



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration



Discussion Paper

Workflow practices within the Drug Safety and Evaluation Branch of the TGA

1 November 2005

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GLOSSARY OF TERMS AND ACRONYMS USED

ADEC	Australian Drug Evaluation Committee
AEP	Application Entry Process
ARTG	Australian Register of Therapeutic Goods
CBER	Centre for Biologics Evaluation and Research (within the US Food and Drug Administration)
CDER	Centre for Drug Evaluation and Research (within the US Food and Drug Administration)
CHF	Consumers' Health Forum
CHMP	Committee for Medicinal Products for Human Use (Europe)
DSEB	Drug Safety and Evaluation Branch of the TGA
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
FDA	Food and Drug Administration (US)
PBAC	Pharmaceutical Benefits Advisory Committee
TGA	Therapeutic Goods Administration
TG Act	<i>Therapeutic Goods Act 1989</i>
TG Regulations	Therapeutic Goods Regulations 1990
TPD	Therapeutic Products Directorate (within Health Canada)

INTRODUCTION

The purpose of this Discussion Paper is to provide a basis for discussions with stakeholders about possible means by which to streamline processes for evaluation of applications for prescription medicines and increase transparency of decision-making.

This Discussion Paper draws on the valuable work undertaken by a Working Party formed in late 2002 to review Australia's Prescription Medicines Regulation Workflow Practices. The current practices are described in detail in the *Australian Regulatory Guidelines for Prescription Medicines* available at <http://www.tga.gov.au/pmeds/argpm.pdf>.

Initially, it is anticipated that the TGA will wish to implement any improvements that can be made to their current business processes as a result of this review ahead of the commencement of the joint trans-Tasman regulatory scheme (planned for 1 July 2006). The consultation paper has therefore been drafted to reference current Australian practice when describing the status quo and commenting on alternative approaches.

Because the feedback from this consultation will also flow through into the development of business practices for the joint agency, the consultation is being conducted jointly by the Drug Safety and Evaluation Branch (DSEB) and the Joint Agency Establishment Group (JAEG) and feedback is being sought from both New Zealand and Australian stakeholders.

The DSEB and JAEG are therefore keen to consult widely with industry, health professional and consumer groups in both Australia and New Zealand on this Discussion Paper and intend conducting face to face consultations with key stakeholders in late November 2005. The firm mpconsulting has been engaged to undertake these consultations in Australia. In New Zealand consultation will be undertaken by Medsafe's joint agency project team. Feedback from the consultations will be reported back to the DSEB and the JAEG.

Stakeholders may also wish to make written submissions. Written submissions may be forwarded to:

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The closing date for submissions is 20 January 2006.

CHAPTER 1: OBJECTIVES OF THE REVIEW

1.1 The key objectives of this review are to:

- identify opportunities for improving the current pre-market workflow processes for regulation of prescription medicines (including those for approval of new substances and for variations to existing products) so that the processes better reflect the modern work processes of relevant stakeholders;
- explore any means by which processes can be streamlined to better meet the needs of industry;
- provide greater capacity for planning by the TGA (including enabling better planning and more efficient allocation of resources within the TGA); and
- improve the transparency of the TGA's decision making processes for the benefit of both industry and consumers.

1.2 To this end, this Discussion Paper explores 4 aspects of the evaluation process:

- the Application Entry Process (Chapter 3);
- the timing and handling of data and requests for additional information including informal requests, section 31 requests and management of supplementary and additional data (Chapter 4);
- the Australian Drug Evaluation Committee (ADEC) process (Chapter 5); and
- the transparency of decisions made by the TGA (Chapter 6).

1.3 While the TGA is keen to identify means by which to improve its business practices (including through appropriate streamlining) it is equally important to ensure that this in no way impacts on the rigor of the TGA's evaluation of medicines.

CHAPTER 2: BACKGROUND

The TGA Approval process

2.1 Before a prescription medicine can be supplied in Australia, it must be included in the Australia Register of Therapeutic Goods (ARTG)¹. In order to register a new medicine in Australia a sponsor (usually a pharmaceutical company) must submit an application together with supporting data to the TGA.

2.2 The *Australian Regulatory Guidelines for Prescription Medicines* (ARGPM) describe the TGA's data requirements and administrative processes. In summary the TGA's current administrative processes are as follows:

- after an application is submitted, there is an initial period during which the application is assessed on an administrative level to make sure that the application complies with basic guidelines (the Application Entry Process). This process can take up to 40 working days depending on the nature of the evaluation;
- following the Application Entry Process, the data are then evaluated by three different areas, depending on whether they relate to chemical, pharmaceutical and biological; non-clinical (animal toxicology); or clinical aspects of the evaluation;
- following evaluation, the Evaluation Reports are provided to the sponsor who is invited to respond (except for Category 3 and minor Category 1 applications). Evaluation Reports (and the response from the sponsor) is provided to the Australian Drug Evaluation Committee (ADEC) for advice. The Drug Safety and Evaluation Branch (DSEB) is not obliged to refer applications to ADEC but generally does so for major applications (in particular, new products and extensions of use). A "Request for ADEC Advice" is also prepared by a senior medical officer within the TGA and the sponsor is given an opportunity to respond directly to ADEC;
- ADEC considers and advises on the application (through a resolution);
- after receipt of the ADEC resolution the TGA Delegate determines whether the application for registration is to be approved or rejected and the sponsor is advised of the decision (the initial decision). If the TGA delegate proposes to approve the application, he/she will communicate with the sponsor to address any outstanding issues relating to the application prior to the issue of a Certificate of Registration. If the Delegate proposes to reject an application, a letter of decision is sent to the sponsor. If the

¹ Subject to certain exceptions

rejection has not previously been foreshadowed by the TGA, the Delegate usually offers the sponsor a further opportunity to provide input. Once the decision is finalised, the sponsor may also elect to appeal the decision of the Delegate; and

- upon approval of a new register entry, the sponsor will be sent a Certificate of Registration with a unique AUST R number.

