Commonwealth Department of Health and Ageing

GUIDELINES FOR THE PHARMACEUTICAL INDUSTRY ON PREPARATION OF SUBMISSIONS TO THE PHARMACEUTICAL BENEFITS ADVISORY COMMITTEE

Including major submissions involving economic analyses

September 2002

ISBN 0 642 82144 5

Publications approval number: 3145

Publications Production Unit (Public Affairs, Parliamentary and Access Branch)
Commonwealth Department of Health and Ageing
Canberra

CONTENTS

INTRODUCTION TO THE CONSOLIDATED UPDATE OF THE PBAC GUIDELINES

New items incorporated into the 2002 *PBAC Guidelines*

- The PBAC Guidelines for Fixed Combination Products (letter to industry in June 1999) *are referred to on page 4, "Situations in which a recommendation to list is unlikely", item (a); page 11, Major submissions, item (e); and are located on page 40, Appendix A.*

- The Checklist of Materials to be provided for a minor submission: now request provisional relevant TGA and ADEC documents (letter to industry in May 2000). *Located on page 10.*

- Procedures relating to consideration of straightforward major submissions by the ESC (letter to industry in June 1997) *are located on page 12.*

- The Checklist of Materials to be provided for a major submission: now request the provision of TGA and, when available, ADEC documents with a major submission to the PBAC (letter to industry in May 2000). *Located on page 14.*

- Sponsors are encouraged to include an electronic copy of the main body of its major submission (letter to industry in April 2000). *Located on page 15.*

- The number of copies of submissions to the PBAC (letter to industry in September 1999), *is located on pages 15 and 20.*

- Acceptance of PBAC submissions after a positive recommendation by the TGA delegate (ie earlier lodgement, letter to industry in March 1996). *Referred to in Action or Event Checklist, page 7, in Modification to checklist on page 14 and additional detail in the directions (red type) of Section 1.2, located on page 21.*

- The maximum length of the executive summary of a submission increased from 5 pages to 10 pages (letter to industry in July 1999), *located on page 18.*

- The hierarchy of sources of evidence for equi-effective doses (letter to industry in April 1997), *are referred to on page 30 and located in Appendix F on page 48.*

- Reference is made to the *Glossary to accompany the Guidelines for the Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee: including major submissions involving economic analyses (May 1997) on page 85.* The *Glossary* was published in 1997 and has been in circulation since then as an accompaniment to the *PBAC Guidelines.*

- Section 4.3 now refers to the new Section 9 from the updated *Manual of Resources and their Associated Costs, located on page 37.*

In March 2000, the PBAC endorsed changes to Sections 2.1. 2.2 and 3 and two new associated appendices on the grounds that they represented substantial agreement between applicants to the PBAC and the PBAC on presenting models and the identification of trials from literature searches in major submissions to the PBAC. These changes were published in April 2000 as an Interim Document (http://www.health.gov.au/pbs/pubs/pharmpac/interim/index.htm) which can be obtained from the PBS website: http://www.health.gov.au/pbs/pubs/pharmpac/interim/index.htm. It was envisaged that applicants, evaluators and Committees would adopt the new approaches and that experience gained in their use would be fed back into the revision process. Although the contents of the Interim Document have not been finally reviewed or endorsed by the PBAC, they are included in this edition of the PBAC Guidelines with a view to continuing to build on this experience base for the more substantial revision of the PBAC Guidelines.

SUBSTANTIAL REVISION OF THE 2002 PBAC GUIDELINES

Substantial revision of the *2002 PBAC Guidelines* is ongoing. The *PBAC Guidelines* are finally endorsed by the PBAC itself. The PBAC has delegated responsibilities for revising the Guidelines to its Economics Sub-Committee (ESC). The ESC is required to give consideration to current and likely future technical developments relevant to the Guidelines and to consult widely on an on-going basis with all stakeholders, including those who prepare submissions. Consultation takes many forms depending on the nature of the items under review. It includes small working groups of ESC and industry members, larger workshops and seeking formal comment on written drafts and proposals.

Revision process involving website publication

The 2002 *PBAC Guidelines* are currently under active revision by the ESC on an item by item basis. It is proposed that once each item has been revised by the ESC, it will be uploaded onto the PBB website in draft form to enable wider consultation. All interested stakeholders will be informed when this document is available on the Internet. This will provide an opportunity for all such stakeholders to provide comment and to ensure that the proposals are appropriate and practical. The cut off date for comment will be determined for each draft document as it is up-loaded on the website. Following review of comments, the ESC will recommend a final version of the item for PBAC consideration and endorsement as final *PBAC Guidelines.*

A list of the items to be subject to further revision is presented below.

Section 2 and associated Appendices: Clinical Evidentiary Requirements

The Section and Appendices anticipated to change and the new inclusions are:

Section 2 – Data from comparative randomised trials for the main indication.

Appendix B – Description of the search of the published literature.

New Appendix – Presenting the selection of the comparative randomised trials.

Appendix D – Measures taken by investigators to minimise bias in each trial listed in response to Section 2.2.

Appendix E – Characteristics of each trial listed in response to Section 2.2.

Appendix F – Analysis of the outcomes of each trial listed in response to Section 2.2.

Appendix J – Use of meta-analysis.

New Appendix – Equivalence, equi-effective doses and indirect comparisons.

New Appendix – Treatment effect modification and sub-group analysis.

New Appendix – Time-to-event data.

New Appendices: Valuing Health Outcomes

The ESC has been considering the methods to value health outcomes for several years. The drafting of new Appendices for the valuing of health outcomes is based on the information collected in the two literature reviews commissioned by the Department of Health in 1997 and the ensuing peer reviews of these documents, the workshop held collaboratively with the pharmaceutical industry and their consultants in 1999, and further developments and discussions since then.

Three appendices are proposed to address the valuing of health outcomes. They are:

New Appendix – Trial-based Utility Valuation of Health Outcomes

New Appendix – Scenario-based Valuation of Health Outcomes

New Appendix – Monetary Valuation of Health Outcomes

Section 3 and associated Appendix: Modelling

An Interim Document that revises Section 3 of the *PBAC Guidelines*, "Modelled economic evaluation in its main indication" has been available on the Internet since April 2000.

It has been decided that this Interim Document should be developed further, focussing on new experience with applying this document. As with other items, this redraft will be up-loaded onto the PBB website as a draft document, allowing time for comment before a final version is recommended for PBAC endorsement. An area of particular interest is extending the presentation of sensitivity analyses, including scenario analyses which investigate the impact of changing the context of the economic evaluation (for example to different patient eligibility criteria or to different comparators).

Section 5 and associated Appendix: Other Relevant Factors

The Tambling Review Group of the PBS listing process recommended in 2000 that the *PBAC Guidelines* revision process give particular emphasis to providing guidance on the matters relating to other relevant factors and to encourage the submissions of Orphan Drugs. A proposal for a new Section 5 and an associated explanatory Appendix to be included in the revision is under active consideration.

This new Section is not intended to limit the information that a sponsor company may include in its submission as being relevant to the decision of the PBAC.

Further items for the PBAC Guidelines revision

There are other matters that need to be reviewed in the future for a more complete revision of the *PBAC Guidelines*. These include:

Sections 1.2 and 1.5 –	Indications/Main comparator (as agreed with the pharmaceutical industry);
Section 2 –	Hierarchical evidence;
Sections 2.9 and 3 –	Valuation of productivity gains (following APMA-sponsored literature review);

Section 4 - 4.1, 4.2, 4.3 (given recent Government focus on usage beyond expectations);

Section 4.4 –	the appropriate perspective for this section;
Appendix A –	Consideration of Fixed Combination Products; and
Appendix S –	Expert Opinion.

These are matters which are yet to receive active ESC consideration since 1999 and will require further consultation with other stakeholders.

PART I

ROLES AND RESPONSIBILITIES OF THE PBAC

ROLE OF THE PBAC

The Pharmaceutical Benefits Advisory Committee (PBAC) is established under the *National Health Act 1953* to make recommendations to the Minister for Health about which drugs and medicinal preparations should be available as pharmaceutical benefits, and to advise the Minister about any other matter relating to the Pharmaceutical Benefits Scheme (PBS) which is referred to it by the Minister. The Committee is also required by the Act to consider the effectiveness and cost of a proposed benefit compared to other therapies.

The membership of the Committee is prescribed in the Act and members who are appointed by the Minister are medical practitioners, pharmacists and health economists. The membership is published in the *Government Gazette* and details are available on request from the PBAC Secretariat.

New pharmaceutical entities must be registered by the Therapeutic Goods Administration (TGA) before being marketed in Australia. Registration is based on assessment of quality, safety and efficacy, a process which often involves the Australian Drug Evaluation Committee (ADEC). Products are registered on the Australian Register of Therapeutic Goods (ARTG) for specific therapeutic indications, and, in general, the PBAC will not recommend the listing of products in the PBS for indications other than those registered. The PBAC thus accepts that products included on the ARTG have established safety and efficacy adequate to allow marketing in Australia.

The Committee is required to make recommendations on the suitability of drug products for subsidy by the Australian Government. It therefore considers the effectiveness, cost-effectiveness and clinical place of a product compared with other products already listed in the PBS for the same, or similar, indications. Where there is no listed alternative, the Committee considers the effectiveness, cost-effectiveness, and clinical place of the product compared with standard medical care or the benefits for patients the new product will provide compared to the cost of achieving those benefits. On the basis of its community usage, the Committee recommends maximum quantities and repeats and may also recommend restrictions as to the indications where PBS subsidy is available.

When recommending listings, the Committee also provides advice to the Pharmaceutical Benefits Pricing Authority (PBPA) regarding comparison with alternatives or their cost-effectiveness ("value for money").

The range of drugs and formulations available under the Scheme provides a formulary of drugs to meet the health needs of the majority of the Australian community.

SUB-COMMITTEES

Under the *National Health Act* the Committee may establish sub-committees, consisting of members with appropriate expertise, to assist it in performing its functions. There are presently two sub-committees - the Drug Utilisation Sub-Committee (DUSC) and the Economics Sub-Committee (ESC).

The DUSC monitors the patterns and trends of drug use and makes such utilisation data available publicly.

The ESC advises on cost-effectiveness policies and evaluates cost-effectiveness aspects of major submissions to the PBAC.

QUALITY USE OF MEDICINES

The PBAC encourages the quality use of medicines through the inclusion of cautions and notes in the PBS Schedule, the wording of PBS restrictions, its initiation of national consensus conferences and the provision and publication of Australian drug utilisation data. From time to time it also makes recommendations to the Pharmaceutical Health and Rational Use of Medicines Committee (PHARM) on educational activities to support the appropriate use of pharmaceutical benefits.

PROCESSING OF SUBMISSIONS

The Committee considers submissions not only from industry sponsors of drug products, but also from medical bodies, health professionals, private individuals and their representatives. However, for new products or new indications, it is normally the sponsor or manufacturer who will hold the necessary data required for such a submission.

The Committee is conscious of the need to be as open as possible in its proceedings, consistent with the secrecy provisions of the *National Health Act*. The Committee therefore provides to sponsors relevant documents and evaluations considered by the Committee. It also provides the opportunity for a pre-PBAC consultation with the sponsor in relation to submissions for drug products. The Committee is also conscious of the need to avoid unnecessary delays between marketing approval and subsidised listing where the latter is appropriate. To this end, all submissions received by a reasonable cut-off date are considered at the next meeting of the Committee. These cut-off dates are provided to the pharmaceutical industry well in advance of meetings. The PBAC will accept submissions prior to finalisation of marketing approval provided registration has been recommended by the TGA delegate in the pre-ADEC overview.

Advice of Committee decisions are provided to sponsors in writing within 15 working days of a meeting, and PBAC and PBPA meetings are coordinated to minimise processing time.

GENERAL GUIDELINES FOLLOWED BY THE COMMITTEE

The Committee bases its deliberations on the requirements of the *National Health Act*. The role of a drug product in meeting the health needs of the Australian community is of primary consideration. For drugs considered appropriate for PBS listing on medical grounds, economic factors including cost-effectiveness are taken into account, as required by the *National Health Act*.

