Pharmaceutical Benefits Scheme Post-market Reviews

Information for stakeholders

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Introduction

Post-market Reviews

Post-market reviews are a systematic and formal approach to monitoring medicines listed on the Pharmaceutical Benefits Scheme (PBS). The post-market review programme was established to achieve five main goals:

- Improved patient safety through better understanding of adverse events and medicine-related harms.
- Ensuring the ongoing viability of the PBS through targeted medicines usage and avoiding preventable wastage or inappropriate prescribing.
- A better understanding of medicines utilisation, to review intended clinical benefit and inform medicines evaluation processes.
- Ongoing cost-effectiveness, including through better management of clinical and economic uncertainty.
- Overall improvements to the quality use of medicines and education for patients and prescribers.

Applications to list a medicine on the PBS are considered by the Pharmaceutical Benefits Advisory Committee (PBAC) on a case-by-case basis at the time a submission for listing is made. This means that a medicine is only considered in the context of treatments and evidence available at that time. Over time, new medicines are listed on the PBS, more data on medicine safety and efficacy becomes available, and treatment guidelines change. As a result, the actual use or health outcomes of a medicine may be different to what was considered by the PBAC at the time of listing.

The post-market review process provides a mechanism for medicines to be considered in the full and current treatment context. This includes actual utilisation, comparative efficacy, treatment guidelines, health outcomes, and for measures to be implemented that address concerns that may have arisen, for example, improving education around medicines and their use, or revised restrictions. Post-market reviews contribute to achieving the aims of the National Medicines Policy[1], a broad framework that aims to improve health outcomes for all Australians through improving both access to and appropriate use of medicines. The four central objectives of the policy are:

- timely access to the medicines that Australians need, at a cost individuals and the community can afford;
- medicines meeting appropriate standards of quality, safety, and efficacy;
- quality use of medicines; and
- maintaining a responsible and viable medicines industry.

[1] http://www.health.gov.au/internet/main/publishing.nsf/Content/national-medicines-policy

Quality use of medicines is defined as[2]:

- selecting management options wisely;
- choosing suitable medicines if a medicine is considered necessary; and
- using medicines safely and effectively.

The definition of quality use of medicines applies equally to decisions about medicine use by individuals and decisions that affect the health of the population.

Pharmaceutical Benefits Advisory Committee (PBAC)

The PBAC has a broad statutory function under the *National Health Act 1953*, to advise the Minister for Health on any matters concerning the operation of the PBS, which includes making further recommendations regarding the safety, effectiveness and cost-effectiveness of medicines after they have been listed. Therefore, the PBAC also considers the need for, and provides recommendations on, post-market reviews.

The PBAC is an independent expert body appointed by the Australian Government, comprised of doctors, health professionals, health economists and consumer representatives. The PBAC meets three times a year, usually in March, July and November.

The PBAC is responsible for evaluating the clinical and cost-effectiveness of medicines in order to make recommendations relating to listing on the PBS. Recommendations for new listings are informed by evidence of a medicine's clinical effectiveness, safety, and cost-effectiveness ('value for money') compared with other treatments.

The PBAC has two sub-committees to assist with analysis and advice in these areas: the Drug Utilisation Sub-Committee (DUSC) and the Economics Sub-Committee (ESC).

Drug Utilisation Sub-Committee (DUSC)

The DUSC assesses estimates on projected usage and the financial cost of medicines to be listed on the PBS. It also collects and analyses data on actual use of PBS listed medicines (including in comparison with other countries). All new medicines on the PBS are routinely monitored by DUSC 24 months after listing. These analyses examine the actual use of a medicine and medicine utilisation trends in comparison to the predicted usage when recommended by the PBAC and listed on the PBS. DUSC can also analyse the utilisation of a class or category of medicine, or a group of medicines that are used to treat a particular condition, and compares these with the basis of PBS listings. These analyses can highlight medicines use issues that need to be considered by the PBAC, which may result in a recommendation for a post-market review by the PBAC.

DUSC meets three times a year in February, June and October each year, and is constituted by a broad range of experts, such as clinicians, academics, a consumer representative and industry representatives from Medicines Australia and the Generic Medicines Industry Association.