Timeframes

2.3 The nature of, and timeframe for, evaluation depends on the category of application:

- Category 1 applications include applications for a new chemical entity or a new indication for a registered prescription product as well as other major changes such as changes to product information or approval of a new generic medicine. Essentially, Category 1 catches applications not included in Category 2 or 3;
- Category 2 applications are those where there are two independent evaluation reports available from acceptable countries (USA, UK, Canada, Sweden and Netherlands); and
- Category 3 applications involve a change to a product that is already registered where the change does not require clinical, toxicological or bioavailability data to support the change.

2.4 The legislated timeframes for assessment of applications are:

- for Category 1 applications - 255 working days;
- for Category 2 applications - 175 working days; and
- for Category 3 applications - 45 working days.

2.5 The TGA also develops target mean timeframes in consultation with industry for various sub-categories of applications.

2.6 The TGA targets the following mean evaluation times, excluding time taken for applicants to respond to S31 questions, for different types of applications:

- new chemical entities, 150 working days;
- new generics, other than additional trade names only, 100 working days;
- new indications, 160 working days;

- product Information changes, 90 working days;
- additional trade names only, 45 working days (subject to certain exceptions); and
- other Category 1 applications, 130 working days.

2.7 Formal timeframes have not been established for priority evaluations. It is expected that priority evaluations will be completed as quickly as possible and within the above target timeframes.

CHAPTER 3: APPLICATION ENTRY PROCESS

A. Current TGA process and timelines

Process

Pre-submission meetings

- 3.1 Currently pre-submission meetings are not a regulatory requirement but are strongly encouraged by the TGA.
- 3.2 Sponsors can request a pre-submission meeting with the TGA by submitting a written request detailing a clear purpose of the meeting, relevant background information, a proposed agenda and a list of requested representatives from the TGA². The TGA expects supporting information for the meeting to be received by the TGA in hard copy at least 2 weeks in advance of the scheduled meeting.
- 3.3 Some of the issues that the TGA discusses with sponsors during pre-submission meetings include the availability of evaluation reports from other regulatory agencies, the possibility of negotiating shared evaluations and drug specific issues.
- 3.4 At present the pre-submission meetings are relatively informal and decisions are not binding. While meeting minutes are not taken, official action sheets are prepared by the TGA after meetings with sponsors and distributed to attendees.

Application Entry process

- 3.5 After an application is submitted, there is an initial period during which it is assessed on an administrative level to make sure that the application complies with basic guidelines. This Application Entry Process (AEP) is designed to ensure that grossly deficient applications do not end up within the evaluation system causing delays for themselves and other products. At the end of this phase a decision is made whether to accept the application for evaluation or to reject it.
- 3.6 During the AEP the submission is assessed to ensure that:
 - it complies with TGA format requirements as currently set out in the ARGPM. For example, the application is checked for overall presentation and binding and to ensure that the correct number of copies of the documentation have been received;

² Appendix 5 of the Australian Regulatory Guidelines for Prescription Medicines describes the conduct of meetings between the TGA and sponsors. The document details the responsibilities of the sponsor and the TGA and also procedures for meetings and meeting follow up.

- it contains an accurate and comprehensive index based on a coherent system of volume and page numbering;
 - it contains suitable statements regarding confidentiality;
 - it contains information on the overseas status of the products (for example, the application should include a list of countries in which a similar application has been lodged and the status of these applications);
 - the applicant has advised whether a similar application has been rejected or withdrawn in the USA or Canada; and
 - it contains copies of the draft Australian Product Information and the proposed Australian Consumer Medicine Information and that these comply with the relevant sections of the ARGPM and the therapeutic goods legislation.
- 3.7 As a final part of the AEP, the submission is briefly reviewed by each of the three evaluation areas to ensure that the data relevant to that particular area appears sufficient and complies with any administrative requirements.
- 3.8 Over 99% of applications are accepted for evaluation at this point in time, although many require further questions to be asked of the sponsor (refer discussion on section 31 questions below) in order to define the indication being sought or to substantiate that additional information will be provided in the future.

Timeframes

- 3.9 The timeframes for the AEP are currently as follows:
- for Category 1 applications – 40 working days;
 - for Category 2 applications – 20 working days; and
 - for Category 3 applications – 5 working days.

B. Issues and options for consideration

- 3.10 The Working Party formed in late 2002 to review Australia's prescription medicines regulation workflow practices, identified a number of options for streamlining the AEP stage, reducing timeframes for the AEP stage and ensuring that the TGA has more information available to it at an early stage to enable it to appropriately allocate resources (which should also assist in reducing timeframes for the full evaluation).

3.11 Some of the options for consideration that have been identified by the Working Party (and by the TGA) include the following.