A new drug entity may be recommended for listing if:

(a) it is needed for the prevention or treatment of significant medical conditions not already covered, or inadequately covered, by drugs in the existing list and is of acceptable cost-effectiveness;

(b) it is more effective, less toxic (or both) than a drug already listed for the same indications and is of acceptable cost-effectiveness; or

(c) it is at least as effective and safe as a drug already listed for the same indications and is of similar or better cost-effectiveness.

At the direction of the Minister for Health:

(a) the Committee takes into account the community need or benefit, particularly for additional formulations of an already listed drug where proliferation of products may cause confusion;

(b) a drug intended specifically for in-hospital use is given a lower priority for listing since the PBS is primarily for community-based patients; and

(c) a drug for the treatment of clinically minor or trivial conditions is given a "low priority" for listing.

Situations in which a recommendation to list is unlikely:

(a) a fixed combination of drugs (see Appendix A);

(b) a drug where this may increase problems of abuse or dependence; or

(c) a drug solely to treat an individual patient whose response to, or need for, a drug is unique.

Circumstances which may result in removal of a drug from the list include the following:

(a) a more effective or equally effective but less toxic drug becomes available;

(b) evidence becomes available that the effectiveness of the drug is unsatisfactory;

(c) evidence becomes available that the toxicity or abuse potential of the drug outweighs its therapeutic value;

(d) the drug has fallen into disuse or is no longer available; or

(e) treatment with a drug is no longer deemed cost-effective compared with other therapies.

RESTRICTED BENEFIT AND AUTHORITY REQUIRED LISTINGS

A drug or drug formulation will be considered for Restricted Benefit or Authority Required listing:

(a) to limit PBS usage so that this is in accordance with the approval and registration granted by the TGA;

(b) to allow the controlled introduction of a drug in a new therapeutic class;

(c) to limit PBS usage to the indications, conditions or settings seen as being appropriate for clinical, cost-effectiveness, or other reasons; or

(d) because of concerns about adverse effects, possible misuse, overuse or abuse.

LISTED MAXIMUM QUANTITIES AND REPEATS

The Committee makes recommendations about the maximum quantity and the number of repeat prescriptions which should be available for each formulation of a drug. For acute conditions, the maximum quantity usually provides sufficient for a normal single course of treatment (bearing in mind the size of the manufacturer's pack). For chronic conditions, the maximum quantity and repeats usually provide for up to six months' therapy depending on the need for clinical review of the condition to be treated. For

patients requiring higher than average doses, generally, increases in the listed maximum quantities and repeats are available through the Authority system.

HIGHLY SPECIALISED DRUGS

Following an agreement between Commonwealth and State health ministers and the establishment of the Highly Specialised Drugs Working Party, highly specialised high cost drugs may be recommended for availability through hospital out-patient departments where use of the drugs for the treatment of community patients is not suitable to a community medical practice setting.

SOURCES OF ADVICE

In formulating its conclusions, the Committee may seek expert opinion from relevant professional bodies and/or appropriate specialists and may meet with representatives of relevant medical professional organisations and colleges. Where this occurs, the relevant sponsor is informed and given an opportunity to reply.

REVIEW OF LISTINGS

The Committee regularly reviews the list of pharmaceutical benefits including restrictions, maximum quantities and number of repeats.

GENERAL INFORMATION

Secretariats

The PBAC and its Sub-Committees are serviced by secretariats which are part of the Commonwealth Department of Health and Ageing:

PBAC: PBAC Secretariat and Listings Section

Telephone: (02) 6289 7099
Facsimile: (02) 6289 8633

ESC and DUSC: Pharmaceutical Evaluation Section

Telephone:
ESC Secretary: (02) 6289 7486
DUSC Secretary: (02) 6289 7293

Facsimile: (06) 289 8633

The Secretariats are available for discussion about proposed submissions or related matters at any time. They are also the first point of contact concerning PBAC discussions and decisions.

Addresses

All correspondence should be addressed to:

The Secretary
Pharmaceutical Benefits Advisory Committee
GPO Box 9848
CANBERRA ACT 2601

Submissions should be delivered to:

5th Floor
Alexander Building
Furzer Street
PHILLIP ACT 2606

Timing of submissions

The meeting dates for the following year, and the associated cut-off dates, are advised to the industry following the August/September PBAC meeting.

The cut-off date for major submissions is 11 weeks prior to the PBAC meeting (12 weeks over the Christmas-New Year period).

Minor submissions may be accepted up to four to five weeks later and minor matters may be accepted later still depending on the number of submissions already received. Contact should be made with the PBAC secretariat before presentation.

Submissions should be presented on time and should be complete. No guarantee can be given that material supplied late will be incorporated into the submission or included in the agenda papers.

Timing of implementation of recommendations

The time scale for PBS listings in tabulated form is:

Action or event	Timing relative to PBAC meeting
TGA Delegate's Overview/Advice to ADEC and/or ADEC resolution and/or TGA registration granted	
Cut-off date for major submissions	11 weeks prior
Cut-off date for minor submissions	7 weeks prior
ESC agenda to ESC members	4 weeks prior
PES evaluation plus PBAC secretariat overview of submissions provided to sponsor	$2^1/_2$ weeks prior
Meeting of ESC	$2^1/_2$ weeks prior
PBAC agenda to PBAC members	$2^1/_2$ weeks prior
Pre-PBAC comments provided by sponsor	$1^1/_2$ weeks prior
ESC reports plus sponsor comments to PBAC members	1 week prior
PBAC meeting	
Written advice to sponsor	3 weeks post
Meeting of Pricing Authority	4-6 weeks post
Approval by the Minister/Cabinet	10-12 (or more) weeks post
Listing in the Schedule	5 months post (providing assay and other matters resolved)

PART II

BASIC INFORMATION ON PREPARING A SUBMISSION TO THE PBAC

SUBMISSIONS WHICH DO NOT REQUIRE AN ECONOMIC EVALUATION

Minor submissions

An economic evaluation is not required in order to apply to the PBAC to:

(a) list on the Schedule of Pharmaceutical Benefits a new formulation (or strength) of a currently listed drug for which a price premium is not requested, or for which the likely volume and proportion of use is expected to be small (in which case the main aspect of the submission is to justify the **clinical** need for the product on the PBS);

(b) request a change to the maximum quantity per prescription of a currently listed drug;

(c) request a change to the number of repeats per prescription of a currently listed drug; or

(d) clarify the wording of a restriction (while not altering the intended use).

Submissions which are classified into categories (a) to (d) above are examples of minor submissions. They do not require evaluation by the Pharmaceutical Evaluation Section nor presentation to the ESC prior to consideration by the PBAC. The cut-off for lodgement of minor submissions with the PBAC Secretary is 7 weeks prior to the date of each PBAC meeting. The above list is not necessarily exhaustive as there may be other types of minor submission; if a sponsor is in any doubt about the status of a submission, the advice of the PBAC Secretariat may be sought.

A checklist of materials to be provided for a minor submission:

(a) **two** copies of the full submission (which may just be a simple letter explaining or justifying the change and detailing the timing involved);

(b) **one** copy of the **current** TGA-approved product information with approval date (if and when available, with the **latest** draft product information in the meantime); and

if the submission is for a new formulation or strength of a currently listed drug:

(c) **one** copy of the PB11 (the official application form);

(d) **one** copy of the letter of registration with details of marketing approval and registration (if and when available); and

(e) **one** copy (bound as a set) of

(i) the full TGA Clinical Evaluator's Report (including any expert reports);

(ii) the TGA Delegate's Overview (advice to ADEC);

(iii) the ADEC resolution (if and when available); and

(iv) the relevant extract of the ADEC minutes (if and when available).

If a registration application has been considered more than once by the ADEC, documentation relating to all ADEC considerations should be supplied.

Submissions to list generic equivalents

A submission to the PBAC is not required to list a generic equivalent (or new brand) of the same formulation of an already listed drug (while this should still go to the PBAC Secretary, it is dealt with within the Pharmaceutical Benefits Branch and not forwarded to the PBAC). Further information can be obtained from the PBAC Secretariat and Listings Section.

SUBMISSIONS WHICH DO REQUIRE AN ECONOMIC EVALUATION

Major submissions

This document primarily provides guidelines for the formatting of evidence in order to apply to the PBAC to:

(a) list a new drug on the Schedule of Pharmaceutical Benefits;

(b) request a significant change to the listing of a currently restricted drug (including a new indication or a de-restriction);

(c) enable a review of the comparative cost-effectiveness of a currently listed drug in order to change a PBAC recommendation to the PBPA on its therapeutic relativity or price premium;

(d) list a new formulation (or strength) of a currently listed drug for which a price premium is requested; or

(e) list a new fixed combination product (see Appendix A).

Submissions which are classified into categories (a) to (e) above constitute major submissions. They require evaluation by the Pharmaceutical Evaluation Section and presentation to the ESC prior to consideration by the PBAC. The cut-off for lodgement of major submissions with the PBAC Secretary is at least 11 weeks prior to the date of each PBAC meeting.

Re-submissions

A re-submission asks the PBAC to re-consider a matter which has been the subject of a previous submission. Even if it is based entirely on new data, modifies the previously requested indication or changes the comparator, it will be regarded as a re-submission. This is because the information in the re-submission will have to provide the basis for any change to the Committee's earlier decision.

The re-submission must highlight the following aspects:

(a) the main matters of concern to the PBAC and/or the matters that the PBAC has requested be addressed in a re-submission and how the re-submission addresses them;

(b) if the sponsor disagrees with the previous decision, the matters in dispute and how the re-submission addresses them; and

(c) all new data, new circumstances, new arguments or new approaches included in the re-submission should be identified.

Previous information clearly not in dispute (eg pharmacology, actions and uses, marketing status, approved indications) need not be included in the re-submission.

ESC consideration for straightforward submissions

Submissions that are straightforward may be considered by the PBAC without modified advice being prepared on the submission by the ESC. The criteria to allow submissions to proceed straight to the PBAC for consideration are at the discretion of the ESC and may include:

(a) a submission which only contains only a cost-minimisation analysis; or

(b) a re-submission in which the sponsor is simply following advice given in the PES commentary, ESC advice and/or PBAC minutes relating to the previous submission.

The procedure to be followed is that at the ESC meeting, the ESC discussant and any other member are invited to state whether any submission does not warrant further discussion and the preparation of any particular ESC advice (if not, the ESC will not modify the Executive Summary of the PES Commentary).

GENERAL ADVICE ON PREPARING A MAJOR SUBMISSION

These guidelines are designed to assist sponsors identify and format the basic information needed by the PBAC and its ESC and provide guidance on the most appropriate form of economic evaluation in a particular instance. They should be adhered to wherever possible, although the suggested layout will not always be the most appropriate so deviations, which may be necessary for some drugs, are permitted if accompanied by a justification. Sponsors should not assume that justifications will be accepted, so consultation is advised in such circumstances.

The guidelines are presented as a "desk-top" analysis, in which usually available data are presented in the suggested layout. This is to be distinguished from a "field" analysis in which a specially designed study is commissioned to gather the data. Few sponsors will have access to such studies at the present time, particularly in Australia. In most cases, a desk-top analysis will be sufficient. If not, the results should indicate to the sponsor the areas in which further data need to be collected in a field study.

Throughout the guidelines, questions and data requirements are in double-ruled boxes with relevant advice provided in normal type and elaborated in the appendices. The schema at page 16 illustrates the logical flow of the guidelines.

Section 1 establishes the context for the submission. It asks for a description of the proposed drug, its use on the PBS and the therapies which will be co-administered or substituted.

Section 2 asks for the best available evidence on the comparative clinical performance of the proposed drug. It also gives guidance on factors such as the degree of detail, the scientific rigour of the randomised trials and the appropriate degree of statistical rigour and culminates in a preliminary economic evaluation based on the evidence from the randomised trials.

Section 3 describes situations in which extrapolating beyond this preliminary economic evaluation may be necessary and advises on how adjustments can be made in a modelled economic evaluation. Both economic evaluations are from the perspective of society.

Section 4 requests a financial analysis from the perspective of the PBS and government health budgets.

A submission should be as succinct and informative as possible. The PBAC and its ESC are most likely to be influenced by arguments based on scientifically rigorous data rather than opinions. Try as far as possible to follow the guidelines. Use suitable scientific language, but avoid jargon.

