
Workflow Practices within the Drug Safety and Evaluation Branch

A Report to the Therapeutic Goods
Administration

Prepared by mpconsulting

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[Note: Attachment A of the web version of the report has been removed pending clarification of issues concerning confidentiality. Similarly, in the main report, comments by stakeholders have been de-identified.]

GLOSSARY OF TERMS AND ACRONYMS USED

ADEC	Australian Drug Evaluation Committee
AEP	Application Entry Process
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
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)
CMI	Consumer Medicine Information
DSEB	Drug Safety and Evaluation Branch of the TGA
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
FDA	Food and Drug Administration (US)
NCE	New Chemical Entity
PBAC	Pharmaceutical Benefits Advisory Committee
PI	Product Information
PSC	Pharmaceutical Sub-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)

BACKGROUND

Context

The Therapeutic Goods Administration (TGA) requested mpconsulting to develop options around improving the business practices of the Drug Safety and Evaluation Branch (DSEB) of the TGA based on the considerations of a Working Group formed in 2002.

The TGA requested mpconsulting to:

- develop a Discussion Paper on appropriate DSEB workflow processes for the receipt and evaluation of applications;
- conduct further consultations with industry and consumer stakeholders based on the Discussion Paper; and
- develop a report including recommendations on the implementation of the proposals in Australia and/or as part of the implementation of the trans-Tasman arrangements.

mpconsulting identified (and the TGA endorsed) the following objectives for the review:

- identifying opportunities for improving the current pre-market workflow processes within the DSEB¹ so that the processes better reflect the modern work processes of relevant stakeholders;
- exploring any means by which processes can be streamlined to better meet the needs of stakeholders;
- providing greater capacity for planning by the TGA (including enabling better planning and more efficient allocation of resources within the TGA); and
- improving the transparency of the TGA's decision-making processes for the benefit of both industry and consumers.

¹ During consultations to inform this review there was some confusion regarding whether the review (and recommendations) apply to all medicines assessed by DSEB or only prescription medicines. The TGA has agreed that the review applies to all matters considered by DSEB including both prescription medicines and non-prescription medicines evaluated by the DSEB (as listed in Schedule 10, Part 1 of the TG Regulations).

Discussion Paper

After reviewing current DSEB practices, international practice, and the work of the 2002 Working Group, and undertaking internal discussions with TGA staff, mpconsulting prepared a Discussion Paper.

The purpose of the Discussion Paper was to provide a basis for discussions with stakeholders about possible means by which to:

- streamline processes for evaluation, by the DSEB, of prescription and non-prescription medicines; and
- increase transparency of decision-making.

The Discussion Paper identified four areas of the business process for consideration:

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

In relation to each area, the Discussion Paper explained the current practices, options for future practices and the advantages and disadvantages of each option. The Discussion Paper called for stakeholder comment on the options proposed, and also on any other options for improving processes.

The Discussion Paper was posted on the TGA website on 2 November 2005 and direct mailed to key stakeholders (by the TGA). Stakeholders were given until 20 January 2006 to provide any written comments on the Discussion Paper.

A total of 9 submissions were received. Attachment A details the organisations and individuals who provided a submission, and the key points made by each.

Public Forums

Stakeholders were also invited to attend forums in Sydney on 24 November 2005 and in Melbourne on 28 November 2005. Approximately thirty people attended the forum in Sydney and twelve people attended the forum in Melbourne.

EXECUTIVE SUMMARY

On the basis of responses at the public forums and the written submissions made on the Discussion Paper, there was strong support for this initiative and for most of the options detailed in the Discussion Paper. A number of submitters also made additional suggestions for improving the DSEB processes and increasing transparency.

The recommendations detailed below are based on a consideration of:

- the preferred approach identified by stakeholders (both industry and consumer);
- international precedent (and the desirability, where possible, of consistency); and
- mpconsulting's analysis of the maximum return (against the objectives of the review) for minimum increase in costs (to both the TGA and industry).

It is expected that each of the recommendations will require detailed consideration by the TGA, particularly in terms of the necessary changes to practice that would be required, and the cost implications.