[2] http://www.health.gov.au/internet/main/publishing.nsf/Content/nmp-quality.htm

Economics Sub-Committee (ESC)

The ESC assesses clinical and economic evaluations of medicines submitted to the PBAC for listing, and advises the PBAC on the technical aspects of these evaluations. The ESC may also provide technical advice to the PBAC regarding whether the safety or efficacy evidence presented in a post-market review may impact on the economic models previously presented by sponsors.

Clinicians and academics with relevant expertise, and an industry representative from Medicines Australia, are members of ESC. ESC meets the week following DUSC, three times a year.

Additional Information

Information relating to the PBS, the PBAC meeting dates, agendas and outcomes, as well as details of current and completed post-market reviews is available on the PBS website. Public announcements regarding each review will be made available on the Post Market Review section of the PBS website.

Sponsors and stakeholders are encouraged to subscribe to news updates on the PBS website for the latest information and to be advised of timing of processes for each review.

Post-market Review Framework

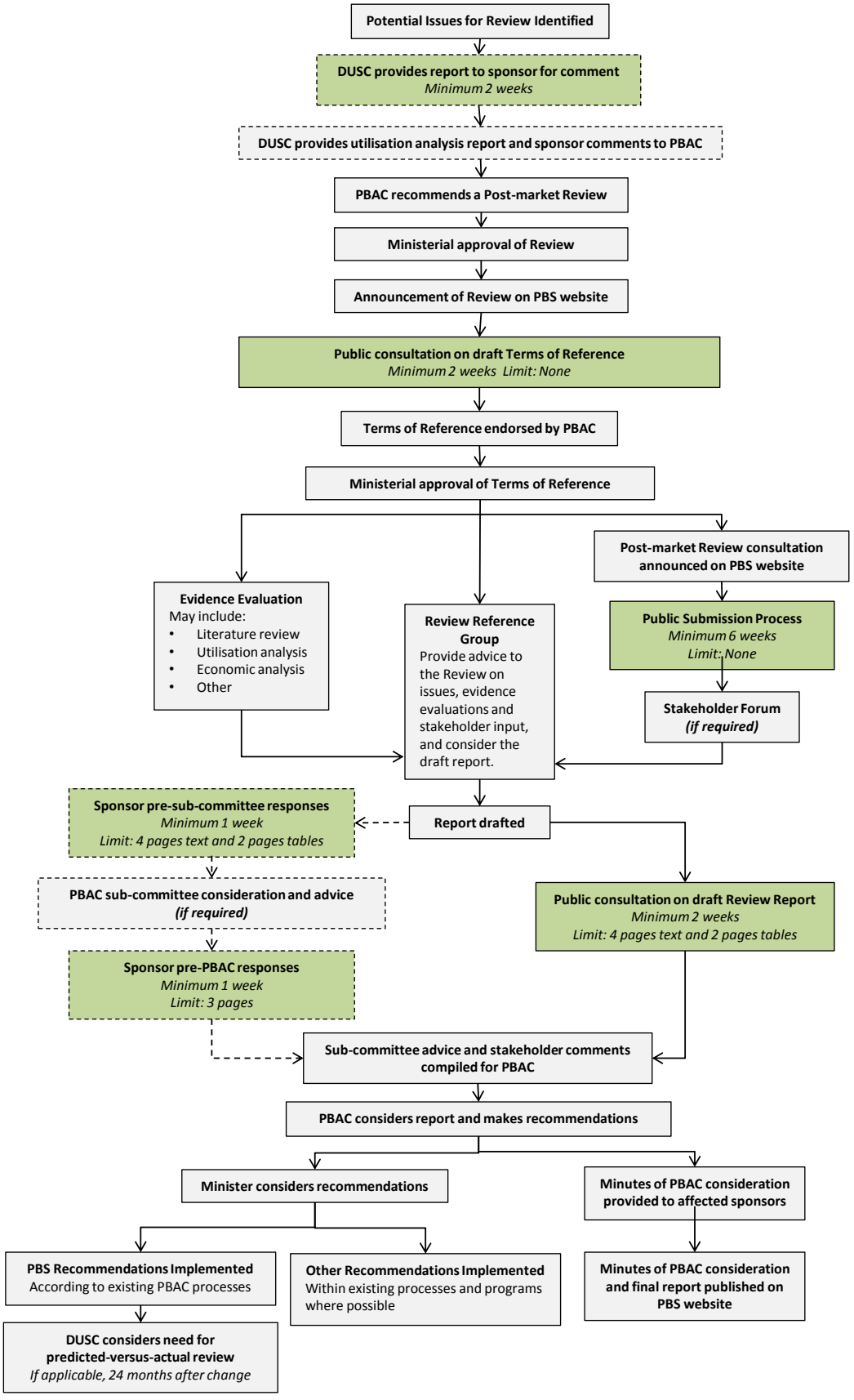
The framework described in this document relates to post-market reviews for medicines only. However, post-market reviews can be conducted for a range of health-related issues, including programme reviews. An ongoing post-market review does not prevent the usual PBAC processes such as assessing medicines for listing on the PBS, from progressing.