Sponsors should be aware that each major submission will be assessed at three levels: evaluation by the Pharmaceutical Evaluation Section, consideration by each ESC member and consideration by each PBAC member. The executive summary is the document from the submission which is included in the ESC and PBAC agenda papers. The main body of the submission should be a separate bound document including reports of the key trials, but not other information of less importance. Other supplementary material provided as necessary is evaluated primarily by the Pharmaceutical Evaluation Section (which also checks the detailed calculations in the supplementary material and any computer disc), but is also available to Committee members on request.

It is vital therefore that the submission provides frequent and accurate cross-references between the executive summary and the main body of the submission, and between the main body of the submission and reports of the key trials, attachments, technical documents and computer discs. This will assist those who have to evaluate and consider the submission.

CHECKLIST OF MATERIAL TO BE PROVIDED FOR A MAJOR SUBMISSION

Use the following checklist as a final check before lodging a major submission with the PBAC Secretary. The checklist is designed to ensure that each submission lodged is sufficient for a complete assessment while not unnecessarily wasting paper.

Include one (1) separate version of:

(a) the original, signed covering letter for the submission;

(b) the original, signed PB11, (the official application form (for a new drug, formulation or strength and stating the requested price);

(c) any technical document(s) as necessary (in addition to the main body of the submission and which must be suitably and separately bound); and

(d) any computer disc as necessary (with any spreadsheet compatible with Microsoft Excel 97, and any word processed document compatible with Word 97).

Include two (2):

(a) samples of the pharmaceutical presentation **if it is novel** (for example, a "compliance" pack or a type of formulation not currently listed - in such a case, the submission should also explain how this pharmaceutical presentation impacts on the clinical and economic performance of the drug);

(b) copies of the covering letter for the submission (each copied single-sided and stapled);

(c) copies of the PB11 (each copied single-sided and stapled);

(d) separate sets of copies of

(i) the full TGA Clinical Evaluator's Report (including any expert reports);

(ii) the TGA Delegate's Overview (advice to ADEC);

(iii) the ADEC resolution (if and when available); and

(iv) the relevant extract of the ADEC minutes (if and when available).

If a registration application has been considered more than once by the ADEC, documentation relating to all ADEC considerations should be supplied.

Include three (3) separate copies (each copied single-sided and stapled) of:

(a) the document entitled **"Answers to key questions to help determine the acceptability of the submission"** (see page 17);

(b) the executive summary of the submission (see page 18);

(c) the **current** TGA-approved product information with approval date (if and when available, with the **latest** draft product information in the meantime);

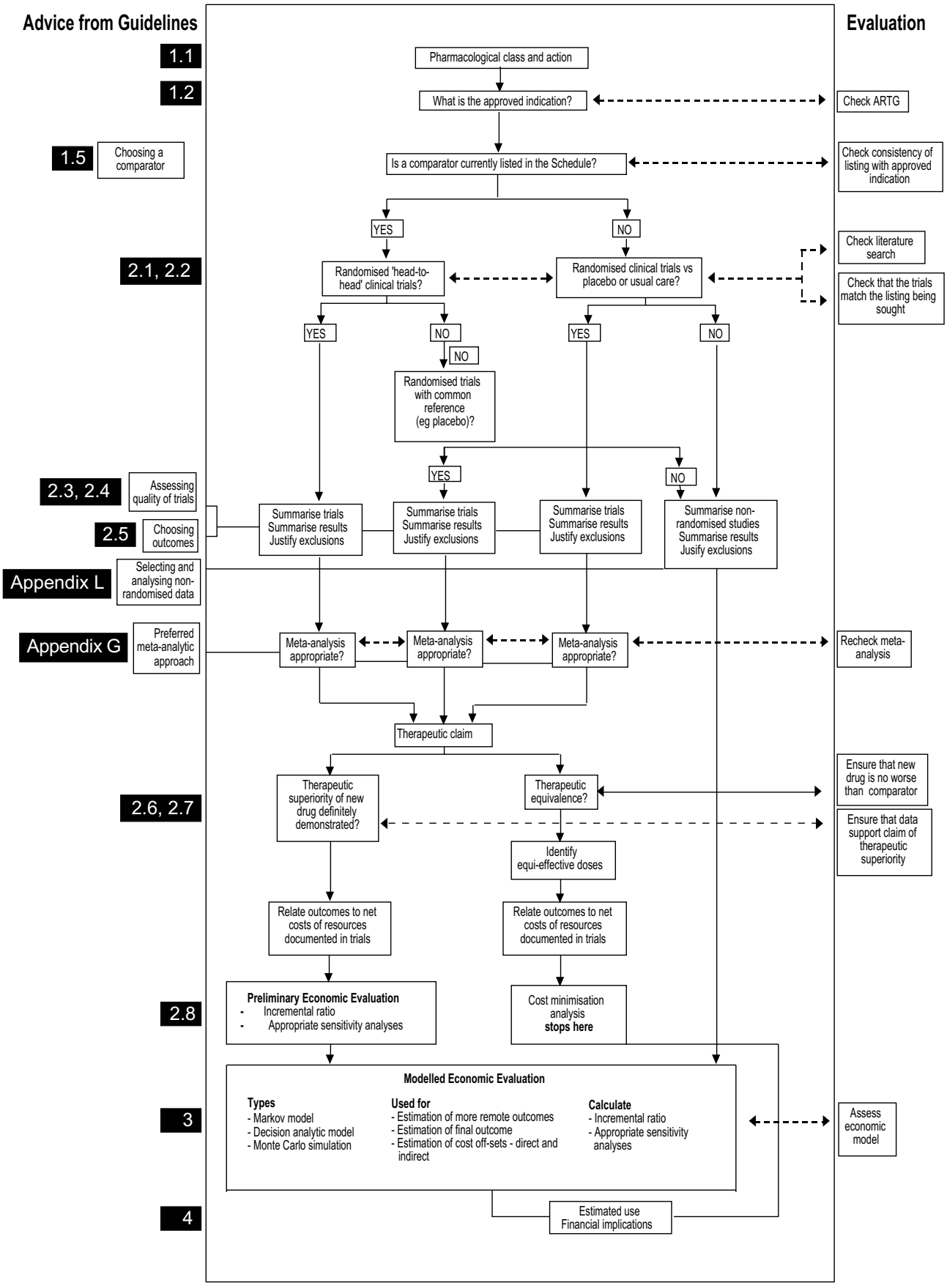
(d) the letter of registration with details of marketing approval and registration (if and when available; and

(e) any additional references (suitably and separately bound; all references must be legible and in English or be accompanied by a reputable translation and copied single or double-sided).

Include twelve (12) suitably bound copies of the main body of the submission itself (see page 20).

Sponsors are encouraged to send a copy of the main body of a major submission in electronic format (with any word processed document compatible with Word 97). The electronic version would supplement, not replace, the associated paper-based submission.

Schema of key decisions in preparing and evaluating major submissions to the PBAC



KEY QUESTIONS TO HELP DETERMINE THE ACCEPTABILITY OF A MAJOR SUBMISSION

Answer the following questions concisely. This will help the PBAC Secretariat and the Pharmaceutical Evaluation Section determine the acceptability of the submission.

(a) Are the indication(s) proposed for PBS listing within the TGA-approved indications (or, if necessary, the ADEC-recommended indications)?

(b) When was the proposed drug recommended by the ADEC (or if not considered by the ADEC, give the date of registration and indicate whether a TGA evaluation report is available)?

(c) Is the comparator justified according to the criteria given in Section 1.5? Give the page number of the submission where the choice of comparator is justified.

(d) Has a thorough search for relevant comparative randomised trials been conducted? Give the page number of the submission where the search strategy is presented.

(e) Does the key clinical evidence in the submission relate to the proposed main indication for PBS listing?

(f) Have the measures taken by the investigators to minimise bias in the key clinical evidence been assessed? Give the page number of the submission where the assessments are presented.

(g) Have the outcomes of the studies been clearly defined? Give the page number of the submission where these definitions are presented.

(h) Has a meta-analysis been conducted? Give the page number of the submission where the methods of the meta-analysis are presented.

(i) Where Section 2.9 and/or Section 3 has been completed, are the cost components tabulated according to the approach given in Appendix L? Give the page number of the submission where the table is presented.

ADVICE ON THE EXECUTIVE SUMMARY OF A MAJOR SUBMISSION

Provide an executive summary of no more than 10 pages. This will be included in the agenda papers for the PBAC meeting and so should be regarded as the sponsor's primary vehicle for communicating with each PBAC member. The executive summary should therefore lay out clearly the key aspects and issues presented in the main body of the submission which is forwarded to each PBAC member along with the agenda. As a minimum, the executive summary must provide the details to address each of the following key aspects.

(a) The Australian approved name, brand name, marketing status and principal pharmacological action of the proposed drug.

(b) The formulation(s), strength(s), pack size(s), maximum quantity(ies), number(s) of repeats and dispensed price(s) requested for PBS listing.

(c) The indication(s) and any restriction(s) being proposed for PBS listing.

(d) The recommended course of treatment.

(e) The main comparator(s).

(f) Whether the key clinical evidence in the submission comes from randomised head-to-head trials, from an analysis of two sets of randomised trials involving a common comparator (eg placebo or other active therapy), or from non-randomised studies.

(g) The main clinical results of the randomised trials and, from these results, the category from Section 2.8 which best describes the proposed drug.

(h) The main results of the cost analysis in the preliminary economic evaluation based on the evidence from the randomised trials, the type of economic evaluation and the results of this incremental evaluation.

(i) The justification for proceeding (or not) to undertake a modelled economic evaluation.

(j) If a modelled economic evaluation has been undertaken:

  (i) the type of economic evaluation;

  (ii) the pivotal assumptions underlying the model (as tested in the sensitivity analysis in Section 3.7); and

  (iii) the incremental ratios from the modelled evaluation.

PART III

GUIDELINES FOR PREPARING THE MAIN BODY OF A MAJOR SUBMISSION

PREPARING THE MAIN BODY OF A MAJOR SUBMISSION

Provide 12 copies of the main body of a major submission.

One copy is provided to each PBAC and ESC member nominated as the discussant for the submission alongside the Committee agenda papers. Other copies are for Departmental advisers and the group allocated to evaluate the submission Each copy must:

(a) be suitably bound;

(b) have a clear and adequate index;

(c) have consistent pagination throughout;

(d) have all cost calculations in Australian dollars ($); and

(e) have attachments containing reports of the key clinical trials, which must be:

    (i) either the published paper and/or the investigator's summary of unpublished trials and adequate details of the trial methods and of any results used in the economic evaluation(s);

    (ii) legible; and

    (iii) in English or be accompanied by a reputable translation.

The main body of a major submission should follow the guidelines in the remainder of this Part as far as possible. To facilitate its evaluation, it should also use the headings of each Section in this Part as appropriate.

1. DETAILS OF THE PROPOSED DRUG AND ITS PROPOSED USE ON THE PBS

1.1 Pharmacological class and action

Give the brand name, Australian approved name and therapeutic class for the proposed drug. What is its principal pharmacological action? What pharmaceutical formulation(s) (ampoule, vial, sustained release tablet etc), strength(s) and pack size(s) is proposed for PBS listing? Appendix A gives details of the information requirements of submissions containing fixed combination products.

1.2 Indications

State the indication(s) approved by the TGA (or recommended by the ADEC or by the TGA delegate or, if none are specifically mentioned in the TGA delegate's report, the indication(s) as contained in the draft product information supplied). Then state the type of restriction sought for PBS listing. If a restricted listing is sought, suggest a wording for the requested restriction. If an unrestricted listing is sought, identify the main indication(s).

Specify the meeting at which the ADEC recommended the proposed drug for the proposed indication(s). If the TGA has not yet granted final approval, base the submission on the recommendation of the ADEC. If a submission is based on the ADEC recommendation, the sponsor must advise the PBAC Secretariat immediately of any variation between the recommended and final approval. If the proposed drug or new indication was not considered by the ADEC, give the date of registration onto the Australian Register of Therapeutic Goods and indicate whether a TGA evaluation report is available.