Recommendation 1 – Application Entry Process (AEP)

It is recommended that the TGA replace the existing AEP for Category 1 and 2 applications with a new AEP as follows:

- the sponsor would provide prior notification to the TGA of their intention to lodge an application. Prior notification would:
 - be provided a minimum of 3 months prior to submission and a maximum of 12 months prior to submission; and
 - address key aspects of the application including, for example;
 - the legal basis for the application (for example, the category of the application);
 - important administrative matters (for example, the priority of the application); and
 - a summary of relevant data (for example, the draft table of contents, identification of overseas reports etc).
- if necessary, a pre-submission meeting² would be held to ensure that all required data will be included in the application, and to identify any data deficiencies. Outcomes of the meeting would be documented, and

² A pre-submission meeting would be unlikely to be necessary in the majority of cases. A pre-submission meeting could be held at the request of the sponsor (with the agreement of the TGA) or at the request of the TGA.

sponsors would be expected to address, in their application, any commitments made in the meeting. If not, reasons would be expected to be provided;

- one month prior to submission, the sponsor would confirm the proposed week of submission (or any change to the proposed date for submission);
- at the time of submission of the application, the sponsor would also submit a checklist confirming that all relevant information has been included in the application;
- the DSEB screening time would be reduced from 40 working days to 10 working days (for both Category 1 and Category 2 applications); and
- the current process for sponsors to discuss, with the TGA, the development of new chemical entities or biological products (Scientific Advice meetings) would be retained.

This process offers a number of benefits to both sponsors and the TGA including alerting the TGA to likely submissions (enabling resource planning), imposing greater discipline on sponsors for ensuring submissions are appropriate, and reducing the timeframe for the AEP.

It should be noted that while this approach was broadly supported by industry, most industry submitters suggested that this new process should be in addition to the existing process and that sponsors should have the option of choosing which process suits them best. However, it is considered that this has the potential to increase confusion, complicate reporting of evaluation times by the TGA, and increase required TGA resources.

Recommendation 2 - Additional information and data

It is recommended that:

- the current rolling section 31 questions be replaced with a consolidated list of section 31 questions being sent to the sponsor at a pre-determined time. Subject to TGA consideration of practical issues, it is suggested that:
 - the consolidated set of questions could be sent, at the latest, at day 135 of the evaluation (noting that questions should be sent before this time if they are ready);
 - sponsors should be provided with a maximum of 6 months to respond to the questions; and
 - further questions may be put to the sponsor where they relate to the original consolidated list of questions and are not “new” questions.

- the above reform be accompanied by measures to improve coordination of evaluation start times within the TGA;
- ongoing communication between the TGA and sponsors would be encouraged with a view to resolving questions informally (without stopping the clock). This should streamline processes and ensure that only major issues are included in the consolidated list of questions; and
- the current approach to additional and supplementary data be retained (noting that data that is supplied in response to the consolidated section 31 questions would not be considered to be supplementary data).

While there is broad industry support for this approach, it is unlikely to result in an overall reduction in evaluation time. However, it is considered that this approach would streamline the process, would better align with international practice, and would provide greater certainty for sponsors.

Recommendation 3 – Australian Drug Evaluation Committee (ADEC) process

It is recommended that:

- TGA consider reducing the number of applications that are routinely provided to ADEC. For example, it is suggested that ADEC could consider only:
 - NCE applications or major extension of indications applications (for example, where the application is the first in its class); and
 - applications for which there has been a negative recommendation.

It is understood that the TGA is already intending to reduce the number of applications provided to ADEC, from mid-2006.

- Sponsors be provided with the opportunity to be available to answer any questions raised by ADEC members. It is not proposed that the sponsor would make a presentation to ADEC nor that they would be present for ADEC discussion about the application. If adopted, it is important that this initiative does not unduly increase ADEC timeframes (or increase ADEC costs).
- A process be adopted to enable consumer involvement in the ADEC process (noting the importance of ADEC as an advisory body to the TGA).

Recommendation 4 - Transparency

It is recommended that the TGA increase the level of transparency and the information available to the public by:

- publishing the TGA Delegate’s decision (and the rationale for the decision) on the TGA website. It is suggested that this could:
 - include a summary of the ADEC advice to the Delegate;
 - be modeled on the European Medicines Agency (EMA) “Abstract” that is included on the EMA website; and
 - be published once all avenues for review have been exhausted.
- subject to the outcomes of the separate review of consumer access to CMI and PI, making the CMI and PI available on the web.

Recommendation 5 – Implementation

It is noted that the capacity to achieve a more streamlined process, and greater transparency, will depend to a large extent on:

- resources within the TGA;
- the commitment of both industry, and the TGA, to the reforms;
- changes to internal TGA processes to support the proposed reforms; and
- improved IT capacity, noting that electronic communication, tracking of information and provision of information to ADEC all assist in streamlining processes.

