical evidence of surrogate endpoints,
- Evaluated under priority review,
- Supported by the submission of additional data throughout the evaluation process, and
- Granted conditional approval on 15 January 2008 (8 month evaluation time) with multiple post-market obligations from the sponsor to submit additional clinical data to the TGA.