Ensure that any restriction requested for PBS listing is within the approved indications (it may be narrower, for example to identify the patient group likely to benefit most). Without limiting the option of being narrower, the restriction(s) requested should also be generally consistent with other sections of the product information, such as any eligibility criteria in the clinical trials section. If a restricted listing ("Restricted Benefit", "Authority Required" or other arrangements such as distribution of Highly Specialised Drugs from hospital out-patient departments) is sought for more than one indication, submit separate Sections 1 to 3 for each indication. If an unrestricted listing is sought for more than one indication, identify the main indication. This is defined as the indication likely to account for the largest proportion of patients treated with the proposed drug and should be based on the

estimates of the numbers of patients provided in answer to Section 4.1. Usually the submission need only be for this main indication. However, where there are two or three major indications, none of which is likely to dominate usage of the drug, the submission should repeat Sections 1 to 3 for each indication. If a sponsor is in doubt, the advice of the PBAC Secretariat and/or the Pharmaceutical Evaluation Section may be sought (see also Section 1.5).

If the indication is likely to be unfamiliar to the members of the ESC or the PBAC, it may be helpful to provide a summary of the disease suitable for an informed layman. If so, take no more than two pages to describe the relevant characteristics and the likely impact of the disease, and of its current and proposed management.

1.3 Treatment details

What is the proposed course of treatment?

List the dose, frequency per day, length of course and anticipated frequency of repeat courses of treatment recommended in the current TGA-approved product information.

1.4 Co-administered and substituted therapies

What other therapies, if any, are likely to be prescribed with the proposed drug as part of a course of treatment?

List the therapies, particularly existing PBS drugs, which are likely to be prescribed for use in conjunction with the proposed drug, for each diagnosis/symptom area. This should include drugs which are likely to be used to manage side effects of the proposed treatment. Provide the details requested in Section 1.3 for each drug included in the economic evaluation.

If the proposed drug is listed, what therapies, if any, are likely to be prescribed less for the target patient population:

(a) for the therapeutic indication; or

(b) for the treatment of side-effects of current therapies?

List the therapies, particularly existing PBS drugs, which are likely to be substituted by the proposed drug. Provide the details requested in Section 1.3 for each drug included in the economic evaluation.

1.5 Main comparator

Of the substituted therapies, identify the main comparator(s) and justify the selection.

The experience of the PBAC is that it is infrequent for there to be disagreement over the selection of comparator, but as this is usually an important part of a submission, disagreement can be critical when it occurs. In theory, the main comparator is the therapy which most prescribers will replace in practice. In practice, this has often proved to be difficult to identify. In some cases, comparisons with more than one comparator will be necessary. The following will assist in selecting the appropriate comparator.

(a) If the proposed drug is in a therapeutic class for which pharmacological analogues are already listed, the main comparator will usually be the analogue, which is prescribed on the PBS for the largest number of patients. A reasonable exception would be if there is an important difference between the indications for the proposed drug and the analogues. If so, it may be appropriate to compare with the drug which is prescribed on the PBS to treat that indication for the largest number of patients. If a sponsor is in any doubt the advice of the PBAC Secretariat and/or the Pharmaceutical Evaluation Section may be sought (see below).

(b) If the proposed drug is in a new therapeutic class but will be used for an indication for which there are other drugs widely used to treat that indication, the main comparator will usually be the drug which is prescribed on the PBS to treat that indication for the largest number of patients. (Section 2.2 gives further advice if there is relevant evidence from a comparison of the proposed drug with several drugs widely accepted as clinically equivalent to the main comparator or of the main comparator with several drugs widely accepted as clinically equivalent to the proposed drug).

(c) If no currently listed drug is available, the main comparator will usually be standard medical management (this could include a surgical procedure or conservative management). This should be clearly and consistently defined in both the submission and the comparative randomised trials.

If the drug is supplied in a special formulation (eg sustained release tablets, oral pressurised inhalation), the main comparator selected according to the above criteria should be in a similar formulation, if available.

Prescribing practice can change rapidly and a drug chosen on reasonable grounds at the outset as the main comparator may not always be so. This is particularly likely given the long lead times necessary to obtain primary data as part of Phase III or Phase IIIb trials. Allowance will be made for this during the evaluation of submissions. If a sponsor is designing such a trial with a view to eventual submission to the PBAC, the advice of the PBAC Secretariat and/or the Pharmaceutical Evaluation Section may be sought. No guarantee can be given that the PBAC will be constrained by this advice when considering the eventual submission, as important factors could change, such as a different approved indication to that originally anticipated. A submission incorporating a trial based on this advice will be accepted for evaluation, but it may be necessary to present an analysis based on two sets of randomised trials involving the originally chosen comparator as a common reference (see Section 2.6 for further information).

If the only comparative randomised trials available use a comparator that is different to the main comparator chosen by following the three categories above (for example, these may be trials conducted overseas where the appropriate comparator is different), it may also be necessary to present an analysis based on two sets of randomised trials involving the overseas comparator as a common reference.

If an expert panel or survey has been used to help identify the main indication or the main comparator, Appendix S gives further advice on the necessary background information.

1.6 Differences between the proposed drug and the main comparator

What are the main differences in the indications, contra-indications, cautions, warnings and adverse effects between the proposed drug and the main comparator?

These can generally be determined by a comparison of the current TGA-approved product information for the respective drugs.

2. DATA FROM COMPARATIVE RANDOMISED TRIALS FOR THE MAIN INDICATION

2.1 Description of search strategies for relevant data

Selection of trials for analysis **must** start with a consideration of **all** relevant trials that enable a comparison between the proposed drug and the main comparator for the main indication. An adequate search strategy must be used to locate these trials. This should involve at least three approaches: a search of the published literature (see Appendix B for details of how to describe this search); a search of the Cochrane Controlled Trials Register; and a check with the sponsor's head office and other subsidiaries of the company for further trials (which may be unpublished).

> Describe the search strategies used to retrieve relevant clinical and economic data from the published literature, the Cochrane Controlled Trials Register and from unpublished data held by the company.

This may involve explaining refinements such as the use of "electronic delimiters". These are used to better focus any initial search strategy to the objectives of the search outlined in Sections 2.2 and 2.3.

2.2 Listing of all comparative randomised trials

The PBAC has a strong preference for economic evaluations that are based on so-called "head-to-head" randomised trials that directly compare the proposed drug with the main comparator **where these are available**. There is **no** absolute requirement for head-to-head randomised trials. There is no expectation that companies will carry out a head-to-head trial in Australia or elsewhere solely for the purpose of an economic evaluation for submission to the PBAC.

Where no head-to-head trials are available, other forms of evidence are accepted and given full and proper consideration. An analysis of two sets of randomised trials involving a common reference represents a possible alternative (see Section 2.6 for further information). It is recognised that randomised trials are not always available (for example some drugs for cancer or rare diseases). However, without any evidence from randomised trials, it has often proved difficult to determine whether there is a clinical or economic difference between the proposed drug and the main comparator. If the submission is based on data from non-randomised studies, see Appendix P in place of Sections 2.3 to 2.9 for further guidance.

This hierarchy is intended to identify most easily the key evidence for a major submission. Supplementary evidence can be useful, see Section 2.3 for further advice.

The listing of comparative randomised trials must be complete. The Pharmaceutical Evaluation Section will run an independent literature search. If this search retrieves relevant trials that were not listed in the submission, processing of the submission will stop until the matter has been resolved.

List citation details of all randomised trials that compare the proposed drug directly with the main comparator for the main indication ("head-to-head" trials). If there is none, state this and then list citation details of all randomised trials comparing the proposed drug with other therapies, including placebo, for the main indication. Provide the same details for all randomised trials comparing the main comparator with the same reference treatments for the main indication. If there are no randomised trials of either the proposed drug or the main comparator, state this and then list all non-randomised studies that are relevant to the main indication.

2.3 Selection of the comparative randomised trials

Describe how the comparative randomised trials for reporting have been selected from the results of the literature search. In a technical document or an attachment to the submission, provide the full results (printouts) of the searches. Justify the exclusion of all remaining citations from these searches. List the key trials that remain for further reporting in Sections 2.4 to 2.9.

Appendix C gives further advice on how this should be presented. This identifies exclusions that are likely to be controversial. In such a case, include a copy of the paper in the references to enable independent verification of the decision not to include the trial in the remainder of the submission.

The assessment of the description of trials in response to Appendix D may provide the basis for excluding trials that have methodological flaws. The answers to questions (c), (d) and (e) of Appendix E may provide the basis for excluding some trials which are not relevant to the submission. The answers to questions (a) and (b) (i) of Appendix F may provide the basis for excluding some trials (for example those reporting surrogate outcomes when final outcomes are being reported in other trials).

The main body of the submission should include sufficient details of the key randomised trials as attachments. Where there is more than

one report of a randomised trial (eg a published paper and the sponsor's internal trial report held for regulatory purposes), provide both the published paper and key extracts from the sponsor's trial report (see checklist at the beginning of this Part for details). The results may vary between the reports of the same trial. If so, justify the selection of the source of results extracted for the submission.

If the primary source of evidence in the submission is an independently-conducted meta-analysis published in a peer-reviewed journal and incorporating all important trials listed in this Section, then consult Appendix J in place of Sections 2.4 to 2.6. Alternatively, if the primary source of evidence is a single large trial, then complete Sections 2.4 to 2.9 only for this trial and provide a meta-analysis of any other trials (see Appendix J) which examines whether the other trials are consistent with this trial.

Justify the inclusion of any supplementary randomised trial data. List the supplementary trials that are added for further reporting in Sections 2.4 to 2.9.

To enable evidence of the highest scientific rigour to be considered, in some circumstances it may be reasonable to support the key head-to-head trials with evidence from additional randomised trials, for example if only one under-powered head-to-head trial is available. Possible supportive information includes:

(a) an analysis of two sets of trials involving a common reference that is based on much larger subject numbers;

(b) a meta-analysis including all trials of the proposed drug against several drugs widely accepted as equivalent to the main comparator in terms of effectiveness and safety as well as the head-to-head trials; or

(c) a meta-analysis including all trials of the main comparator against several drugs widely accepted as equivalent to the proposed drug in terms of effectiveness and safety as well as the head-to-head trials.

Supportive randomised trials should be separately identified and included with any other references to the submission. This supportive information should be clearly labelled to distinguish it from the information from the key trial(s).

The clear preference for evidence from the most scientifically rigorous sources does not imply that a minimum standard must be met. The PBAC has and will continue to consider all evidence, but will be most influenced by the results of the most rigorous randomised trials.

2.4 Assessment of the measures taken by investigators to minimise bias in the comparative randomised trials

Provide information on the measures taken to minimise bias in each of the randomised trials listed in response to Section 2.3.

Appendix D lists three sets of methodological topics that are to be used to describe each trial and a supplementary question that is also to be answered for each trial. This is a useful guide to help the PBAC and the sponsor review the scientific rigour of the evidence by assessing the measures taken by the investigators to minimise bias. It is not intended to discourage the presentation of data.

2.5 Characteristics of the comparative randomised trials

Provide information on other characteristics of each of the randomised trials listed in response to Section 2.3.

Appendix E lists a short series of questions that are to be answered for each trial.

2.6 Analysis of the comparative randomised trials

State how the outcomes of each of the randomised trials listed in response to Section 2.3 were analysed.

Appendix F lists a series of questions to help describe the type of information which should be presented for each trial. Additional advice is provided in Appendices H and I on quality of life measures and identifying economic inputs and outcomes respectively.

Appendix J gives advice on deciding whether meta-analysis is appropriate and, if so, what methods may be appropriate. The method(s) of statistical pooling and statistical tests used should be described and justified. If any of the trials listed in response to Section 2.3 are excluded from the meta-analysis, the reasons for doing so (eg on grounds of inadequately minimising bias) should be explained and the impact each exclusion has on the overall meta-analysis should be examined.

In the case of an analysis based on two sets of randomised trials involving a common reference, further information is required. This analysis indirectly compares the proposed drug with the main comparator by comparing one set of trials in which subjects were randomised to the proposed drug or to a common reference with another set of trials in which subjects were randomised to the main

comparator or to the common reference. The common reference is often placebo, but may be a drug from another therapeutic class. Before comparing the proposed drug with the main comparator, the comparability of the two sets of trials must be established. The answers to (c) and (d) in Appendix E for the trials in the two sets should be assessed for any important differences. The results for the common reference should also be assessed for any important differences.