The framework described in this document, and illustrated at Figure 1, outlines the usual approach to medicines reviews and provides approximate time frames where possible. The framework is not intended to be prescriptive, as reviews will differ in their complexity and focus – it promotes consistency in approach, while providing the flexibility necessary to accommodate the different requirements of each review.

A review takes approximately twelve months. More complex reviews may vary from this structure, and could potentially take longer to complete. Information on timeframes will be posted on the PBS website as it becomes available.

Stakeholders can access more specific information about each review on the PBS website.

Figure 1. Post-market Review Framework



Initiation of Post-Market Reviews

Sources of Potential Reviews

A review may involve a single medicine, a class or category of medicine, or multiple classes of medicines that are used to treat a particular condition. Post-market reviews may be initiated at any time, and be triggered by a number of issues including, but not limited to:

- clinical efficacy and safety;
- use that is inconsistent with treatment guidelines and emerging clinical data;
- use outside of PBS restriction; and
- cost-effectiveness.

These issues can be identified through a number of sources, including:

- the PBAC;
- a routine analysis by the DUSC that indicates a medicines use issue;
- a request by the Minister for Health;
- a Senate Inquiry; or
- stakeholders contacting PBAC or the Department.

The Minister for Health will have the final decision on whether a review should proceed or not. During the course of a post-market review new medicines that fall within the scope of the review may be listed on the PBS, and will therefore be affected by the review and its outcomes.

Sponsors are encouraged to subscribe to news updates on the PBS website for the latest information regarding reviews including public consultation and publication review.

PBAC-identified issues

The PBAC may itself identify a potential issue that could lead to a post-market review, and may request the DUSC to conduct a medicines utilisation analysis, and/or request additional information to provide a more comprehensive overview of the potential issues.

At the request of the PBAC or in response to issues raised by other sources, the Department of Health may conduct or contract preliminary research, such as a literature review or an analysis of medicine use, to be provided to the PBAC and relevant sub-committees for consideration.

DUSC-identified issues

Issues that may lead the PBAC to initiate a post-market review come from a number of sources. However, most issues are raised through routine DUSC's utilisation analyses of medicines (see the Appendix for more details).

All new medicines on the PBS are routinely monitored by DUSC at 24 months post-listing. DUSC may also identify additional medicines for utilisation analysis at their regular meetings.

DUSC publishes an Outcomes Statement following every meeting, usually five weeks after each meeting. This includes information on which medicines have been selected for a DUSC utilisation analysis, for discussion at the next or subsequent DUSC meetings. These Outcome