Should the recommendations be accepted by the TGA, it is further recommended that:

- the TGA continue to consult with industry and consumer representatives as the TGA implements the recommendations. Issues that will require consideration include:
 - the matters that must be addressed in a prior notification to the TGA of a sponsor’s intention to lodge an application. Some suggestions have been made by [a stakeholder] in their submission to this review (including a template “Pre-Evaluation Notification of Intent to File”). However, further advice is needed from TGA regarding the information required at this early stage in order to enable the TGA to plan resources (and hence derive a benefit from this process);
 - the matters to be addressed in a checklist to be completed at the time of submission. Again, a suggestion has been made by [a stakeholder], but further advice from TGA is needed regarding what should be included in the checklist to enable the TGA to complete the AEP in a much shorter period (reduced from 40 to 10 working days);

- any agreed recommendations be implemented no later than the commencement of the trans-Tasman Agency. It is also recommended that information/education sessions be provided to both consumers and industry prior to the introduction of the new processes; and
- a review of the success of the new approach be undertaken 12 months after implementation.

Other

A number of submitters also made other suggestions for consideration by the TGA, but these have not been considered in detail by mpconsulting. The TGA may, however, wish to consider these issues further:

- Expressing existing timeframes in calendar days rather than working days (mainly to align with international practice). This was a very strong recommendation made by a number of submitters who noted that it is difficult to compare processing times between countries when the number of days taken are expressed differently. It is noted that even if the TGA commenced reporting in calendar days there may still be difficulties making direct comparisons with other countries noting the different processes operating in different countries.
- Assigning a Project Manager to all applications. It was suggested that this would provide each applicant with a contact point for information on the progress of their application. While this would appear to be desirable, it is suggested that there may be significant costs associated with such an initiative. It was also suggested that additional information on the progress of applications could be included as part of the existing on-line service. It was not clear what additional information would be sought. The TGA may also wish to consider providing further education to stakeholders about the existing service, in order to encourage its utilisation.
- Extending priority assessment to include existing drugs which offer major clinical benefit in different indications (and formally establishing reduced timeframes). On the basis of discussions with the TGA, it was confirmed that the priority criteria apply to new substances only, and not to extensions of indication (and that this is also the case internationally). However, the TGA has indicated that it works with industry to expedite review if there is a potential major public health benefit associated with a proposed extension of indication.

CHAPTER 1: APPLICATION ENTRY PROCESS

A. Current TGA process and timelines

Pre-submission meetings

Currently, pre-submission meetings are not a regulatory requirement but are strongly encouraged by the TGA. 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.

Application Entry Process (AEP)

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. This AEP is designed to ensure that seriously 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.

During the AEP, the submission is assessed to ensure that:

- it complies with TGA format requirements as currently set out in the Australian Regulatory Guidelines for Prescription Medicines (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;
- 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 (PI) and the proposed Australian Consumer Medicine Information (CMI), and that these comply with the relevant sections of the ARGPM and the therapeutic goods legislation.

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.

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 in Chapter 2) in order to define the indication being sought or to substantiate that additional information will be provided in the future.

Timeframes

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. Option considered by stakeholders

The Discussion Paper circulated to stakeholders suggested that the AEP could be reformed such that:

- sponsors could provide prior notification to the TGA of their intention to lodge an application, including an application summary;
- 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;
- at the time of making the application, sponsors would complete a checklist and confirm that they have fulfilled all submission requirements (including any agreed outcomes from any pre-submission meeting);
- applications made in accordance with this process would be accepted for evaluation within 10 working days; and
- scientific advice meetings would be retained, and would be distinct from pre-submission meetings.

C. Results of consultations

Overall, stakeholders strongly supported the approach detailed above. It was noted that:

- this would align the TGA's processes more closely with those of the EMEA and the US FDA;
- the TGA would gain predictability of incoming applications, allowing for more efficient allocation of resources;
- this provides an opportunity for sponsors to address potential issues (including any administrative issues) before submission of the application, and hence greater predictability; and
- the time currently spent by the TGA filtering applications would be reduced, and would occur at an earlier point in the process.

The majority of stakeholders suggested that this new process should be in addition to the existing process, and that sponsors should have the option of choosing which process suits them best. For example, one submitter noted that having dual processes would allow sponsors to select the most appropriate option depending on the type of dossier to be considered and the work practices of a sponsor's international head office.

In relation to specific aspects of the proposals, it was suggested that:

- the pre-submission meeting should be held on an "as needs" basis, and the purpose of the meeting should be to present the dossier to the TGA, seek guidance on Australian specific issues, and to clarify administrative issues concerning the application; and
- the pre-submission meeting should not be used for evaluation purposes.