(i) Pre-submission process

3.12 The TGA's pre-submission process could be reformed as follows:

- sponsors could provide prior notification to the TGA of their intention to lodge an application³ including an application summary. This would provide the TGA with an early indication of when an application is likely to be submitted and the resources that will be required by the TGA to manage the application;
- sponsors would have the option of attending a pre-submission meeting to discuss the proposed application or may be requested to do so by the TGA if the information provided in the application summary suggests that the application may raise contentious issues or be missing important data. As detailed in the previous Part, the TGA currently has a system of informal pre-submission meetings. However, a more formalised system could be implemented that would enable a reduction in the time taken for the AEP. Pre-submission meetings provide an opportunity for sponsors to obtain procedural, regulatory and scientific advice from the TGA before submitting their application for evaluation. In many cases such a meeting may not be necessary. For example, it is not anticipated that a pre-submission meeting would be necessary for minor Category 1 applications such as for Product Information changes but a meeting may be particularly useful for new chemical entities;
- at the time of making the application, sponsors would complete an administrative checklist and confirm that they have fulfilled all submission requirements (including any agreed outcomes from the pre-submission meeting if such a meeting has been held); and
- applications made in accordance with this process would not be screened in accordance with the full AEP but would be accepted for evaluation within 10 working days.

3.13 The advantages of a pre-submission process of this type (with a pre-submission meeting where appropriate and a shortened filter period) appear to be as follows:

- this option would align TGA's processes more closely with those of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) (refer discussion below);

³ Please note that for the purpose of this paper the term "application" has been used in a general sense to describe both applications in respect of one product and submissions in respect of multiple strengths of products.

- the TGA would gain predictability of incoming applications allowing for more efficient allocation of resources;
- it provides an opportunity for sponsors to address potential issues (including any administrative issues) before submission of the application. This provides greater predictability to sponsors and should also lead to a reduction in evaluation times. In particular it should lead to a reduction in the number of times that the clock is stopped in order for the TGA to seek additional information from sponsors;
- the time currently spent filtering applications would be reduced and would occur at an earlier point in the process; and
- there would be greater predictability for sponsors to the extent that many issues are likely to be resolved prior to the application being made.

3.14 Some issues for consideration in the context of examining this option include:

- the information that should be included in the sponsor's notification of their intent to make an application. In general terms the TGA anticipates that it would be looking for sufficient detail to enable the TGA to assess the suitability of the application based on international core documents rather than the fine detail of the application;
- when the notification should occur (that is the minimum time prior to lodgment of the application);
- the circumstances in which a pre-submission meeting will be necessary; and
- the issues to be addressed in the administrative checklist.

(ii) Scientific Advice meetings

3.15 Should the option described above be adopted (prior notification of intent to lodge, pre-submission meeting where necessary and completion of an administrative checklist by the sponsor), it is intended that it would supplement rather than replace meetings to discuss product development (scientific advice meetings).

3.16 Currently, sponsors can informally meet with the TGA to discuss the development of a new chemical entity or biological product and request advice on the dossier contents. These meetings enable sponsors to seek advice on the requirements for various tests and trials necessary to

demonstrate the quality, safety and efficacy of therapeutic goods. They also provide the TGA with valuable background information on the development of a new chemical entity or product.

C. International precedent in relation to application entry processes

3.17 Please note that for the purposes of comparison the following information is based on application filter times for Category 1 applications.

Europe - EMEA

3.18 Sponsors are required to alert the EMEA of their intention to submit an application at least 4-6 months prior to submission and must also attend, at this time, a compulsory pre-submission meeting at which there is extensive presentation of the dossier so that agreement can be reached on the acceptability of the dossier.

3.19 The EMEA then decides if an application is acceptable for evaluation within 10 working days of receipt of the application.

Canada - TPD

3.20 In Canada the Therapeutic Products Directorate within Health Canada (TPD) allows 45 calendar days for the application filtering phase, but there is also a “pre-screening” phase prior to this which lasts 10 calendar days. The Canadian review system is somewhat unique in that a queuing process occurs between acceptance of the application and the start of the scientific assessment. Applications are released from the queue for scientific assessment according to available internal resources.

US - FDA

3.21 In the US, the FDA has significant involvement with sponsors throughout a drug’s development, as it does not have a trial notification system. The FDA discusses applications with sponsors prior to submission and requires sponsors to provide sufficient information to enable planning of the evaluation processes and trial site auditing for the application.

3.22 On final receipt of a new drug application, the Centre for Drug Evaluation Research (CDER), allows 60 calendar days to evaluate whether or not an application is acceptable. The validation of the application is carried out in parallel with the start of the scientific assessment and is not a sequential activity as is the case with other regulatory authorities. This means that the scientific evaluation starts immediately upon receipt of an application. Like the EMEA, the FDA requires notification of a pending application 6-9 months prior to the proposed submission date (and may

also hold pre-submission meetings to identify key data requirements and pivotal studies).

New Zealand - Medsafe

3.23 Unlike the other countries described above, in New Zealand there is no application entry filter, which means that all applications are accepted for evaluation upon submission. Medsafe also differs from other regulatory agencies in that it does not have formal targets or time limits for new chemical entity applications.

Table 1: Summary of application filter times for a new chemical entity

	Australia	Europe	USA	Canada
Application entry phase (AEP)	40 working days	10 working days	60 calendar days AEP occurs concurrently with scientific evaluation	55 calendar days Queue before scientific evaluation

CHAPTER 4: ADDITIONAL INFORMATION AND DATA

A. Current processes

4.1 As noted in Chapter 2, following the AEP, work is allocated to each of the evaluation areas and evaluation of different aspects of the application proceeds in parallel (with each evaluation area responsible for preparing an independent report by a certain date). Where evaluators have questions or concerns about an application, there are two ways in which additional information is requested from sponsors:

- through informal requests; and
- through section 31 requests.