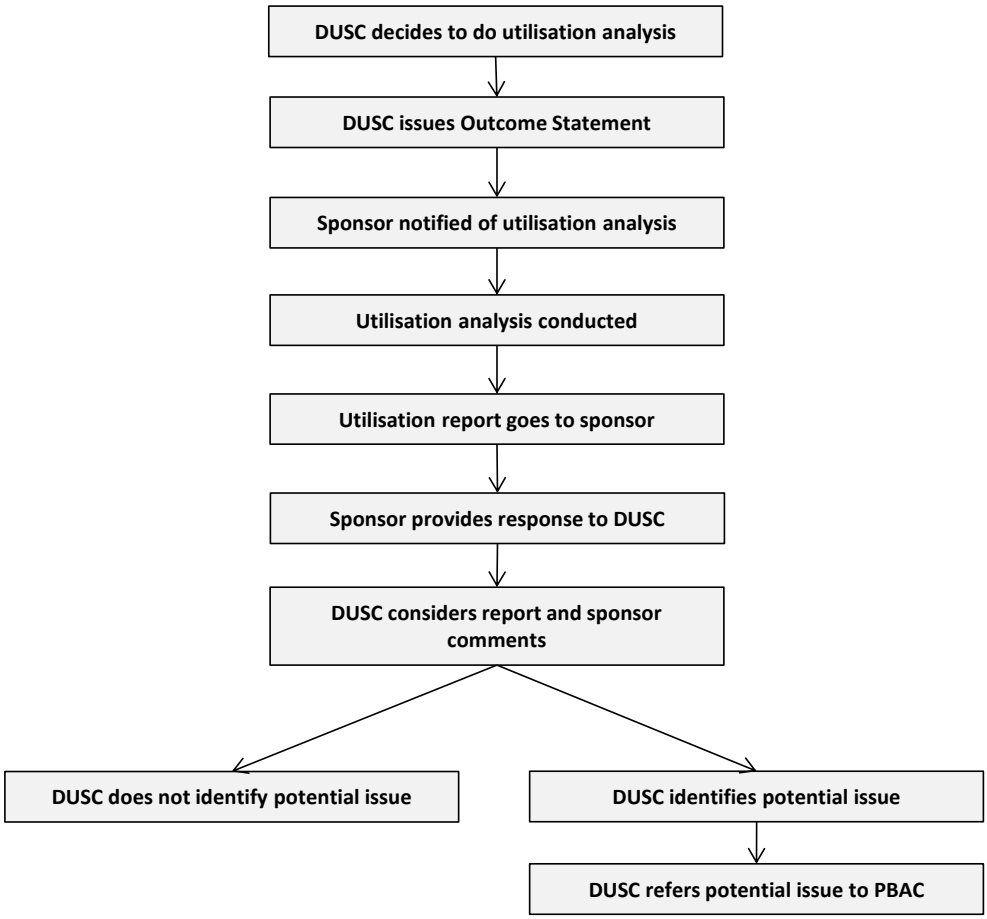
Statements provide the first notification to stakeholders that an analysis of medicine will be undertaken.

Two to three weeks after the Outcome Statement is released, relevant sponsors will be advised in writing by the Department of Health that a DUSC utilisation analysis is being conducted for review at an upcoming DUSC meeting. Sponsors will be advised when they can expect to be provided with the report of the DUSC utilisation analysis for comment.

The report of the DUSC utilisation analysis will be provided to the sponsor four weeks before the DUSC meeting where it will be discussed. The Sponsor is given two weeks to review the report and provide comment. There is no limit imposed on the length of the response. The sponsor's response to the DUSC utilisation analysis is an important opportunity to provide information to assist DUSC in determining if an issue should be further referred to the PBAC for consideration.

The DUSC will review and discuss the report, and the sponsor comments. Sponsors will receive an extract of the DUSC minutes relevant to this discussion when the Outcome Statements are released. If DUSC considers there is a potential issue, the PBAC will be provided with the report, sponsor comments and the DUSC minutes for consideration.

Figure 2. DUSC Process.



Consideration by PBAC

Regardless of their source, all potential issues identified are referred to the PBAC to determine if any action is required. A brief summary of the PBAC consideration will be available two weeks after publication of the PBAC meeting outcomes on the PBS website.

The PBAC may recommend that the evidence indicates there is no need for a post-market review, that the issue should be re-evaluated at a later date, or that a post-market review is required. The PBAC may also request further information or evidence on an issue prior to making a recommendation.

If the PBAC recommends a post-market review be initiated, Ministerial approval from the Minister for Health is required before a post-market review may commence. Following Ministerial approval, the post-market review is announced on the PBS website.

Stakeholder Communication

There are usually four key opportunities for interested stakeholders to provide input during the post-market review process:

- public consultation on the draft Terms of Reference;
- the public submission process;
- a stakeholder forum; and
- comments on the draft report.

In addition to this:

- Relevant sponsors have the opportunity to respond to DUSC utilisation analyses, where concerns regarding the utilisation of PBS medicines are most often raised.
- Where the draft report is provided to DUSC or ESC for advice, relevant sponsors are also able to provide pre-sub-committee responses to the draft report and pre-PBAC responses to the DUSC and/or ESC.
- Progress on each post-market review is regularly updated on the PBS website and where appropriate, and possible, one to two weeks notification of the release of consultation drafts and the commencement of consultation periods will be posted on the website.