D. Recommendation and rationale

It is recommended that the TGA replace the existing AEP for Category 1 and 2 applications with a new AEP as follows:

- the sponsor would provide prior notification to the TGA of their intention to lodge an application. Prior notification would:
 - be provided a minimum of 3 months prior to submission and a maximum of 12 months prior to submission;
 - address key aspects of the application including, for example;

- the legal basis for the application (for example, the category of application);
 - important administrative matters (for example, the priority of the application); and
 - a summary of relevant data (for example, the draft table of contents, identification of overseas reports etc).
- if necessary, a pre-submission meeting³ would be held to ensure that all required data will be included in the application, and to identify any data deficiencies. Outcomes of the meeting would be documented, and sponsors would be expected to address, in their application, any commitments made in the meeting. If not, reasons would be expected to be provided;
 - one month prior to submission, the sponsor would confirm the proposed week of submission (or any change to the proposed date for submission);
 - at the time of submission of the application, the sponsor would also submit a checklist confirming that all relevant information has been included in the application;
 - the DSEB screening time would be reduced from 40 working days to 10 working days (for both Category 1 and Category 2 applications); and
 - the current process for sponsors to discuss, with the TGA, development of new chemical entities or biological products (Scientific Advice meetings) would be retained.

This process offers a number of benefits to both sponsors and the TGA, including alerting the TGA to likely submissions (enabling resource planning), imposing greater discipline on sponsors for ensuring submissions are appropriate, and reducing the timeframe for the AEP.

While this approach was broadly supported by industry, most industry submitters suggested that this new process should be in addition to the existing process, and that sponsors should have the option of choosing which process suits them best. However, this is not recommended as it has the potential to increase confusion, complicate reporting of evaluation times by the TGA, and increase TGA resources.

It will be important that clear guidance be provided to industry regarding what should be included in the initial notification. This information should be detailed enough to provide the TGA with a clear understanding of the nature of the application, the likely category of application, the priority of the application and the data expected to be provided in support of the application. This will enable the TGA to ensure that appropriate resources are available

³ A pre-submission meeting would be unlikely to be necessary in the majority of cases. A pre-submission meeting would be held at the request of the sponsor (with the agreement of the TGA) or at the request of the TGA.

when the application is lodged. This should also assist in aligning evaluation start times (so that all evaluations start at approximately the same time).

It is also important that guidance be developed on the matters that should be addressed in the “checklist” that is submitted at the time of submission. This must be sufficiently detailed (and the information included in it sufficiently reliable) to allow the required reduction in the initial assessment time for the TGA.

CHAPTER 2: ADDITIONAL INFORMATION AND DATA

A. Current processes

Informal requests

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.

Section 31 requests

In addition, section 31 of the *Therapeutic Goods Act 1989* (the TG Act) provides that the TGA may, by notice in writing given to the applicant, require the applicant 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, composition, design specifications, presentation and/or 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 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.

Currently, evaluators in each evaluation area send out section 31 requests for further information at the time that the need for such information is identified. This results in a number of section 31 requests being issued 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.

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.

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.

For applications received in 2003/04, section 31 questions were asked during the AEP in 26% of cases. During the evaluation phase, 92% of submissions relating to New Chemical Entities (NCEs) 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.

Additional and supplementary data

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

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 includes non-clinical data (Module 4) or clinical data (Module 5) submitted at the initiation of the sponsor. It requires evaluation, as it is intended to address any possible or perceived deficiencies that may be identified in a primary evaluation report received by the sponsor.

Supplementary data may be submitted after a sponsor has received either or both of the Module 4 and 5 Evaluation Reports. Supplementary data is not accepted by the TGA after commencement of the pre-ADEC process. Acceptance of supplementary data is at the discretion of the TGA, and a clock stop is dependent on mutual agreement.

B. Options considered by stakeholders

The Discussion Paper noted that one alternative option for managing TGA questions is specifying set times for formal questions and responses.

For example, after a maximum of 135 days of evaluation, the TGA could 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, and the TGA would evaluate the response.

C. Results of consultation

On the whole, stakeholders agreed with the advantages and disadvantages of the current approach as set out in the Discussion Paper. The main advantages of the current approach are that a request for information is made as soon as the need for the information is identified, and in many cases the

evaluation process is continued on other aspects of the application while evaluators are awaiting a section 31 response (avoiding unnecessary delays). The main disadvantage (as communicated by industry stakeholders) is that this limits the capacity of sponsors to use global teams to respond to questions at a known point in time. Some submitters also suggested that transparency of evaluation timeframes is jeopardised because evaluators continue to work on applications while the clock is stopped and another area is awaiting a response to questions.

The proposed alternative approach (a consolidated set of questions at a set point in time) received support from the majority of submitters.