4.2 In addition, sponsors have the opportunity to submit new data. Either additional data (where the intention to submit such data is identified prior to the acceptance of an application) or supplementary data (which is provided by the sponsor to address any possible or perceived deficiencies that may have been identified in a primary evaluation report).

4.3 The processes and timeframes surrounding each of these requests are detailed below.

(i) Informal requests

4.4 At any time the TGA may informally request additional information to assist in its evaluation of an application. In such circumstances the evaluation process does not formally stop while the applicant is providing the information to the TGA. This option is therefore predominantly used for smaller issues that are easily remedied rather than for seeking further advice on larger, more complex questions.

(ii) Section 31 requests

4.5 Section 31 of the *Therapeutic Goods Act 1989* (TG Act) provides that the TGA may, by notice in writing given to the applicant, require the person to give to the TGA (within such reasonable time as is specified in the notice and in such form as is specified in the notice) information or documents relating to one or more of the following:

- the formulation of the goods;
- the composition of the goods;
- the design specifications of the goods;
- the quality of the goods;

- the method and place of manufacture or preparation of the goods and the procedures employed to ensure that proper standards are maintained in the manufacture and handling of the goods;
- the presentation of the goods;
- the safety and efficacy of the goods for the purposes for which they are to be used;
- the conformity of the goods to a requirement relating to advertising applicable under Part 5-1 or under the regulations;
- the regulatory history of the goods in another country; or
- any other matter prescribed by the regulations.

4.6 Currently evaluators in each evaluation area send out section 31 requests for further information at the time the need for such information is identified. This results in a number of section 31 requests being issued at times simultaneously, during the evaluation phase. This system of rolling questions was originally introduced after negotiations with industry, and reflected a desire to deal with issues as they arise.

4.7 Generally a delegate will allocate up to 20 working days for response to a section 31 request but this time may be extended. The number of days allocated will vary depending on the information required and the officer making the request.

4.8 Response times are generally geared either to the preferred due date of the evaluation (for example, for a particular ADEC meeting) or to the time which it is expected the sponsor will need to respond.

4.9 For applications received in 2003/04, during the Application Entry Phase, section 31 questions were asked in 26% of cases. During the evaluation phase, 92% of submissions relating to New Chemical Entities were subject to one or more section 31 questions and 63% of all Category 1 applications were subject to one or more section 31 questions.

(iii) New data

4.10 New data are classified as either:

- additional data; or
- supplementary data.

4.11 The decision to submit new data remains solely with the sponsor. However, Appendix 6 of the ARGPM details the processes surrounding submission of new data. Appendix 6 provides that:

- TGA acceptance of supplementary data for evaluation depends on the sponsor's agreement to stop the clock (in accordance with regulation 16A(2)(C) of the TG Regulations) for a period adequate for its processing and evaluation. For additional data, the agreed data must be lodged by the agreed date;
- new data should be submitted in the format of a Common Technical Document;
- new data must relate to the scope of the original application and must not relate to an extension of indication, new population or dosing regime etc;
- new data can be submitted in relation to Category 1 submissions only; and
- any new data may not be accepted if they do not have a reasonable prospect of facilitating registration of the relevant application. The TGA may decline to accept new data if either the format or content of the submission is considered inadequate to determine the application.

Additional data

4.12 Additional data are data, identified prior to the acceptance of an application, which the TGA agrees to accept during the course of the subsequent evaluation. Additional data are circumscribed, relate to a particular aspect of the submission and are not intended to facilitate submission of inadequate or premature applications.

4.13 Any additional data must be submitted to the TGA by a date mutually agreed between the TGA and the sponsor at a pre-submission meeting. The clock is not stopped while the TGA considers additional data.

Supplementary data

4.14 Supplementary data are non-clinical data (Module 4) or clinical data (Module 5) submitted at the initiation of the sponsor, that require evaluation and which address any possible or perceived deficiencies that may be identified in a primary evaluation report received by the sponsor.

4.15 Supplementary data may be submitted after a sponsor has received either or both of the Modules 4 and 5 Evaluation Reports. The sponsor must notify their intention to submit supplementary data within 5 working days of receipt of the last Evaluation report. Only one submission of

supplementary data is permitted for each of Modules 4 and 5 unless otherwise agreed in writing by the TGA.

4.16 Supplementary data is not accepted by the TGA after commencement of the pre-ADEC process, which is signified by the issuing of the *Delegate's request for ADEC advice* and recommendation.

4.17 Acceptance of supplementary data is at the discretion of the TGA and is dependent on mutual agreement to a clock stop:

- up to 60 working days is permitted for all data to be presented to the TGA following the sponsor's notification of an intention to submit supplementary data; and
- up to 135 days is taken for evaluation of the supplementary data after all data have been received by the TGA.

B. Issues and options for consideration

4.18 The key advantages and disadvantages of the current approach to rolling section 31 requests appear to be as follows:

- a request for information is made as soon as the need for the information is identified. This can be time effective in that evaluators are not waiting until a specified time to request the information. However, sponsors have on occasion expressed concern that additional information may be requested before the full data package has been reviewed and the issues may be addressed elsewhere in the data package;
- in many cases the evaluation process is continued on other aspects of the application while evaluators are awaiting a section 31 response (this avoids unnecessary delays); and
- the approach has advantages for smaller companies with a local base but does not address the concern of larger global companies that favour using project teams to address questions. A number of companies now manage international regulatory matters through project teams that are formed for periods of time aligned to the international submission period. Industry has advised that rolling questions are not easily managed in this drug regulatory model.