A stakeholder forum will be held unless the Reference Group considers it unwarranted because of the size or scope of the post-market review, or because alternative consultation processes are considered more appropriate. Stakeholders may also recommend that a stakeholder forum should be held.

Submissions received during consultation processes will be made public unless otherwise advised. Anonymous submissions will not be accepted. All participants are welcome to suggest any stakeholders that they feel should be informed of the review.

Development of Review Terms of Reference

The Terms of Reference for each review outlines the key issues and guides the focus of each review and the evidence that informs it. Draft Terms of Reference are developed with regard to the preliminary research, comments made by the PBAC when considering the review, and relevant programme areas. The Department develops the draft Terms of Reference.

Consultation on Draft Terms of Reference

The Terms of Reference are also subject to a public consultation process involving key stakeholders. Once the post-market review has been approved by PBAC and provided to the Minister for Ministerial approval, key stakeholders are advised via email that a review is to be undertaken, and when the consultation on the Terms of Reference will occur.

The draft Terms of Reference and an outline of the scope of the review are published online, with a minimum two week period for stakeholders to provide written comments on the draft Terms of Reference. The Department may, however, determine that more complex post-market reviews require a meeting or a teleconference in addition to written comments.

The key stakeholders contacted at this stage of the review include, but are not limited to:

- sponsor companies of medicines involved in the review;
- Medicines Australia;
- Generic Medicines Industry Association;
- AusBiotech;
- Royal Australian College of Physicians;
- Australian Medical Association;
- Royal Australian College of General Practitioners;
- Relevant consumer organisations; and

- Peak organisations related to the disease/condition the medicines under review are intended to treat.

Endorsement of Terms of Reference

The draft Terms of Reference and comments received during consultation are then provided to the PBAC for consideration and endorsement, usually at a standard PBAC meeting.

The Terms of Reference are then provided for Ministerial approval. The final Terms of Reference are posted on the PBS website, along with a call for public submissions.

The public submission process typically commences eight to twelve weeks after the PBAC meeting where the draft Terms of Reference were endorsed by PBAC.

Reference Group

A Reference Group is formed for each post-market review to provide independent, expert advice on specific clinical and consumer issues, including advice on issues associated with use of the medicine/s of interest, its place in clinical practice, sources of evidence and data analyses that should be used, the quality and implications of gathered evidence, and issues raised by stakeholders.

The Reference Group meets as often as required across the term of the post-market review. At least two meetings will be held to enable the Reference Group to consider:

- initial evidence and submissions received during the public submission process, and provide advice whether any additional evidence is needed; and
- additional evidence, input from the stakeholder forum, and options for addressing the issue (if required) to be included in the report.

The Reference Group also considers and provides advice on the report prior to sub-committee and the PBAC consideration.

In general, members of the Reference Group are nominated for each post-market review by their organisation, or recommended on the basis of demonstrated relevant expertise. Membership of a Reference Group may include:

- independent specialist clinicians and/or nurse practitioners;
- researchers and representatives of peak healthcare provider or prescriber bodies related to the medicines under review;
- health educators;
- health economists;
- NPS MedicinesWise; and
- Consumer representatives or advocates.

The Department of Health requires all Reference Group members to declare any conflicts of interest prior to joining the Reference Group. Information on the membership of the Reference Group for each post-market review will be published on the PBS website and included in the final report. Stakeholders must not discuss the review with members appointed in a private capacity (for example, experts and technical members). Organisational representatives may discuss the review with their stakeholders, but only within the bounds of the Deed of Confidentiality agreement.

Internal Working Group

The Department will establish an Internal Working Group, if required for each review, to assist in steering the review and work in parallel to the review Reference Group. The Working Group will usually include staff from agencies with an involvement in, or affected by the review, including the Department of Health, Therapeutic Goods Administration, National Health and Medical Research Council, Department of Veterans' Affairs and the Department of Human Services.

The Working Group will meet throughout the course of the post-market review process, and may meet after final PBAC consideration of the review, to discuss PBAC's recommendations and how these may be implemented.