2.7 Results of the comparative randomised trials

Present the results of each type of patient-relevant outcome of each trial (or meta-analysis) separately as the extent of any differences in outcomes between the proposed drug and the main comparator in terms of their natural units.

Present data collected for both resources used and health outcomes gained. For each patient-relevant outcome listed in response to (a) in Appendix F, report differences between the proposed drug and the main comparator, as well as the 95% confidence intervals for these differences.

In the case of an analysis of two sets of randomised trials involving a common reference, present the extent of any difference between the proposed drug and the main comparator after adjusting for any differences in the trial populations and/or the results of the common reference.

2.8 Interpretation of the results of the comparative randomised trials

The interpretation of the clinical data presented in the previous sections is crucial in determining the success of the submission. If claimed clinical advantages for the proposed drug do not have a basis in the results of randomised trials, they are unlikely to be accepted by the PBAC.

Based on the results of the trials presented in Section 2.7, state the category which best describes the proposed drug.

(a) The proposed drug has significant clinical advantages over the main comparator:

  (i) it is significantly more effective than the main comparator and has similar or less toxicity; OR

  (ii) it has similar effectiveness to the main comparator, but has less toxicity; OR

  (iii) it is significantly more effective than the main comparator, but has more toxicity.

(b) The proposed drug is no worse than the main comparator in terms of effectiveness and toxicity.

(c) The proposed drug is less effective than the main comparator, but has less toxicity.

Categorising the proposed drug as above helps determine the most appropriate form of economic evaluation.

State which type of economic evaluation has been conducted.

(a) In the case of a clinical advantage, the importance of any advantage in the context of the severity and prognosis of the indication should be discussed (see (b) (v) of Appendix F for advice). It is important to quantify the increase in benefits and weigh them against any increase in costs. Cost-effectiveness analysis (CEA) or cost-utility analysis (CUA) are suitable forms of evaluation in this situation (see Appendix K for further discussion of the types of economic evaluation).

  It is preferred that, wherever possible, the outcomes presented include final outcomes such as deaths prevented, life-years gained, or quality-adjusted life-years gained (see also Appendix O).

  In the case of (ii), take care when incorporating the differences in adverse outcomes between the proposed drug and main comparator into the economic evaluation (see below). In the case of (iii), the therapeutic advantage is less clear as there are clinical trade-offs as well as cost trade-offs.

It is important to take care when including information on adverse outcomes in the evaluation. Adverse outcomes have two main impacts on an economic evaluation - they affect the medical outcomes of drug treatment and they contribute to the total cost of therapy. Avoidance of an adverse outcome typically associated with use of a class of drug may be an important and intended outcome of therapy. Adverse outcomes may affect quality of life particularly if they have to be tolerated over long periods. Adverse outcomes may also lead to discontinuation of the drug leading to substitution of another drug or other medical intervention. A comparative analysis of time to treatment cessation of the proposed drug and the main comparator on the basis of "intention-to-treat" is useful in this situation. Adverse outcomes themselves can contribute to costs through unintended hospitalisation, additional procedures and investigations. Take care to ensure that these factors are dealt with appropriately.

(b) When the proposed drug is regarded as therapeutically equivalent to existing drugs, the appropriate type of economic evaluation is a cost-minimisation analysis. Effectively this means that the proposed drug is unlikely to be granted a higher price than competitors' drugs on the PBS and any restrictions applying to these drugs will apply to the proposed drug.

A claim of no advantage must also be based on the results of well-conducted studies, preferably "head-to-head" randomised trials. The possibility of failing to find a clinically important difference should be discussed (see (b) (v) and (c) of Appendix F for advice). If the claim of no advantage is not also supported by clinical data which enables a judgement regarding equi-effective doses, the submission will be difficult to evaluate. Evidence of the highest scientific rigour should therefore be provided to support the PBAC judgement regarding equi-effective doses. See Appendix G for the hierarchy of sources of evidence for equi-effective doses.

A submission need not include Sections 2.9 or 3 in the case of cost-minimisation except where there are differences in the costs of prescribing or administering the two alternatives. Take particular care in the justification of any decision to model a therapeutic difference due to some factor that is excluded in the trials. Only rarely has a model been accepted which contradicts a conclusion from the evidence of randomised trials that the alternatives are therapeutically equivalent.

(c) The therapeutic advantage is less clear in this case as there are clinical trade-offs as well as cost trade-offs. It is important to take care when including the information on adverse outcomes in the evaluation.

2.9 Preliminary economic evaluation based on the evidence from the comparative randomised trials

Provide a preliminary economic evaluation of substituting the proposed drug for the main comparator based on the results of the randomised trials presented in Section 2.7.

The preliminary economic evaluation provides transparency in the move from the clinical and economic comparison of the proposed drug and its main comparator under trial conditions to an appropriate modelling of the clinical and economic comparison under conditions that are likely to apply to its use on the PBS. The preliminary evaluation is not the primary decision aid where the modelled economic evaluation is judged to be valid.

Identify and justify the outcome that best reflects the comparative clinical performance of the alternatives (eg the primary outcome and/or the final outcome; see also Appendix O). Using the data presented in Section 2.8, relate this outcome to the net cost of resources provided to deliver the therapies in the trial. Value the extent of use of each resource type in dollar terms from the perspective of society using the unit prices recommended in the *Manual of Resource Items and their Associated Costs* (see Appendix L - present sources of unit costs and calculations in a technical document or an attachment to the submission). Discounting to estimate the net present value of both outcomes and resources may be needed (see Appendix L). Present the results of this economic evaluation as an incremental ratio. Conduct a sensitivity analysis on this ratio by substituting the upper and lower 95% confidence limits of the difference in outcomes achieved. In the case of an analysis of two sets of randomised trials involving a common reference (see Section 2.7), also provide the separate incremental ratios of the proposed drug against the common reference and of the main comparator against the common reference.

3. MODELLED ECONOMIC EVALUATION FOR THE MAIN INDICATION

3.1 Need for a modelled evaluation

Justify the decision as to whether or not to present a modelled economic evaluation.

Frequently the randomised trials will provide insufficient information on which to base a judgement about the full clinical and economic performance of the proposed drug. In these circumstances (which are a matter of judgement), a modelled economic evaluation will be useful to the PBAC. Appendix N contains advice on the circumstances where a modelled economic evaluation is likely to be informative.

A submission that does not include a modelled economic evaluation may omit the rest of Section 3.

All models have three basic attributes: input variables, a structured arrangement to manipulate those variables and the outputs that form the results. Sensitivity analyses are conducted to clarify those components of variables or structure that drive the model and thus to assess the robustness of its results and conclusions. This Section is intended to facilitate the transparent presentation of these three attributes of a model and its sensitivity analyses.

3.2 Population used in the modelled evaluation

What population has been used as a basis for the calculation of costs and outcomes?

This may be a hypothetical population (eg 100 typical patients with angina; 1000 hypertensive males aged 40-60 years). If necessary, justify the definition of the population in relation to both the target population for the PBS and the population in the trials.

3.3 Approach used in the modelled evaluation

Describe the type of economic evaluation that was modelled (see Appendix K) and the approach used.

The approaches to modelling an economic evaluation are varied. The following list is not exhaustive, but include one or more of a

spreadsheet; a decision analysis; a Markov process or a Monte Carlo simulation. Appendix M gives specific advice on the presentation of a decision analysis involving more than one time period, including a Markov models or a Monte Carlo simulation.

In the case of a complex analysis, provide a technical document or an attachment to the submission to give details of calculations and a copy of any computer model used. Ensure that clear cross-references are provided as appropriate between the technical document or attachment and the relevant item in the main body of the submission. Spreadsheet computer models should be formatted in the software used by the PES (currently Microsoft Excel 97) or be in a format that can be read by this software. Check with the PES if using software other than the current software. Copies of the original sources of data or opinion used in the model should also be provided. These separate documents are assessed during the evaluation, but are forwarded to a Committee member only at his or her request.

3.4 Variables in the modelled evaluation

All variables in the model must be listed and documented. It would be preferable to do this in a table. Each variable's name (and definition as necessary), quantity and source must be provided.

Variables include:

(a) probabilities in each branch of a decision analysis, paying particular attention to the probabilities that simulate a treatment effect by differing between the two decision models that represent the proposed drug and its main comparator;

(b) patient-relevant outcomes; and

(c) resource items (these variables must also include the unit cost).

Names of variables should be sufficiently precise; for example an AN-DRG item number is more precise than an episode of hospitalisation. For each source, provide full citation details, including item number or page number as appropriate. It may be necessary to cite more than one source for some variables (eg the quantity and unit cost of a resource item). For some variables, an assessment or justification should be provided as appropriate (eg if using data or opinion that differs from the evidence previously provided in Section 2.7, or in the case of a resource, if the proposed unit cost is different to that recommended by the *Manual of Resource Items and their Associated Costs*).

For assistance in identifying items for (b) and (c), and in defining how each is measured, see (a) and (b) (i) of Appendix F and Appendices H and I.

3.5 Structure of the modelled evaluation

The model's structure must be described.

Identify the options considered and justify the option chosen when designing the model. Consider implicit assumptions built into model structures and comment if appropriate. Indicate whether the modelled outcomes represent the final outcomes of treatment. Where appropriate, explain and justify the linking of measured short-term and/or surrogate outcomes to the modelled final outcomes, including a justification for how these are quantified over time. Define and justify the appropriate time horizon for follow-up.

For assistance in considering and justifying the final outcomes of treatment, see Appendix O. The modelled evaluation should be based on the outcome measure(s) that most closely and validly estimates the final outcome (see Appendix O). The choice of any outcome measure should be justified – more than one type of outcome measure may be needed in some model types and/or to cover both desired and adverse outcomes.

If not directly measured in the randomised trials, the modelled evaluation may include derived utility weights for the outcomes in this Section (see Appendix H).

For assistance in using data from non-randomised studies and expert opinion in modelling, see Appendices P and S respectively.

Where outcomes have been quantified over time, explain the underlying assumptions and rationale. For instance, the number of relapses of peptic ulcer is unlikely to remain constant over successive time periods. In other diseases, assuming a linear relationship between outcomes and time may be clinically plausible. For further assistance on modelling the relationship between surrogate outcomes and final outcomes, see Appendix O.

The appropriate time horizon for follow-up relates to the disease and treatment patterns and an estimation of the time period(s) in which the outcomes are expected to occur from the natural history of the disease. In the case of urinary tract infection, 15-20 days might be appropriate. In the case of hypertension or peptic ulcer, a time horizon over several years might need to be considered.

3.6 Results of the modelled evaluation

> Present the results of the model firstly in disaggregated form, then in increasingly aggregated form (with discounting as appropriate, see Appendix L). Present the appropriately aggregated and discounted results separately for outcomes and resources and separately for the proposed drug and its main comparator. Finally, present the incremental cost of achieving each additional unit of outcome with the proposed drug when substituted for the main comparator.

If the model estimates change over time, present key outputs (such as incremental costs, incremental outcomes and incremental cost-effectiveness) on a graph with time on the x-axis against the changing outputs on the y-axis.

The presentation of disaggregated results depends on the type of model. For example, where possible, present the quantity of each type of resource provided in its natural units as well as its cost valued in dollar terms, and/or present the costs and outcomes associated with each branch in the tree of a decision analysis.

For assistance in valuing each type of resource in dollar terms, see Appendix L.

If the submission includes a claim for indirect benefits, present the results both with and without these included (see Appendix L for rationale).

If the proposed drug is both more expensive and more effective, it is helpful to know how much more it costs to achieve the extra units of outcome in the form of an incremental ratio. Where provided, incremental ratios should be highlighted. Examples include:

(a) extra AU$ per extra bacteriological cure;

(b) extra AU$ per extra quality-adjusted life-year (QALY);

(c) extra AU$ per extra patient free of ulcer for 1 year; and

(d) extra AU$ per extra year free of progression to AIDS.