4.19 One alternative option for managing TGA questions is specifying set times for formal questions and responses (for example, a maximum of 135 days after commencement of evaluation). This would not prevent evaluators informally contacting companies to resolve smaller issues (and in fact this practice would continue to be encouraged).

4.20 Under this option, after a maximum of 135 days of evaluation, the TGA would provide a consolidated list of formal, outstanding questions for

consideration by the sponsor. The sponsor would be expected to respond within a timeframe agreed by the TGA but not exceeding 6 months and the TGA would then evaluate the response. The maximum timeframe would not preclude a formal list of questions being provided to the sponsor at an earlier point in the evaluation process if all three evaluation areas have completed their initial evaluation and identified questions for inclusion in a consolidated list.

4.21 This approach ensures predictable timeframes for requests for information and enables project teams to be established to address the questions raised. It also minimises the possibility of inconsistencies or overlap in information requested by individual evaluators (because all questions from the TGA would be consolidated into a single list).

4.22 Should the option of having a fixed evaluation period and a consolidated list of questions be preferred, consideration may also need to be given to:

- the appropriate time for TGA to issue a consolidated list of questions;
- an appropriate upper time limit for responses to be provided by sponsors;
- the processes and opportunities for negotiations and clarification of issues during the response time;
- the handling of supplementary data. One option is that such data be supplied at the same time as the sponsor's response to the consolidated list of issues (section 31 questions);
- whether the preliminary draft evaluation reports should be provided to the sponsor at the same time as the consolidated list of section 31 questions;
- the means for distinguishing supplementary data from responses to the consolidated list of section 31 questions. For example, any new, complete studies and any data not directly related to questions asked would be regarded as supplementary data; and
- whether this approach is likely to reduce overall evaluation time (or streamline the process to the advantage of both sponsors and the TGA).

C. International precedent in relation to additional information and data

Europe - EMEA

4.23 The Committee for Medicinal Products for Human Use (CHMP) considers a preliminary assessment report and identifies any outstanding issues the applicant should address. A consolidated list of questions detailing “major objections” and/or “other concerns” is sent to the applicant together with the CHMP recommendation and scientific discussion by no later than day 120 (being 120 calendar days after the commencement of the process). The clock is stopped at this point. The applicant would normally be expected to respond within the timeframe agreed by the CHMP not exceeding 6 calendar months from the date of receiving questions. At calendar day 180 the clock is stopped again if there is a need for an oral explanation by the applicant. The time limit is suspended for the time allowed to the applicant to prepare an oral explanation (not longer than 1 calendar month).

United States - FDA

- 4.24 As noted in the previous Chapter, the CDER determines within 60 days whether an application is acceptable and if substantive or voluminous data needs to be submitted within this time. In this case, the 180 day evaluation period (inclusive of the 60 day review period) will restart.
- 4.25 In order to allow applicants to submit supplements early in the review period, the FDA notifies the applicant of easily correctable deficiencies. Additional information does not stop the review clock.
- 4.26 Requests for substantive information are in the format of a formal letter and the time to respond is decided by the director of the division making the request. The FDA may not extend the period by more than 180 days. A Ninety Day Conference is convened for sponsors to meet with the agency and reviewing officials to advise on progress and status and to identify deficiencies. An End of Review Conference may be convened if deemed necessary at the time.

Canada - TPD

- 4.27 No legislated time limits exist for review of submissions in Canada. If deficiencies are identified during initial screening, the sponsor will be given 45 calendar days to respond. After receipt of the requested information a new screening period (55 calendar days) recommences.
- 4.28 Canada also uses “clarifaxes” to request information. The purpose of a “clarifax is to expand on, add precision or to re-analyse existing information. The TPD uses this mechanism as frequently as possible. Response to these requests must be submitted within 15 calendar days.

Review will not be interrupted if a complete response is submitted within the given timeframe. Clarifaxes do not contain requests for new clinical and/or preclinical data including new bioavailability data not previously submitted. Substantive data deficiencies are notified to the applicant via a “Notice of Deficiency”. Only one “Notice of Deficiency” is issued per submission and applicants are given up to 90 calendar days to respond (and if a sponsor does not respond within the timeframe the application may be treated as being withdrawn).

CHAPTER 5: ADEC PROCESS

A. Background

- 5.1 The Australian Drug Evaluation Committee (ADEC) is a statutory committee that provides independent advice to the Minister for Health and Ageing or the TGA. ADEC's composition and terms of reference enable it to make medical and scientific recommendations relating to applications referred to it by the Minister or the TGA.
- 5.2 ADEC's core membership consists of eminent medical practitioners, and pharmaceutical scientists or pharmacologists. The particular expertise of associate members is drawn on as appropriate to the applications under consideration. ADEC is also supported by the Pharmaceutical Subcommittee (PSC) and the Adverse Drug Reactions Advisory Committee (ADRAC).
- 5.3 All NCEs and significant extensions of indications are referred to ADEC for advice, as are applications where there is disagreement between the sponsor and the TGA. The total number of submissions reviewed by ADEC is approximately 10% of all Category 1 and 2 applications.