Role of the Department of Health

The Pharmaceutical Benefits Division in the Department of Health is responsible for the management of post-market reviews. This includes, but is not limited to: establishing and providing secretariat support for the Reference Group and Internal Working Group; sourcing and managing contracts for research done by external parties; organising the public submission process and stakeholder forum; and the drafting and editing of the Report to be presented to the PBAC.

Public Submission Process

A call for public submissions to the review is posted on the PBS website when the final Terms of Reference are endorsed and published. All interested parties are invited to make a submission to the review.

The standard submission period is a minimum of six weeks.

This is an opportunity for stakeholders to identify issues and provide any evidence or data that may inform the review, particularly evidence that the PBAC may not have previously considered.

All submissions received are published on the PBS website at the conclusion of the public submission period, unless otherwise requested. Where submissions indicate commercial-in-confidence or sensitive personal information, this is redacted before publication.

The full stakeholder submissions are considered by the Reference Group. They are also made available to the PBAC for consideration with the review report, along with a summary of the submissions including any relevant comments from the Reference Group.

Stakeholder Forum

Following the public submission process, a stakeholder forum will normally be held to offer interested parties an opportunity to provide additional input to the review. This would particularly be the case in reviews that are of significant public interest, complex reviews, or large scale reviews. Stakeholders may request that a stakeholder forum be held, but the Reference Group may determine that a stakeholder forum is unwarranted, for example, if the post-market review is small and all relevant stakeholders have already provided

comment. If it is decided that a stakeholder forum is not necessary, advice will be provided on the PBS website.

Forums are usually held in Canberra, and each is based on discussion questions, developed around the key points raised during the public submission process or evidence analyses, with additional input from the Reference Group. At the forum, stakeholders can provide further comment on these issues and propose options to address them.

A summary of the forum is provided to the Reference Group, published on the PBS website and included in the review report.

Evidence Collation and Evaluation

Post-market reviews consider the most recent, relevant evidence available regarding the clinical safety, efficacy and utilisation of the medicine/s of interest, as guided by the Terms of Reference. During the public consultation phase of the post-market review, sponsors and stakeholders may provide detailed information on what might be the most appropriate information and evidence for the reviewer to be considered as part of the review.

It is not necessary for all evidence to be in the same form as that provided as part of initial PBAC listings, although it must be robust and defensible. In particular, evidence on the efficacy and safety of the medicine outside the clinical trial setting is valuable. Research projects are typically contracted to independent external providers with demonstrated subject matter and technical expertise, selected from a panel of experts maintained by the Department of Health.

An outline of the proposed research for each review is provided to the PBAC by the Department of Health for advice when they consider the Terms of Reference. Most post-market reviews will involve a literature review and/or utilisation analysis. Additional evaluations may involve a systematic literature review, an economic analysis, further utilisation analysis, or other sources of evidence relevant to the review (see the Appendix for further details).

Stakeholder input through the public submission process and stakeholder forum may help identify additional areas for evaluation. The Reference Group also provides guidance on data collection, interpretation of results, and stakeholder input).

Draft Report

The review report is prepared by the Department of Health, and can include a summary of stakeholder input, methods of data collection and analysis, the results and discussion, advice from the Reference Group, and the Reference Group membership.

Reference Group Consideration

The Reference Group may consider and provide advice on the report at different points in the drafting process. Specifically, the Reference Group reviews and provides advice on the report before it is submitted to the sub-committees as needed, and provides comments on the report before its final submission to the PBAC.

Sub-committee Consideration

Where new evidence relevant to their area of expertise is included in the draft report, the sub-committees of the PBAC (DUSC and ESC) may consider the draft report. Relevant sponsors will be provided with a copy of the draft report to prepare pre-sub-committee responses. Pre-sub-committee responses are limited to four pages of text and two pages of tables, and sponsors will have a minimum of one week to prepare this response.

Following the sub-committee meetings, the sub-committee advice to the PBAC will be provided to relevant sponsors for pre-PBAC responses. Pre-PBAC responses are limited to three pages, and sponsors will have a minimum of one week to prepare this response.

The review report may be revised to incorporate sub-committee advice.

Stakeholder Consultation

The draft report is provided to key stakeholders and made publicly available on the PBS website for comment.