3.7 Sensitivity analyses of the modelled evaluation

One-way sensitivity analyses must be conducted on all variables using extreme values. Present in tabular form and as a tornado diagram. Conduct two-way sensitivity analyses on all variables shown to be sensitive in the one-way analyses. Present in tabular form and as graphs.

Compare any aspect of the model's results against any corresponding results obtained empirically and comment on any differences. It may be helpful to examine the sensitivity of the model to any changes in assumptions concerning the structure of the modelled evaluation which are important but debatable.

These analyses are important to determine how sensitive the evaluation is to changes in the variables that have been used in the evaluation. If discounting has been necessary, the robustness of the conclusions to different discount rates (including a zero discount rate on non-monetary outcomes alone and on both costs and outcomes) should be tested.

4. ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

The preceding sections will assist the PBAC in its decision about whether a drug should be subsidised and are based on a comparison of health benefits and net costs from the perspective of society as a whole. However, the Commonwealth Government will need to make provision for the necessary funds required by a successful submission. The following sections adopt the perspective of government health budgets to assist the Commonwealth Government consider these financial implications and so are calculated in a way which allows the implications for the PBS to be separated from other government costs.

4.1 Estimated extent of use of the proposed drug

> Estimate the likely prescription volume of the proposed drug on the PBS for at least each of the first two full years from the date that it is listed on the Schedule.

An epidemiological approach should be adopted to estimate the likely patient numbers projected to be eligible for the proposed drug and its comparators. In the case of a drug to treat an acute condition (where treatment is expected to last up to a year or two), this will be most accurately reflected in the annual incidence of the disease. In the case of a drug to treat a more chronic condition, estimates of the prevalence of the disease are more appropriate. Where an extension of survival is expected, allowance for an increase in prevalence may be necessary.

Estimate the likely patient numbers for each proposed indication for PBS listing separately and then sum these estimates. This should form the basis of the estimates of the likely prescription volumes of the proposed drug for at least each of the first two full years from the date that it is listed on the Schedule. These estimates can then be modified to account for the likely market share for the proposed drug and any anticipated growth in the overall market. Justify the approach used to make these modifications and provide the source of any data eg market research data or Pharmaceutical Benefits data for therapeutically equivalent drugs which are already listed or data on the use of the drug in similar overseas markets. If the submission is of a cost-minimisation analysis, the important financial consideration is whether and, if so, to what extent listing is likely to increase the overall market for the group of drugs (or is likely to increase the current growth rate of this overall market).

4.2 Estimated extent of substitution of other drugs

Estimate the change in the extent of use of other drugs using the information provided in Sections 1.4 and 4.1.

4.3 Estimated financial implications for the PBS

The implications for PBS expenditure are:

$(d*s_d) - (\Sigma c_i*s_i) + (\Sigma e_j*s_j) - (\Sigma f_k*s_k)$

where:

d = expected sales (quantity) of the proposed drug;

s_d = the PBS unit subsidy on drug d;

c_i = the reduction in the quantity of competing PBS subsidised drug i resulting from a successful submission;

s_i = the PBS unit subsidy on this drug;

e_j = the quantity of PBS subsidised drug j co-prescribed with d;

s_j = the PBS unit subsidy on this drug;

f_k = the reduction in the quantity of PBS subsidised drug k used to treat side effects to the i drugs; and

s_k = the PBS unit subsidy on this drug.

In the case of each drug, up to three subsidies may apply due to three patient co-payments - the general co-payment ($22.40 at time of revision), the general safety-net co-payment and concessional co-payment ($3.60 at time of revision) and concessional safety net (no co-payment at time of revision). Weight the PBS unit subsidy for each drug by the proportion of use in each co-payment category. The weights applied to the main competing drug i should be applied to the proposed drug d. If different weights can be demonstrated as likely to apply, these should be presented instead. Further information is provided in Section 9 of the current *Manual of Resource Items and their Associated Costs*

The j and i drugs should include those identified in Section 1.4. There will be no i drugs if drug d has no competitors and/or it is designed to replace a medical procedure.

Side effects can be ignored if trials have shown that they are insignificant, or if they are similar for drug d and its major competitors. If there is insufficient information available from randomised trials to include the impact of side effects on PBS expenditure, this should be noted.

The time horizon for this analysis should be until the proposed drug is predicted to have achieved a peak or stable market share under the proposed PBS listing. Estimate the annual financial implications to the PBS to this time horizon or for at least two years after the date of listing on the PBS. This analysis should use constant prices, no allowance for inflation and a zero discount rate.

4.4 Estimated financial implications for government health budgets

Estimate the financial implications by adding the following calculations to the costs estimated in the previous equation:

(a) the medical costs of treating side effects to drug d that would be met by Commonwealth or State governments (eg doctor visits, hospital stays, procedures);

minus (b) savings in the same type of medical costs from treating fewer side effects of competing drugs;

minus (c) savings in medical costs met by Commonwealth or State governments from fewer competing procedures (eg drug d substitutes for an operation);

minus (d) savings in medical costs met by Commonwealth or State governments because drug d reduces the burden of illness (eg anti-hypertensives reduce strokes).

This analysis should use constant prices, no allowance for inflation and an annual discount rate of 5% as in Sections 2.9 and 3.6. Justify the choice of time horizon if it is not the same as Section 4.3.

The costs in this and the previous section should be estimated in terms of the payments actually made or the financial savings actually realised by the governments. These involve different unit prices than those recommended in the current *Manual of Resource Items and their Associated Costs* (which reflect the opportunity cost in an economic evaluation rather than a payment or saving in a financial analysis). Although the calculations appear complicated, in most cases only (d) needs to be added to the costs to the PBS described in Section 4.3. In addition, the unit quantities of drugs and medical inputs required for these estimates will have been collected and used in the analyses presented in Sections 2.7 and 3.6.

APPENDIX A

ADDITIONAL INFORMATION REQUIRED FOR FIXED COMBINATION PRODUCTS

REFER: Section 1.1.

This Appendix applies to submissions for combination products seeking subsidisation under the PBS. These are the minimum requirements that products need to meet to be eligible for PBAC consideration.

This Appendix relates to fixed combination products either presented as combinations of drugs in a single dosage form or as individual dosage forms in composite packaging.

It does NOT relate to drugs which for specific indications are almost invariably used together in fixed dose combinations for clinical reasons such as oral contraceptives, hormone replacement therapy and H. pylori eradication regimens.

Submissions must comply with the remainder of these Guidelines concerning clinical and economic data. Pricing of combination products will normally be no greater than the sum of the individual components (at the current price to pharmacist level). Where a higher price is requested, this must be supported by evidence of enhanced clinical outcomes and acceptable cost effectiveness.

Where the combination product will substitute for two or more products, the price to pharmacist should reflect the sum of the individual components as a function of the anticipated proportion of substitution.

The labelling of the product should clearly identify the component generic drugs.

Conditions required to be met for consideration of a combination product:

(a) the product should be approved by the TGA and meet all clinical criteria required by the TGA;

(b) the component products should preferably be listed on the PBS;

(c) restrictions for the component products should be consistent with those proposed for the combination;

(d) the doses of the listed component products and the proposed combination should be consistent;

(e) there should be additive (not necessarily synergistic) beneficial effectiveness of the components;

(f) the combination should not encourage or result in an inappropriate increase in overall utilisation of the components, nor in inappropriate use of one or both components in specific patient groups;

(g) the combination product should not result in inappropriate dosing of either component, nor contain components which require individual dose titration; and

(h) the combination product should not result in unnecessary proliferation of products and/or dose forms.

A demonstrated clinical outcome advantage with acceptable cost effectiveness will provide strong support for listing.

Where benefits in patient convenience or cost savings to the PBS or the patient are claimed, these should be demonstrated and will be regarded as supportive but not necessarily an adequate basis for listing.

Where improved compliance is used as an argument for enhanced clinical outcomes, data should be provided.

APPENDIX B

DESCRIPTION OF THE SEARCH OF THE PUBLISHED LITERATURE

REFER: Section 2.1

The methodology used to search the literature is pivotal to assessing the completeness of the search. Specify:

(a) the medium (eg dial-up, CD-ROM etc) and service provider(s) (eg Dialog, Silver Platter) used to conduct the search;

(b) the specific databases searched (including at least MEDLINE, EMBASE, the Cochrane Controlled Trials Register and possibly SCISEARCH), as well as databases internal to the company;

(c) the date the search was conducted;

(d) the date span of the search (which should be up to date to the most recent database update);

(e) the complete search strategies used, including the search terms (key or MeSH words) and the relationship (sets and boolean) between the search terms; and

(f) any supplementary searches, especially manual checking of references in the retrieved papers from the database searches.

APPENDIX C

PRESENTING THE SELECTION OF COMPARATIVE RANDOMISED TRIALS

REFER: Section 2.3, Appendices D, E and F

Against each citation in the results (printout) of the literature search that is not presented further in Section 2, indicate the reason for its exclusion. Present a summary of the selection process and outcomes in Section 2.3.

Indicating the reason for excluding a citation in the results of the searches

Not all citations in the results (printout) of a literature search need be presented in Section 2. There are many possible reasons for excluding citations that are unlikely to be disputed. Some of these may be also used to exclude citations in focussing the strategy of some electronic literature searches (see Section 2.1). The reason for excluding any remaining citation should be indicated alongside the citation in the printout.

If a trial is excluded for any of the following reasons, the exclusion may be disputed. Annotate the printout of the literature search accordingly and provide a copy of the full paper.

1. The trial has a serious methodological flaw in randomisation, follow-up or blinding (see Appendix D).

2. Trial subjects do not overlap with patients likely to receive the proposed drug on the PBS (see (c) in Appendix E).

3. The trial uses a different dosage regimen or form to that proposed for listing (see (d) in Appendix E).

4. The trial has inadequate duration of follow-up (see (e) in Appendix E).

5. The trial measures an outcome that is not relevant to the submission (see (a) and (b) (i) Appendix F).

These exclusion criteria are optional. Depending on the data available, applying these exclusion criteria would not be appropriate if they exclude the most scientifically rigorous evidence available (eg it would not be appropriate to exclude a randomised trial if no more relevant randomised trial is available). If there is uncertainty about whether to exclude a trial, it is usually wiser to include it.

Presenting a summary of the selection of citations in Section 2.3.

Use a flow chart or table to summarise the exclusion of citations from the results of the searches reported according to Section 2.1. The reasons for exclusion should be cross-referenced to the detailed reasons indicated on the printout of the literature search. The summary should also indicate the citation details of any excluded citation that reports a relevant systematic overview or meta-analysis.

APPENDIX D

MEASURES TAKEN BY INVESTIGATORS TO MINIMISE BIAS IN EACH TRIAL LISTED IN RESPONSE TO SECTION 2.3

REFER: Section 2.4; Appendix F (b) (iv)

This appendix is designed as a useful guide to help the PBAC and the sponsor review the scientific rigour of the evidence by assessing the measures taken by the investigators to minimise bias. It is not intended to discourage the presentation of data.

For each of the following methodological topics, choose the description that best fits each trial and answer the supplementary question for each trial. If there is more than one trial, tabulate the responses.

Randomisation: it is important that clinical staff are unable to predict which treatment a patient will receive prior to a final decision being made regarding entry to the trial. Which of the following best describes the randomisation technique used?

1. No details of randomisation were reported, or the method used was inadequate (eg randomisation according to the day of the week, even/ odd medical record numbers).

2. An insecure randomisation method was used, where clinical staff could possibly learn of the treatment assignment (eg randomisation sequence kept in the clinical area and open/unblinded trial; treatment assignment kept in consecutive "sealed" envelopes and open/unblinded trial).

3. A secure randomisation method was used, where the randomisation sequence was kept away from the clinical area and administered by staff not directly involved in patient care (eg randomisation performed at a separate site available through a toll-free telephone number or by the pharmacy department after the decision has been made to enter the subject in the trial).

Adequacy of follow-up: it is important that an attempt is made to summarise the trial outcomes for all subjects who were included in the trial. A full "intention-to-treat" analysis is the preferred basis for an economic evaluation that attempts to model the likely impact of the drug in the community. Which of the following best describes the adequacy of follow-up?