B. Current ADEC processes and timeframes

- 5.4 The ADEC phase starts with the completion of all evaluations and finishes with the confirmation of ADEC resolutions.
- 5.5 The ADEC phase comprises:
- the Delegate's proposed action;
 - sponsor consultation and the sponsor's pre-ADEC response;
 - preparation of the agenda for the PSC and ADEC meetings;
 - the PSC meeting;
 - the ADEC meetings; and
 - ADEC resolutions and minutes. ADEC Resolutions are sent to the sponsor 5 working days after the ADEC meeting.
- 5.6 ADEC normally meets 6 times a year (2 consecutive days in February, April, June, August, October and December). The ADEC phase generally takes up to 80 working days.
- 5.7 All positive ADEC recommendations are published in the Commonwealth of Australia Gazette and are listed on the TGA website.

The ADEC minutes are also provided to a number of other regulatory agencies.

C. Issues and options for consideration

5.8 As ADEC operates on a two monthly cycle, there is little capacity for reduction in time in the overall process. Minimum time has already been allocated for preparation of evaluation reports and overviews, response times for sponsors (10 days) and preparation and distribution of agenda (which comprise a very large quantity of data provided to ADEC members on DVD or several CDs).

5.9 Recognising that there may be limited capacity to reduce timeframes for the ADEC phase, consideration has been given to means by which the ADEC process could be improved to better meet the needs of industry, consumers and the TGA.

5.10 Some of the options for consideration that have been identified by the Working Party (and by the TGA) include the following.

(a) Provision of sponsor/industry advice to ADEC

5.11 Currently sponsors have an opportunity to provide information to ADEC through the pre-ADEC response to the evaluation.

5.12 One issue that has been raised by industry is whether this should be supplemented by enabling industry to provide additional information directly to ADEC.

5.13 Some options for consideration include:

- sponsor attendance at ADEC meetings. For example, if a sponsor was having an application considered by ADEC, they could:
 - be available to respond to any specific questions ADEC has regarding the sponsor's application. If this approach were adopted, consideration would need to be given by the sponsor to ensuring that the most appropriately qualified expert was available to respond to the questions of ADEC;
 - be present during ADEC discussion of their item. The major disadvantage of this approach is that it may be seen to constrict the open and robust discussion of ADEC members which is seen as one of the strengths of the ADEC process;
 - make a 10 minute presentation to ADEC on the application. No new data would be allowed to be presented but clarification may be provided on issues included in the submission. While industry would have the opportunity to present on any application, it is likely that industry would only

choose to do so for contentious issues. This may assist in ensuring that any queries that ADEC has are answered and that relevant information is available to ADEC. However, this would also be likely to extend the time taken by ADEC to consider matters.

This approach is consistent with the practice recently adopted by the Pharmaceutical Benefits Advisory Committee (PBAC) whereby industry is permitted to make a presentation to PBAC for a maximum of 10 minutes and PBAC may also ask questions. Industry is not permitted to be present during PBAC discussion of the item;

- industry representation on ADEC. The major disadvantage of this approach is that it may be difficult to identify an industry representative who is able to participate on ADEC and who would not have a conflict of interest in relation to applications considered. This approach would also be unlikely to facilitate provision of expert comment on specific applications to ADEC (as the options above achieve) because the industry representative will not have knowledge on specific applications (and if they did there may be a conflict of interest). Further, it has been noted that ADEC is an expert advisory committee rather than a representative body (and is not a decision making body). Industry representation on ADEC may also create negative perceptions in the broader community and has the potential to undermine the independence of ADEC.

(b) Provision of consumer advice to ADEC

5.14 In relation to consumer input to ADEC, a pilot project was trialed a number of years ago whereby the Consumers' Health Forum (CHF) was advised of applications being considered by ADEC and invited to make a submission to ADEC that was provided to ADEC along with other submissions made including the sponsor's submission. Due to industry confidentiality concerns, the amount of information provided to CHF was limited, there was limited capacity for CHF to consult with members and the response time was very short. As such it was challenging for CHF to provide meaningful comment on applications.

5.15 Options for consideration in terms of increasing consumer input to ADEC include:

- re-activating the process whereby CHF provide comment to ADEC on applications. Further advice would need to be sought from both CHF and sponsors regarding lessons learned from the trial including the advantages and disadvantages of such an approach; or
- including a consumer representative on ADEC in order to provide expert comment about relevant consumer issues and concerns. As

noted above in relation to industry representation on ADEC, one of the issues for consideration is whether consumer representation is appropriate on ADEC recognising that ADEC is an expert committee rather than a representative body (and is not a decision making body).

D. International precedent in relation to input into Expert Committees

Europe - EMEA

- 5.16 The EMEA peer review evaluation system works through a network of European experts made available to the Agency by the national competent authorities of the 25 European Union Member States and of the 3 EEA-EFTA States (Iceland, Liechtenstein and Norway). These experts serve either as members of the EMEA scientific committees, of the working parties or as part of the scientific assessment teams.
- 5.17 The CHMP has a total of 32 members and a chairman. Each of the 25 EU Member States nominates one member and one alternate, after consultation with the EMEA Management Board. In addition, each of the EEA-EFTA States (Iceland, Liechtenstein and Norway) nominates a member and an alternate. The Committee has also co-opted an additional 5 members with specific areas of complementary expertise.
- 5.18 The CHMP largely consists of expert Regulators rather than external experts (as is the case for ADEC). The CHMP may invite companies to answer questions from the Committee but companies are not represented on the Committee itself, nor are they routinely present for the detailed Committee discussion of their particular application.