At least ten working days are provided for stakeholders to submit up to six pages of comments and tables to the review secretariat in the Department of Health prior to the PBAC meeting. This is consistent with the long-standing PBAC submission process, and a timeline industry has been operating within for many years.

All stakeholder comments on the report (including responses to sub-committee advice) are made available to the PBAC for consideration alongside the final report.

PBAC Consideration

The PBAC considers the full post-market review report, including stakeholder comments, sub-committee advice and any Reference Group comments, before making any recommendations. In some cases, the PBAC may request additional work to be carried out. Consideration of a post-market review report will be included on the PBAC agenda on the PBS website. Sponsors and other key stakeholders will be notified when/if a post-market review report will be considered at an out of session PBAC meeting.

Sponsors of the medicines involved in the review are contacted after the PBAC meeting and provided with the minutes. The PBAC minutes and recommendations, along with the final report, are also published on the PBS website.

Consistent with PBAC process, recommendations and options for implementation are provided to the Minister for Health for consideration, where they impact on the PBS. All recommendations are published as part of the PBAC minutes.

The PBAC may make a range of recommendations, including:

- taking no action;
- changes to PBS restrictions;
- measures to improve cost-effective use;
- updating clinical guidelines; and
- education for health professionals or consumers to improve quality use of medicines.

Implementation of Recommendations

PBS-related Recommendations

Recommendations relating to the PBS listing of medicines under review are implemented according to standard PBAC processes. Under this process, sponsors are advised of a PBS-related recommendation following the relevant PBAC meeting. If there is a pricing determination, the relevant sponsor has ten working days to accept the price, consistent with standard PBAC practice.

Where PBS-related recommendations that may affect medicines use have been implemented, the DUSC may consider whether a routine review of medicines use should be conducted usually 24 months after the change is implemented.

Other Recommendations

Recommendations made by the PBAC that do not relate directly to the PBS may be implemented through existing, applicable programmes. Recommendations to improve prescriber education may be implemented through NPS MedicineWise; recommendations for changes to treatment or management guidelines may be implemented through the National Health and Medical Research Council or in consultation with the external developer of the relevant guidelines.

Information regarding the implementation and progress of recommendations for each post-market review is updated on the PBS website as it becomes available.

Appendix

Literature Review

The scope of each literature review is dependent on the requirements of the post-market review. However, there is usually a focus on the most recent clinical evidence that the PBAC has not previously considered. The literature review may focus on one or a combination of the following areas:

- efficacy of the medicine;
- comparative efficacy between medicines used to treat the condition of interest;
- safety of the medicine;
- comparative safety between medicines;
- clinical guidelines for prescribing the medicines under review or treating the condition; and
- economic utility or cost-effectiveness.

An initial literature review of previously conducted meta-analyses and additional clinical trials may be conducted by the Department or an independent external contractor to provide an overview of the subject area and identify any potential issues. A systematic review may be conducted where a specific or fundamental issue has been identified.

Medicine Utilisation Analysis

Analysis of medicine utilisation provides information on how the medicines of interest are actually being used in clinical practice. Specifically, these analyses can provide information relating to:

- patterns of use (including adherence, persistence, prevalence, incidence, co-prescribing, switching, and use prior to or following initiation);
- adherence to treatment guidelines and PBS restrictions;
- other outcomes associated with medicines use, such as side-effects; and
- the conditions medicines are being prescribed to treat.

The most commonly used source of data for analysis of medicines utilisation in Australia is PBS data, which is also used in the routine medicines utilisation reviews conducted by the DUSC. However, additional data sources may also be used to establish a more complete picture of prescribing and use in clinical practice. These include, but are not limited to:

- Veterans' Medicines Advice and Therapeutic Education Services (MATES);
- National Health Survey;
- Bettering the Evaluation and Care of Health (BEACH) and Supplementary Analysis of Nominated Data (SAND);
- MedicineInsight GP prescriber data;
- Samples of GP activity; and
- Disease registries.

Economic Analysis

An economic analysis may be conducted as appropriate. This analysis may assess the impact of actual use or proposed changes to actual use on the cost-effectiveness of the medicines. Revised or new economic modelling may be required if there is new evidence available that would change previous assumptions used to model cost-effectiveness. A summary of this analysis is included in the report, and stakeholders may request a copy of the full analysis.