1. There were significant numbers of drop-outs with no assessment of trial outcome(s) in the subjects who dropped-out, and drop-out rates differed between treated and control groups.

2. There were some drop-outs with no assessment of trial outcome(s) in the subjects who dropped-out, and drop-out rates were (approximately) equivalent in treated and control groups.

3. Trial outcome(s) were assessed in all treated and control subjects who did not withdraw from the trial.

SUPPLEMENTARY QUESTION: summarise for each comparison group the number randomised to treatment, the number of drop-outs and the number of subjects who were lost to follow-up.

NOTES: a drop-out stops the trial medication for a medical reason or a protocol violation but can and, particularly for an economic evaluation, should still be followed-up, whereas a subject who unilaterally elects to withdraw from the trial is deemed to be lost to follow-up.

Blinding of outcomes assessment: it is important that where the comparator is not indistinguishable by visual inspection or taste, or where there is a high chance of "unblinding" (eg oestrogen or beta-blocker treatment), that the observer responsible for measuring the trial outcome remains unaware of the treatment assignment. Which of the following best describes the blinding of the outcomes assessment?

1. There was an inadequate attempt (or no attempt) to blind observer(s), and the measurement technique was subject to observer bias (eg blood pressure measurement with standard sphygmomanometer, measurement of vertebral height on an X-ray, quality of life instrument).

2. The observer(s) were kept fully blinded to treatment assignment, or the measurement technique was not subject to observer bias (eg measurement of bone mineral density or survival).

NOTES: the observer may be a trial investigator and/or a subject. To maintain "full blinding", it is usually necessary to blind all people directly involved in the care of the trial subjects and the trial subjects themselves (ie double-blinding) to prevent "unblinding" of the observer.

Purpose of these assessments

The intention of these assessments is to provide the sponsor and the PBAC with a clear idea of which trials are of the highest scientific rigour and which are therefore likely to give the most accurate estimate of how well the proposed drug works. There is no minimum standard, but the PBAC is most likely to be persuaded by the data from the trials of the highest scientific rigour.

APPENDIX E

CHARACTERISTICS OF EACH TRIAL LISTED IN RESPONSE TO SECTION 2.3

REFER: Sections 2.5 and 2.6; Appendices N (c) and Q

Answer each of the following questions for each trial. If there is more than one trial, tabulate the responses.

(a) Was the design parallel-group or cross-over?

(b) Was the trial conducted in Australia (or were one or more centres of the multi-national trial located in Australia)?

(c) How do the subjects included in the trial compare with patients who are likely to receive the proposed drug on the PBS? Consider factors known to affect outcomes in the main indication such as demographics, epidemiology, disease severity, setting.

(d) What dosage regimens were used in the trial - are they within those recommended in the current TGA-approved product information?

(e) What was the median (and range) duration of follow-up of the trial?

NOTES:

FOR (a) If the submission includes one or more cross-over trials, indicate for each such trial whether a carry-over effect is likely.

FOR (b) This may be particularly useful in assessing the extent to which there is a change in the patterns of resource provision. For several reasons (such as different incentives), patterns of resource provision seem to differ between health care systems more than patient responses to a drug across different health care systems.

FOR (c) This forms the basis of the consideration of the following three points.

Firstly, how do the trial subjects compare with typical Australian patients suffering from the relevant condition(s), for example in terms of age and sex distribution or of the natural history of the condition(s)? Are any differences likely to matter?

Secondly, how do the trial subjects compare with Australian patients in terms of disease severity? This can be important. A new drug may be cost-effective when use is confined to patients with severe disease but not when it is used to treat patients with milder disease who may respond to less effective and less expensive therapies. It may be possible to estimate the likely impact of this by performing sensitivity analyses in a modelled evaluation (see Section 3.7).

Thirdly, is the trial setting relevant to that of the PBS? For example, most PBS drug use is in the community rather than in a hospital, so a trial in subjects with severe disease requiring hospitalisation may only be relevant in particular circumstances (such as a Highly Specialised Drug or a drug for use in private hospitals).

FOR (d) The trial should use the correct doses of the proposed drug and the main comparator (and a suitable duration of therapy where this is relevant). Doses and duration should be those recommended in the product information as optimal for the relevant indication. These may differ from those shown by market research to be actually used in the community. However prescribing of higher than recommended doses (at higher cost) of a comparator drug is unlikely to be accepted as an argument for a higher price for the proposed drug.

FOR (e) The duration of follow-up for a trial subject is the length of time between randomisation and the end of blinded follow-up of that subject. The duration of non-blinded follow-up of drop-outs should be excluded from the calculations.

APPENDIX F

ANALYSIS OF THE OUTCOMES OF EACH TRIAL LISTED IN RESPONSE TO SECTION 2.3

REFER: Sections 2.6, 2.7, 2.8 and 3.4; Appendices O and Q

Answer each of the following questions for each trial. If there is more than one trial, tabulate the responses.

(a) Define the patient-relevant outcomes measured. Specify enough details of the measurement for the PBAC to assess its importance (eg supine/ erect blood pressure).

(b) For each outcome at (a):

(i) describe the natural unit of measurement;

(ii) report the size of the effect;

(iii) provide a 95% confidence interval;

(iv) state whether "intention-to-treat" was used for the analysis - if not, can this form of analysis be conducted from the data available from the trial? Explain how data from drop-outs and withdrawals were incorporated into the analysis; and

(v) discuss definitions of any clinically important differences.

(c) If the trial was "negative" (failed to detect a difference), was the power of the trial calculated? If so, what was the result?

(d) If the trial measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.

NOTES:

FOR (a), See also Appendix O for further assistance. Examples of patient-relevant outcomes include:

(i) primary clinical outcomes;

(ii) quality of life or utility measures (see Appendix H for further assistance); and

(iii) economic inputs and outcomes (see Appendix I for further assistance).

FOR (b) (i) It is an advantage in economic evaluation if trial outcomes can be expressed as the time to a particular event (examples of relevant events are death - as in a survival analysis, or cessation of the drug). In such instances, differences in outcomes can be measured as the integral between the curves in time-to-event plots for the two therapies. If not available, the number of successes or failures of treatment (eg number of patients surviving; number of patients achieving target blood pressure; number of patients achieving a specified level of airways control; number of patients achieving a target Hamilton rating score for depression etc) are preferable to a mean change in the physiological variables. An exception could be in the case of a cost-minimisation analysis, where the mean change to a physiological variable may be sufficiently responsive to detect small but clinically important differences.

FOR (b) (ii) For dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic.

FOR (b) (iii) The respective p-value is an alternative, but is less preferred.

FOR (b) (iv) For all important outcomes (both resources provided and health benefits) the trials should be analysed on the basis of "intention-to-treat". This form of analysis is the most appropriate for estimating the likely benefits of general use of a drug in the community. For a definition of drop-outs and withdrawals, see the note for "adequacy of follow-up" in Appendix D.

FOR (b) (v) This is particularly important in the case of continuous variables where large trials may detect statistically significant but clinically unimportant differences between treated and control groups. It is helpful if a clinically important difference can be specified.

FOR (c) In the case of "negative" trials, it is helpful if an estimate can be provided of the power of the trial to detect a clinically important difference between the treated and control groups. This can be important in the interpretation of the results of cost-minimisation analyses where the two drugs are claimed to have equivalent effects.

FOR (d) Trials often target many outcomes at a variety of different times resulting in a large number of hypotheses to be tested. If not adjusted for multiple comparisons, the odds will be high that through chance alone a statistically significant difference will emerge in one of these comparisons.

APPENDIX G

HIERARCHY OF SOURCES OF EVIDENCE FOR EQUI-EFFECTIVE DOSES

REFER: Section 2.8

Hierarchy

Level 1: HEAD-TO-HEAD RANDOMISED TRIAL(S) WHERE DOSES OF BOTH DRUGS ARE TITRATED AGAINST A RESPONSE OR WHERE DOSES OF BOTH DRUGS ARE FIXED IF THE DRUGS ARE GIVEN ACCORDING TO A FIXED PROTOCOL. These trials should generally use doses within those recommended in the drug's Australian product information. The principle of full follow-up is addressed below under how calculations should be performed.

Level 2: HEAD-TO-HEAD RANDOMISED TRIAL(S) WHERE DOSES OF ONE OR BOTH DRUGS ARE ARBITRARILY FIXED. The concern here is that the drugs may not have reached the same point on their respective dose-response curve if the doses are fixed. Fixing the dose of both drugs may be better than fixing the dose of just one drug as the latter introduces a clearly unbalanced approach. Note also that calculating the average dose from a trial in which subjects are randomised to different doses of the same drug does not form an acceptable basis for directly determining equi-effective doses, although such a trial may be important in demonstrating the existence and extent of a dose-response effect.

Level 3: A COMPARISON OF TWO SETS OF RANDOMISED TRIALS WITH A COMMON REFERENCE.

Level 4: NON-RANDOMISED STUDIES WHERE BOTH DOSE AND EFFECT ARE MEASURED.

Level 5: NON-RANDOMISED STUDIES (INCLUDING MARKET RESEARCH DATA) WHERE DOSE, BUT NOT EFFECT, IS MEASURED. At this level, different approaches may have to be justified in different circumstances. If doses can be calculated directly from the Authority Database, then this would be preferable to market research data (eg IMS or Foresearch) which require extrapolation from sampled data. Market research data is limited to GP prescribing, so ad hoc surveys may be needed for drugs extensively prescribed by specialists.

An accurate estimate of the extent of specialist prescribing can be determined by prescriber profiles of PBS drugs. Market research data may also be needed where the same formulation and strength of drug is used at different doses for more than one indication.

The WHO Defined Daily Dose (DDD) does not fit in the above hierarchy, but can provide supporting information.

Calculation of equi-effective doses

Equi-effective doses should be calculated at "steady-state". In other words the dose of each drug should be the average dose used by the remaining patients after dose titrations are complete and excluding patients who discontinue the drug (note that this is similar to the method used to calculate equi-effective doses from Level 5 evidence).

If there is more than one trial/study, the weighted average dose is calculated using the number of patients still on the drug at steady state as the weighting factor. There is no justification for weighting the doses between trials/studies, by the duration of therapy in the trial/study as well as by the number of patients.

It is accepted that, in circumstances where a sponsor does not have access to the primary data from a trial/study, the sponsor will be limited to basing its calculations on the way the doses are reported in the published report. For example, the Sponsor may have to weight the average doses by the number of patients enrolled rather than the number of patients at steady state.

The context for determining equi-effective doses

Determining equi-effective doses has proven a difficult issue for several drugs proposed for listing, but it only applies in the context of a cost-minimisation analysis. On occasion, this may delay the listing of a product as disagreements on equi-effective doses have to be addressed in re-submissions. This is unsatisfactory for both the PBS and drug sponsors.

Determining equi-effective doses is unlikely to be difficult where a standard recommended dose is followed with very little variation in doses.

Determining equi-effective doses is difficult when one or both drugs is at the plateau of its dose-response curve. In this circumstance, a large change in comparative dose makes a large difference in comparative cost but little difference in comparative response.

A related consideration is the likelihood of a “ceiling effect”, in which one but not the other of the drugs has reached the top of its dose-response curve. Where there is evidence to suggest that this has occurred, then further consideration needs to be given to whether the drugs are truly equi-effective.

APPENDIX H

MEASUREMENT OF QUALITY OF LIFE AND UTILITY; ESTIMATION OF QUALITY-ADJUSTED LIFE-YEARS

REFER: Sections 2.6 and 3.4; Appendices F (a) and O

Use of quality of life instruments

For drugs which cure short-term illnesses (eg infections) quality of life is unlikely to be an issue. It may also be reasonable to assume that certain events which may themselves be serious do not greatly impair quality of life in the survivors (eg pneumonia). In these and other instances, quality of life does not need to be considered in the evaluation.

Where a change in quality of life is the principal intended final outcome (Appendix O), a quality of life measure should be considered. This is true for some indications (eg relief of pain, treatment of depression, treatment of some cancers) in which improved quality of life is the principal aim of therapy. Alternatively, quality of life may actually be impaired by the proposed drug or by the main comparator (or other intervention). Quality of life measures may supplement other clinical measures.