US - FDA

- 5.19 The FDA Advisory Committees operate quite differently to ADEC or the committees of the EMEA. Advisory committees may provide the FDA with independent opinions and recommendations on new drugs and on FDA policies.
- 5.20 By contrast to ADEC, the FDA Committees often review major policy issues or issues of interest to the public rather than individual applications for marketing authorisation. In general, the meetings provide a forum for discussing a topical issue and to air issues that are controversial and complex.
- 5.21 Consistent with the different purpose of the meetings, the composition of the committees and the committee processes differ significantly to those of ADEC. Each FDA Advisory Committee comprises a Chair, several members, plus a consumer and patient representative and in most cases an industry representative. Additional experts with specialist knowledge may be added to individual meetings as needed. Committees are

required to dedicate a minimum of 60 minutes of each meeting to "open public comment" and the public is invited to appear before the committee.

Canada - TPD

5.22 The TPD has established a wide range of expert advisory committees to provide ongoing medical, technical and scientific advice and recommendations on regulatory issues for drugs and medical devices in specific therapeutic areas or classes.

5.23 For example, Scientific/Expert Advisory Committees currently exist in relation to the following subject matters:

- Anti-infective therapies;
- Bioavailability and bioequivalence;
- HIV therapies;
- Human reproductive therapies;
- Medical devices used in cardiovascular system;
- Metabolic and endocrine therapies;
- Musculoskeletal therapies;
- Neurological therapies;
- Oncology therapies; and
- Pharmacovigilance.

5.24 Like the committees of the US FDA, the Canadian Advisory Committees provide advice on a wide range of policy issues including the development of standards and issues arising from post-market surveillance activities as well as on issues arising directly from sponsor's drug submissions.

5.25 In addition, the TPD uses ad hoc scientific/expert Advisory Panels to provide medical, scientific and technical advice and recommendations on specific drug and medical device issues. Advisory Panel meetings are open to the public and generally the first day of the meeting includes presentations from TPD and manufacturers and time is set aside for Panel members to hear from members of the public. The second day is generally held in camera for Panel members to deliberate on what they heard and to prepare advice based on the questions posed to them by TPD.

5.26 A key difference between the US, Canada, Europe and Australia is the comparative availability of relevant experts to sit on committees in these larger countries and the resources available to conduct public hearings.

CHAPTER 6: TRANSPARENCY

A. Background

- 6.1 Currently the TGA publishes in the Australian Government Gazette (and on the TGA website) the positive recommendations of ADEC. For example:

The 238th (2005/1) meeting of the Australian Drug Evaluation Committee (ADEC) (3-4 February 2005) resolved to advise the Parliamentary Secretary to the Minister for Health and Ageing and the Secretary, Department of Health and Ageing that the following medicines should be approved for registration, subject to the resolution of all outstanding matters to the satisfaction of the Committee and the Therapeutic Goods Administration. These recommendations for approval may be subject to specific conditions.

- 6.2 The notice then lists those drugs that have been approved, the sponsor of the drug and a brief statement on, for example, the new indication, the new fixed combination, the change in patient group and new route of administration.

B. Issues and options for consideration

- 6.3 One of the issues that a number of stakeholders have raised is whether there are any means by which the TGA can increase the level of transparency of decision making while still ensuring appropriate protection of confidential commercial information.
- 6.4 Some of the suggestions that have been made include the following.
- Publishing a list of applications for registration received by the TGA and under evaluation. This list could, for example, comprise the name of the medicine and the indications. A similar approach has recently been adopted by the Australian Pesticides and Veterinary Medicines Authority in relation to applications for registration of a new chemical product. This does, however, have ramifications for sponsors as the publication of such a summary would alert the market place to the application being made by the sponsor well in advance of registration actually being granted by the TGA. On the other hand it could equally be argued that publishing at the 'application received' stage would allow time for more informed consumer input to the ADEC processes (should this approach be adopted – as discussed in the previous chapter). Consideration would also need to be given to issues such as: at what point the information would be published; what information should be published and what the resource implications are for the TGA and industry.
 - Publishing edited or summarised minutes of ADEC or the full resolutions of ADEC in relation to each application for registration

(excluding confidential commercial information and excluding negative resolutions). One of the issues for consideration is whether this is appropriate recognising that ADEC is an advice giving body and not the final decision maker in relation to the registration of products.

- Publishing a summary of the decision made by the TGA delegate and the rationale for that decision (excluding reference to any confidential commercial information). This could for example, include a copy of the TGA's approval letter that is sent to the sponsor and could also include edited copies of evaluation reports (to remove trade secrets).

Some of the issues for consideration include;

- what would be included in such a summary. For example, should this include only the covering letter sent to the sponsor approving the medicine or also the provisional ARTG record, CMI, PI, standard conditions of registration and particular conditions of registration;
 - whether edited copies of the evaluation report should be published;
 - when such information should be published. For example, the TGA's letter approving the medicine could be published at the time the decision is made and edited copies of the evaluation report could be provided some months later (as is the case with the FDA – refer discussion below);
 - whether a summary would be published in the event that the TGA rejects an application for registration (it is not anticipated that this would occur); and
 - the resource implications for the TGA and industry in preparing such a summary.
- Publishing CMI and/or PI (or linkages to same) on the TGA website at the time of the approval (or direction on how to electronically access up to date CMI and PI). Currently the TGA website does not include any CMI or PI and while many CMI are published by other web-based services there does not appear to be a single source of all CMI and PI. Through a separate process the TGA has been exploring means for improving consumer and health professional's access to up to date web-based CMI and PI. One of the options being explored is including CMI and PI on the TGA website or including links to such information through the TGA website. For more information on this issue please contact the TGA – a Discussion Paper on the issue may also be accessed from the TGA website.