It was noted by some stakeholders that:

- the evaluation reports should be sent at the same time as the consolidated set of questions. It was suggested that this would ensure that the sponsor was aware of any major concerns with the application in a timely manner, and not after responses to the consolidated list of questions had been submitted by the sponsor;
- it would be helpful for a draft of the Delegate's overview to be sent at the same time as the consolidated set of questions;
- the maximum timeframe should not preclude a formal list of questions being provided to the sponsor at an earlier point in the evaluation process;
- where a major clinical question is asked, requiring collection of new data that will take more than 6 months to obtain, a sponsor should not be required to withdraw the application (or have it rejected), unless the need for the data was flagged at a pre-submission meeting or as part of an AEP;
- sponsors should be provided with a maximum of 6 months to respond to the questions (some submitters suggested that 3 months was adequate provided that there was capacity to extend this by a further 3 months);
- the TGA should have the option of putting further questions to the sponsor provided they relate to the original consolidated list of questions and are not "new" questions; and
- the current practice of raising informal questions during the evaluation should remain.

One submitter also suggested that an alternative approach would be for each evaluation area to issue a consolidated list once they have finished the evaluation.

D. Recommendation and rationale

It is recommended that:

- the current rolling section 31 questions be replaced with a consolidated list of section 31 questions being sent to the sponsor at a pre-determined time. Subject to TGA consideration of practical issues, it is suggested that:
 - the consolidated set of questions could be sent, at the latest, at day 135 of the evaluation (noting that questions should be sent before this time if they are ready);
 - sponsors should be provided with a maximum of 6 months to respond to the questions; and
 - further questions may be put to the sponsor where they relate to the original consolidated list of questions and are not “new” questions.
- the above reform be accompanied by measures to improve coordination of evaluation start times within the TGA;
- ongoing communication between the TGA and sponsors would be encouraged with a view to resolving questions informally (without stopping the clock). This should streamline processes and ensure that only major issues are included in the consolidated list of questions; and
- the current approach to additional and supplementary data be retained (noting that data that is supplied in response to the consolidated section 31 questions would not be considered supplementary data).

This approach:

- ensures predictable timeframes for requests for information;
- enables project teams to be established to address the questions raised; and
- 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).

While there is broad industry support for this approach, it is unlikely to result in an overall reduction in evaluation time. However, it is considered that this approach would streamline the process, would better align with international practice, and would provide greater certainty for sponsors.

On the issue of whether the evaluation reports should be sent at the same time as the consolidated set of questions (and/or a draft of the Delegate's overview), the TGA has indicated that this may not be practical in all circumstances. However, the TGA has indicated that where evaluation reports are available, they could be provided. Similarly, where background information is needed to enable the sponsor to respond appropriately to the question raised, the TGA would also expect to provide such information (as it currently does). Sponsors would continue to be able to contact the evaluator to seek clarification of any issues.

The maximum timeframe should 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. Open communication between the sponsor and the TGA should also be encouraged and wherever possible minor questions should be dealt with informally without a need to stop the clock.

As noted in the previous section, it was suggested that each evaluation area could issue a consolidated list of questions once they have finished the evaluation. While this may be an improvement on the current situation (where more than one set of section 31 questions may be issued by each evaluation area), this would not appear to lead to the same advantages as a consolidated list of questions across all evaluation areas.

Sponsors should also be encouraged to provide responses in less than 6 months (this should be a maximum timeframe for submission of responses to questions).

CHAPTER 3: ADEC PROCESS

A. Current practice

All NCEs and significant extensions of indications are referred to the 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.

The ADEC phase starts with the completion of all evaluations, and finishes with the confirmation of ADEC resolutions. 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
- the ADEC resolutions and minutes. ADEC Resolutions are sent to the sponsor 5 working days after the ADEC meeting.

ADEC normally meets 6 times a year, and the ADEC phase generally takes up to 80 working days.

B. Options considered by stakeholders

The Discussion Paper noted that as ADEC operates on a two monthly cycle, there is little capacity for reduction in time in the overall process. Recognising the limited capacity to reduce timeframes for the ADEC phase, the Discussion Paper identified possible means by which the ADEC process could be improved to better meet the needs of industry, consumers and the TGA.

Options detailed were as follows:

- Option A: 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; and/or be present during ADEC discussion of their item; and/or 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.
- Option B: Industry representation on ADEC.

- Option C: Reactivating the process whereby a consumer group (for example, [a stakeholder]) provide comment to ADEC on applications.
- Option D: Including a consumer representative on ADEC in order to provide expert comment about relevant consumer issues and concerns.