6.5 Some of the advantages of increasing the transparency of the TGA's processes may include the following:

- increasing the awareness of, and confidence in, the TGA's regulatory processes. The decisions made by the TGA are complex risk based assessments. Appropriate disclosure of relevant information may assist all stakeholders to better understand the processes that underpin the approval of medicines in Australia;
- providing additional information to those with particular interests and concerns regarding the medicines that they take. While many people will be satisfied with the level of information provided by a health professional or through the CMI provided with the medicine, others may wish to access more detailed information about a particular product; and
- alignment with international practice (particularly that of Europe and the US) and other Australian public health regulators including for example Foods Standards Australia New Zealand and the Gene Technology Regulator.

6.6 Issues for consideration in the context of any of these options include:

- the benefits likely to be achieved balanced against the likely increase in costs to the TGA and sponsors;
- implementation timeframes. If any of these options were preferred, what would be the timeframe for implementation, recognising that work would need to be undertaken by both the TGA and the sponsor in order to implement the changes?
- the nature of information that would be protected as confidential commercial information (and the process for determining such information to be confidential commercial information); and
- the timeframe for publishing any information on the web. For example, at what point would an application be noted on the web or the ADEC minutes or resolutions made available or the TGA's decision published?

C. International precedent

US - FDA

6.7 The FDA publishes very detailed information about decisions made by the FDA. This includes, for example, advisory committee transcripts, enforcement reports, regulatory notices, and product approvals.

- 6.8 The FDA includes on their website full meeting transcripts (and all agenda and meeting papers) for all advisory committees that consider product applications. The FDA also publishes copies of evaluation reports (edited to exclude confidential information), information about decisions made on applications, labeling information, weekly enforcement reports that contain information on actions taken in connection with agency regulatory activities and a searchable database of warning letters issued to individuals and companies for regulatory breaches and any replies to the warning letters (excluding commercial information and personal information).

Europe - EMEA

- 6.9 Since 1 April 2001, the EMEA has been publishing CHMP opinions on initial applications for Marketing Authorisation.
- 6.10 The Summary of Opinion details the CHMP's opinion about the approval of a drug expressed as either a positive opinion or a negative opinion. In the case of a positive opinion, information provided includes the benefits of the product, common side effects, approved indications and the view of the CHMP that, on the basis of quality, safety and efficacy data submitted, the CHMP considers that there is a favourable benefit to risk balance for the product and therefore recommends the granting of the marketing authorisation.
- 6.11 In the case of a negative opinion, the information provided includes the grounds for refusal of the marketing authorisation and a statement that, on the basis of the quality, safety and efficacy data submitted, the CPMP considers that there is an unfavourable benefit to risk balance for the product and that the CHMP therefore cannot recommend the granting of the market authorisation.
- 6.12 Following adoption of the CHMP opinion, the Summary of Opinion is sent to the applicant for information and posted on the EMEA website.
- 6.13 Once the Commission Decision is issued, the Summary of Opinion is deleted from the EMEA website and replaced by the European Public Assessment Report (EPAR).
- 6.14 EPARs reflect the scientific conclusion reached by the CHMP at the end of the centralised evaluation process and provide a summary of the grounds for the CHMP opinion in favour of granting a marketing authorisation for a specific medicinal product. EPARs are made available by the EMEA for information to the public, after deletion of commercially confidential information.

Canada - TPD

- 6.15 The Health Canada website includes detailed records of proceedings of Advisory Committee meetings as well as a drug product database. The drug product database contains product specific information on drugs approved for use in Canada. The database is managed by Health Canada and includes human pharmaceutical and biological drugs, veterinary drugs and disinfectant products. It contains approximately 24,000 products which companies have notified as being marketed. Information available in the database includes the following parameters: Brand Name, Drug Identification Number, Company, Ingredient(s), Route of Administration, Pharmaceutical Form, Package Sizes, Therapeutic Classification (AHFS and ATC), Active Ingredient Group (AIG) Number, Pharmaceutical Standard and Veterinary Species.
- 6.16 Health Canada also regularly publishes "Notices of Compliance". A Notice of Compliance is a notification issued by Health Canada indicating that a manufacturer has complied with relevant provisions in the Food and Drug Regulations with respect to approval of a product. The listings for a given product include: product name; manufacturer; active ingredients; date of issue; Drug Identification Number (DIN); and therapeutic class of the product.
- 6.17 On the basis of the research undertaken to inform this Discussion Paper, it does not appear that Health Canada publish reasons for decisions on particular applications (as does the EMEA and FDA).

CHAPTER 7: OPPORTUNITY FOR COMMENT

- 7.1 This Discussion Paper has raised a number of issues and options for discussion and consideration.
- 7.2 The TGA is keen to receive your comment on these issues and options. The TGA is also keen to receive your advice on any other issues that you consider warrant consideration in the context of examining means by which to improve the DSEB processes and practices so that they better reflect the modern work practices of stakeholders.
- 7.3 When providing comments, either through public forums proposed in Sydney and Melbourne (please refer to the TGA website for details) or through a written submission, please bear in mind the objectives of this review (as detailed in Chapter 1).