C. Results of consultation

In summary there was:

- Support for elements of Option A (sponsor attendance at ADEC meetings).
 - Some submitters supported the sponsor attending ADEC's discussion of the sponsor's item, others supported the sponsor having the option of making a short presentation to ADEC and others supported the sponsor being available to answer any questions that ADEC may have.
 - Some submitters supported all three sub-options.
- No support for Option B (industry representation on ADEC).
 - Most submitters agreed with the concerns detailed in the Discussion Paper which included the difficulty in identifying an industry representative who would not have a conflict of interest, and who would be able to provide expert advice on specific issues. The position may also create negative perceptions in the broader community.
- Some support for Option C (consumer input to ADEC).
 - It was suggested that it may be valuable to identify consumer groups with a specific disease focus who could be invited to provide a statement on the value, from their point of view, of individual drugs under consideration.
 - Others suggested that the [a stakeholder] pilot (whereby [a stakeholder] provided input and advice on certain applications) was a good model, and that this could be reactivated and improved.
- Support from [a stakeholder] for Option D (consumer representative on ADEC) but no support from industry.
 - [a stakeholder] noted that while this would be consistent with good practice, this option has its limitations because consultation with consumers is limited as a result of commercial-in-confidence constraints, timelines and the capacity of the consumer member.

- [a stakeholder] also noted that it would be critical for the consumer representative to be selected by a consumer group.
- Other submitters noted that, just as it is inappropriate for an industry representative to be included on ADEC, it is equally inappropriate for a consumer representative to be included (noting that ADEC is an expert Committee, and not a representative committee).
- During public forums, it was noted that there is some precedent for inclusion of consumer representatives on expert Committees (such as PBAC).

In addition it was suggested that:

- TGA consider reducing the number of applications that are routinely provided to ADEC. In particular it was suggested that all NCEs should continue to be considered by ADEC, but that ADEC should not need to consider product line extensions or new indications where all evaluation reports are positive and the Delegate's overview is positive. It was suggested that the sponsor should be able to request that an application be considered by ADEC;
- sponsors be given the opportunity to make pre-ADEC submissions on issues that relate to a class of medicines that are forwarded to ADEC for advice; and
- specialists from each of the National Health Priority Areas (eg cardiovascular health, cancer, diabetes, mental health etc) be present on ADEC when drugs from those therapeutic areas are being considered.

D. Recommendation and rationale

It is recommended that:

- TGA consider reducing the number of applications that are routinely provided to ADEC. For example, it is suggested that ADEC could consider only applications:
 - that are NCE applications or major extension of indications applications (e.g. where the application is the first in its class); and
 - for which there has been a negative recommendation.

It is understood that the TGA is already intending to reduce the number of applications provided to ADEC, from mid-2006.

- sponsors be provided with the opportunity to be available to answer any questions raised by ADEC members. It is not proposed that the sponsor would make a presentation to ADEC, nor that they would be present for

ADEC discussion about the application. If adopted, it is important that this initiative does not unduly increase ADEC timeframes (or increase ADEC costs); and

- a process be adopted to enable consumer involvement in the ADEC process (noting the importance of ADEC as an advisory body to the TGA).

On balance it is considered that:

- it is appropriate for sponsors to be available to respond to questions raised by ADEC (if any). The option of sending a person to respond to questions should rest with the sponsor, and it should not be mandatory that they do so (particularly noting that this will incur expenses and it is possible that ADEC may have no questions requiring response from the sponsor representative);
- it is not desirable for sponsors to make routine presentations to ADEC as this would increase considerably the time needed for ADEC meetings, and no real benefit has been identified;
- it is not desirable for sponsors to be present during ADEC consideration of a sponsor's item. It is considered that this may impede open and frank discussion of the item by ADEC, and may lead to increased challenges of Delegate decisions;
- it is not desirable for there to be an industry representative on ADEC. As noted by stakeholders, there would be difficulties in identifying an industry representative who would not have a conflict of interest and who would be able to provide expert advice on specific issues; and
- it would be valuable for there to be consumer involvement in the ADEC process. This could occur through a process such as the [a stakeholder] pilot or through a consumer representative on ADEC (and there is some precedent for this approach). It is important that any consumer involvement in the process is meaningful and that the role of any consumer representative (or any process for consumer input) is clear.

CHAPTER 4: TRANSPARENCY

A. Current practice

Currently the TGA publishes in the Australian Government Gazette (and on the TGA website) the positive recommendations of ADEC. 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 the new route of administration.

B. Options considered by stakeholders

The Discussion Paper suggested three different options based on suggestions that had been made to the TGA.

- Option 1: Publishing a list of applications for registration received by the TGA and under evaluation. This list could, for example, include the name of the medicine and the indications.
- Option 2: 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).
- Option 3: Publishing a summary of the decision made by the TGA Delegate, and the rationale for that decision (excluding reference to any confidential commercial information) including, for example, a copy of the TGA's approval letter that is sent to the sponsor, as well as copies of evaluation reports (edited to remove trade secrets).
- Option 4: 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).

The Discussion Paper highlighted the advantages of some of these options including:

- increasing the awareness of, and confidence in, the TGA's regulatory processes;
- providing additional information to those with particular interests and concerns regarding the medicines that they take; and
- aligning with international practice and other Australian public health regulators.

C. Results of consultation

In summary:

- Option 1 (publishing a list of applications) was supported by some but not all submitters.
 - Some submitters noted that they did not have any major objections to the publication of a list of applications received by the TGA, but they considered that the benefit in doing so was not evident.
 - One submitter strongly opposed the option, noting that it would increase both overt and covert pre-approval marketing of products, and may also give false hope to ill consumers.
- Option 2 (publishing ADEC minutes excluding confidential commercial information) was not supported by the majority of industry submitters (largely because ADEC is not the decision-making body). However, a few submitters supported the publication of ADEC minutes, noting that publishing more detail about ADEC's advice to the TGA would improve transparency.
- Option 3 (publishing a summary of the decision) was supported by the majority of submitters. A number of submitters made suggestions regarding the type of information that could be published:
 - one submitter suggested that the approval letter, provisional register record (currently the ARTG), CMI, PI, standard conditions of registration and particular conditions of registration should all be published. Another submitter queried whether conditions of registration, if published, would need to be updated as the registration commitments of the product change throughout its lifecycle; and
 - other submitters suggested that a summary of the decision made by the Delegate, and the rationale for the decision, should be published (modeled on the European EPAR). It was further suggested that it would not be practical or appropriate to provide edited copies of evaluation reports to the public because this would result in increased confusion and anxiety amongst consumers. It would also significantly increase the resources and effort in reviewing the evaluation reports to ensure the exclusion of confidential commercial information.
- Option 4 (publishing CMI and/or PI or linkages to same on the TGA website) was supported by the majority of submitters.

In addition:

- most submitters did not support the TGA publishing the full Evaluation Reports; and
- one submitter suggested that sponsors be advised which ADEC members considered each application, and which members voted which way.

D. Recommendation and rationale

It is recommended that the TGA increase the level of transparency and the information available to the public by:

- publishing the Delegate's decision and the rationale for the decision on the TGA website. It is suggested that this could:
 - include a summary of the ADEC advice to the Delegate;
 - be modeled on the European Medicines Agency (EMA) "Abstract" that is included on the EMA website; and
 - be published once all avenues for review have been exhausted.
- subject to the outcomes of the separate review of consumer access to CMI and PI, making the CMI and PI available on the web.

The rationale for publishing the Delegate's decision and reasons for his/her decision are as follows:

- This more closely aligns practice with the US FDA and the EMA. For example, the EMA publishes a 1-2 page "Abstract" which includes summary information about the product, the clinical trials, the side effects and the CHMP decision based on the quality, safety and efficacy data submitted. It is proposed that the document published by the TGA could be based on this model. For more information about international models please refer to Attachment C.
- This reinforces the role of the TGA as the decision maker. It is proposed that the summary of the decision and the rationale for the decision could include the advice of ADEC. This would contextualise the advice of ADEC and reinforce the role of ADEC as an expert advisory committee. In circumstances where the Delegate does not accept the advice of ADEC, this would be explained in the summary (therefore providing a high degree of transparency and accountability for decisions).
- This provides greater transparency about the rationale for TGA decisions, thus improving potential for increased confidence in the TGA.

It is not recommended that:

- the TGA publish on the web the list of applications received, as it is not clear what value this would add. It is also possible that this could potentially increase pressure on the Special Access Scheme for early access to the drug;
- the TGA publish ADEC minutes. This is not recommended predominantly because ADEC is not the decision-making body, and this has the potential to confuse the role of ADEC and that of the Delegate/TGA;
- sponsors be advised which ADEC members considered each application and which members voted which way. While this was a suggestion made during public forums, it is not considered that this would assist in improving transparency or confidence in the system and it may inadvertently intimidate ADEC members;
- the TGA publish the Evaluation Reports. This is not recommended because this is not considered necessary for consumer information if the important information from the Evaluation Reports forms part of the summary of the Delegate's decision, which would be published. It is not clear what additional benefit would be derived by consumers from accessing the entire evaluation report (rather than the salient points as part of a summary of the Delegate's decision); and
- the TGA publish all of the information that is currently published by the EMEA. In addition to publishing an "Abstract", the EMEA also publishes a range of other information including authorised presentations, scientific discussion, procedural steps taken before authorisation, and steps taken after authorisation and product information (including a summary of product characteristics, information about the Manufacturing Authorisation Holder, conditions of marketing authorisation, labeling and the package leaflet).

While it can always be argued that there may be merit in providing more rather than less information, in the Australian context a strong case would need to be made that the benefits of providing such information outweigh the significant costs. On the basis of the consultations undertaken to inform this review, it would appear that the key pieces of information sought by stakeholders are the TGA's decision (and rationale for it) and the PI/CMI.

CHAPTER 5: IMPLEMENTATION AND ADDITIONAL ISSUES

A. Further work to be undertaken and additional issues raised

Should the recommendations be accepted by the TGA, it is further recommended that:

- the TGA continue to consult with industry and consumer representatives as the TGA implements the recommendations. Issues that will require consideration include:
 - the matters that must be addressed in a prior notification to the TGA of a sponsor's intention to lodge an application. Some suggestions have been made by [a stakeholder] in their submission to this review (including a template "Pre-Evaluation Notification of Intent to File"). However, further advice is needed from TGA regarding the information required at this early stage in order to enable the TGA to plan resources (and hence derive a benefit from this process); and
 - the matters to be addressed in a checklist to be completed at the time of submission. Again, a suggestion has been made by [a stakeholder] but further advice from TGA is needed regarding what should be included in the checklist to enable the TGA to complete the AEP in a much shorter period (reduced from 40 to 10 working days).

As noted in the Executive Summary, a number of submitters also made other suggestions for consideration by the TGA, however these have not been considered in detail by mpconsulting.

The TGA may, however, wish to consider these issues further:

- Expressing existing timeframes in calendar days rather than working days (mainly to align with international practice). This was a very strong recommendation made by a number of submitters who noted that it is difficult to compare processing times between countries when the number of days taken are expressed differently. It is noted that even if the TGA commenced reporting in calendar days there may still be difficulties making direct comparisons with other countries noting the different processes operating in different countries.
- Assigning a Project Manager to all applications. It was suggested that this would provide each applicant with a contact point for information on the progress of their application. While this would appear to be desirable, it is suggested that there may be significant costs associated with such an initiative. It was also suggested that additional information on the progress of applications could be included as part of the existing on-line service. It was not clear what additional information would be sought. The TGA may

also wish to consider providing further education to stakeholders about the existing service in order to encourage its utilisation.

- Extending priority assessment to include existing drugs which offer major clinical benefit in different indications (and formally establishing reduced timeframes). On the basis of discussions with the TGA, it was confirmed that the priority criteria apply to new substances only and not to extensions of indication (and that this is also the case internationally). However, the TGA has indicated that it works with industry to expedite review if there is a potential public health benefit associated with the proposed extension of indication.

B. Timeframes for implementation

It is recommended that any agreed recommendations be implemented no later than at the commencement of the trans-Tasman Agency. It is also recommended that information/education sessions be provided to both consumers and industry prior to the introduction of the new processes.

A review of the success of the new approach could be undertaken after 12 months of operation.

ATTACHMENT A: WRITTEN SUBMISSIONS

[Note: Attachment A of the web version of the report has been removed pending clarification of issues concerning confidentiality. Similarly, in the main report, comments by stakeholders have been de-identified.]

ATTACHMENT B: BACKGROUND INFORMATION ABOUT THE TGA PROCESSES

The TGA Approval process

Before a prescription medicine can be supplied in Australia, it must be included in the Australian Register of Therapeutic Goods (ARTG)⁴. 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.

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) are provided to ADEC for advice. The 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 rejection has not previously been foreshadowed by the TGA, the Delegate usually offers the sponsor a further opportunity to

⁴ Subject to certain exceptions.

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

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.

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.

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

The TGA has previously targeted the following mean evaluation times, excluding time taken for applicants to respond to section 31 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.

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.

ATTACHMENT C: INTERNATIONAL PRACTICE

1. International precedent in relation to application entry processes

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

Europe - EMEA

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.

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

Canada - TPD

In Canada the Therapeutic Products Directorate (TPD) within Health Canada 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

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.

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

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

2. International precedent in relation to additional information and data

Europe - EMEA

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

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.

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.

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

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.

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).

3. International precedent in relation to input into Expert Committees

Europe - EMEA

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.

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.

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

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.

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.

Consistent with the different purpose of the meetings, the composition of the committees and the committee processes differ significantly from 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

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.

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.

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.

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.

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.

4. International precedent in relation to transparency

US - FDA

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.

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

Since 1 April 2001, the EMEA has been publishing CHMP opinions on initial applications for Marketing Authorisation.

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.

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 CHMP 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.

Following adoption of the CHMP opinion, the Summary of Opinion is sent to the applicant for information, and posted on the EMEA website.

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).

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

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, Active Ingredient Group Number, Pharmaceutical Standard and Veterinary Species.

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; and therapeutic class of the product.

It does not appear that Health Canada publish reasons for decisions on particular applications (as do the EMEA and FDA).