Quality of life instruments include global quality of life scales and disease-specific rating scales (eg for pain or depression), which may themselves be the surrogate outcome indicators used as the primary measure of outcome in the trials. Increasingly trials are collecting data using both types of quality of life instrument.

Where a quality of life instrument is used, details should be provided on the instrument. Because currently there is controversy over which quality of life instruments are most acceptable, special attention should be paid to the following parameters:

(a) the validity of the instrument;

(b) the reliability of the instrument;

(c) the responsiveness of the instrument to differences in health states between individuals and to changes in health states over time experienced by any one individual; and

(d) the clinical importance of any differences detected by the instrument.

Where possible, provide any supportive data and references in a technical document or an attachment to the submission (provide clear cross-references between these data and the main body of the submission).

Use of quality-adjusted life-years (QALYs)

"Utilities" may be measured directly in a trial (Section 2.6) or derived (Section 3.4) and are different from quality of life measures. They are weights which are derived for specific health states which are used to adjust the estimated survival. At present outcomes are not required to be expressed in QALYs, but this form of analysis should be considered whenever it is appropriate to the proposed drug.

If utilities have been measured or derived for the purposes of adjusting survival to estimate QALYs, provide details of the methods used. Comment on how the controversy of whose utility is measured (patient, care-giver, taxpayer etc) was addressed and on the likely applicability of any the utilities estimated to those of an Australian population.

APPENDIX I

IDENTIFYING AND DEFINING ECONOMIC INPUTS AND OUTCOMES

REFER: Sections 2.6 and 3.4; Appendices F (a), L and O

Definition of direct medical resources

Identify and list the resource items for which there will be a change in use associated with substituting the proposed drug for the main comparator (see also the *Manual of Resource Items and their Associated Costs*). Sometimes only changes in drug use will need to be identified. The following should be considered where appropriate:

(a) drugs (direct costs of treatment and of drugs used to treat side effects);

(b) medical services including procedures;

(c) hospital services;

(d) diagnostic and investigational services;

(e) community-based services; and

(f) any other direct medical costs.

Definition of direct non-medical resources

Occasionally because of the condition under treatment or the age of the patients, consideration of direct non-medical costs such as social services (home help, day care, meals on wheels, nursing and physiotherapy services etc) may be relevant. Some of these are included in the *Manual of Resource Items and their Associated Costs*.

Definition of natural units of direct resources

Define the natural units (such as number of GP consultations or admissions per DRG) used to measure the change in the amount of resources provided (see also the *Manual of Resource Items and their Associated Costs*). See Appendix L for advice on tabulating the identified resources and their natural units of measurement alongside their associated unit costs.

Definition of indirect economic outcomes

These include potential working time gained or lost measured in time units (days, weeks, years etc). They may also include potential impaired working time gained or lost by sick patients continuing to work measured in similar time units together with a measure of the extent of impairment.

Particular care is needed when considering indirect economic outcomes when using surrogate outcome indicators (their combination may be inappropriate) or utilities (to avoid double-counting the estimates of benefit, see also Appendix O).

Definition of economic outcomes to be excluded

Limit costs to those associated with the disease under treatment. In these evaluations do not attempt to include outcomes of other diseases which, in the fullness of time, are likely to afflict patients who live longer as a result of effective treatment which they receive now.

USE OF META-ANALYSIS

REFER: Sections 2.3 and 2.6

In some cases a meta-analysis of a number of randomised comparative trials will be useful in an economic evaluation. Meta-analysis may increase the precision of the estimates of differences between the proposed drug and the main comparator. It is useful when there are conflicting results from trials of similar scientific rigour. It can also highlight advantages of a proposed drug which are too small to be detected reliably in individual randomised trials, but might be clinically important for a drug which will be used widely.

Presenting a meta-analysis (see Section 2.6)

If the trial results are available as dichotomous data, the following approach should be adopted.

(a) Tabulate the results (point estimates and 95% confidence intervals) of the individual trials.

(b) Plot the results (point estimates and 95% confidence intervals) of the individual trials, both as relative risk reductions and absolute risk reductions.

(c) Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicates the trial results are heterogeneous, try to provide an explanation for the heterogeneity.

(d) Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).

(e) Select one estimate from the four options in (d) for use in the economic evaluation. Justify the selection.

A similar approach to the above should be attempted if the trial results are available as continuous, ordinal, categorical or time-to-event data. Expert biostatistical advice will be helpful in such circumstances. The approach used in the statistical combination of the results (eg pooled hazard ratios) should be justified and explained in a short technical document or attachment to the submission.

Assessing a published meta-analysis (see Section 2.3)

If a published meta-analysis is the principal source of clinical evidence, it should include the following:

(a) a description of the trials and trial subjects;

(b) a description of the patient-relevant outcomes measured in the included trials;

(c) some assessment of the scientific rigour of the included trials;

(d) a tabulated and/or graphical display of the individual and combined results;

(e) an adequate description of the methods of statistical combination; and

(f) a discussion or explanation of any heterogeneity observed in the results.

APPENDIX K

TYPES OF ECONOMIC EVALUATION

REFER: Sections 2.8 and 3.3

Cost-minimisation

The proposed drug is demonstrated to be no worse therapeutically than other drugs at the same or a lower price. Assuming the PBAC accepts the alternative therapies as providing acceptable outcomes for their cost, a new treatment which offers these outcomes at a lower cost is preferable.

Cost-effectiveness

The proposed drug is demonstrated to offer more of a given outcome. This goes beyond cost-minimisation. For example, a drug may have a higher requested price but achieve the desired clinical outcome in a higher proportion of patients than the alternative therapy. The outcome indicators reported from the randomised trials may need to be adapted in a modelled cost-effectiveness analysis, and where this is done the choice of outcome should be justified.

The summary measure of a cost-effectiveness analysis is the incremental cost per additional unit outcome achieved.

Cost-utility

The ultimate benefit of restored health is the restoration of opportunities to undertake activities of daily living. Economists have attempted to identify the value placed by patients, professionals and general public on different activities restored. The basis for this valuation is that each activity gives some satisfaction (termed “utility” by economists) which is the ultimate outcome of life.

A cost-utility analysis presents the outcomes in terms of an extension of life and a utility value of that extension. For example, quality-adjusted life-years have been used to compare the benefits of renal transplantation and hip replacement. The latter does not extend life but improves the quality of the years of life left to a patient. A quality weighting, based on the activities restored by the operation, can be used to convert two different lengths of survival and sets of activities to a common currency.

A cost-utility analysis should report the changes in activities of daily living or other methods used to project the weighted outcomes.

Cost-benefit

In contrast to other forms of analysis, cost-benefit analysis (CBA) expresses all outcomes in monetary rather than physical units. This requires a monetary valuation of these outcomes and CBA often relies heavily on calculations of indirect costs and benefits, principally changes in production capacity. Such analyses are not likely to be helpful to PBAC in its deliberations and are not encouraged.

APPENDIX L

ESTIMATING THE PRESENT VALUE OF COSTS AND HEALTH OUTCOMES

REFER: Sections 2.9 and 3.6; Appendices I and O

Procedure for estimating the present value of direct costs

(a) For each type of resource provided, multiply the number of natural units by the price/unit recommended in the current *Manual of Resource Items and their Associated Costs* (and hence take the perspective of society). The amount of resource provided (eg amount of drug dispensed) is the relevant economic measure rather than the amount of resource consumed. The unit prices should be as current as possible to the date of the submission. If there are particularly pressing reasons to use different unit price(s), then justify each different unit price and supply its source or describe its generation. Ensure that any different unit price is consistent with the perspective of society in keeping with the rest of this document and the *Manual of Resource Items and their Associated Costs*.

As a minimum, provide a table clearly identifying:

(i) each type of resource included in the evaluation(s);

(ii) its natural unit of measurement;

(iii) the unit cost used to value that resource in the evaluation(s); and

(iv) the source of the unit cost.

All steps taken to calculate costs should be clear during the evaluation. If a complete presentation is likely to make the main body of the submission too bulky, the calculations should be presented in a technical document and, if necessary, a computer disc should be provided containing the detailed calculations. Provide clear cross-references between these calculations and the main body of the submission. As advised in Section 3.3, these documents and discs are assessed during the evaluation, but are not routinely forwarded on to Committee members.

(b) Value future costs at current prices. This is consistent with using constant prices in the evaluation. Accordingly, no allowance for future inflation should be included in these calculations.

(c) The present value of future costs should also be estimated. This means that where costs extend over a number of time periods (beyond 1 year), these should be discounted. Discounting of future costs and benefits is a standard feature of economic evaluation. Costs or benefits are discounted at an annual rate of 5%.

As requested in Sections 2.9 and 3.6, present the estimated costs in disaggregated form, ie separately for each type of resource provided.

(d) Calculate the net direct costs for each therapy. The net costs are costs of any increase in resource use minus savings resulting from any improvement in outcome. Thus, for instance, an expensive drug may result in fewer hospitalisations and the net direct costs might be less than those of a cheaper competitor.

Procedure for estimating the present value of indirect economic outcomes (indirect benefits)

In general, changes in productive capacity as an outcome of therapy are not encouraged in submissions to the PBAC. While this may improve quality of life for the patient and could be included, quite legitimately, in a quality of life scale, it should not be assumed that there is an economic benefit to society through the patient's return to productive capacity.

The reasons for this are:

(a) for short-term absence, production will be made up on the return to work;

(b) employers usually have excess capacity in the labour force to cover absenteeism; and

(c) for long-term absence, production will be made up by a replacement worker otherwise unemployed.

In Australia, the economy is constrained by macro-economic factors rather than by the lack of healthy workers. Productivity estimates give the misleading impression that additional output in the economy will pay for the additional drug consumption. If consideration of such indirect benefits can be justified in the submission, the following standard economic practice should be adopted.

(a) Present the results both with and without the indirect benefits and costs included.

(b) When assigning a monetary value to the estimate of potential working

time gained or lost in time units, the underlying assumptions which are made must be explicit. For example, the claim that there has been recovery of production lost due to illness is dependent on demonstrating that:

(i) the worker returns to work;

(ii) the worker is productive;

(iii) the work lost is not made up elsewhere by others in the company or the same worker following return to work (NB if the worker is highly productive, the incentives to replace him/her are stronger); and

(iv) no temporary replacement from outside has been employed (namely that there is full employment).

The net effect is that the **marginal** increase in production due to return of healthy workers to the workplace is over-estimated by simply multiplying the workers' time regained by the labour market value of the workers (usually estimated by their wages). It is not always likely to be zero either, but some proportion in between. The evaluation should estimate the true proportion based on firm evidence.

Procedure for estimating the present value of health outcomes

The present value of future health outcomes measured from the trials or estimated from the model should also be calculated. This means that where health outcomes are anticipated over a number of time periods (beyond 1 year) these should also be discounted. Discounting of future costs and benefits is a standard feature of economic evaluation. Costs or benefits are discounted at an annual rate of 5%. If discounting is important in an economic evaluation, this should be examined in sensitivity analyses using different discount rates (see Section 3.7).

APPENDIX M

PRESENTING A DECISION ANALYSIS INVOLVING MORE THAN ONE TIME PERIOD

REFER: Sections 3.3, 3.4, 3.5, 3.6 and 3.7

The following guidance is intended to help apply the more general comments in Sections 3.4 to 3.7 to the more specific circumstances of a decision analysis involving more than one time period, including Markov models and Monte Carlo simulations. This guidance supplements rather than replaces the general comments.

Variables in the modelled evaluation

In addition to the general variables to be documented in Section 3.4, also include the health states and the transition probabilities of the model. The type of health state should be defined (eg temporary, absorbing). Transition probabilities are usually presented in a matrix. Indicate whether each transition probability is constant - a Markov chain, or varies over time - a Markov process. Pay particular attention to the transition probabilities that simulate a treatment effect by differing between the two Markov models that represent the proposed drug and its main comparator, respectively. Clearly link each patient-relevant outcome and resource item in the model to its relevant health state(s).

Structure of the modelled evaluation

In addition to the general description to be provided in Section 3.5, present the transition diagram (or matrix), which must contain all the modelled health states and arrows reflecting the presence and direction of transitional paths between health states. Justify the health states chosen (and those excluded to avoid excessive complexity). Comment on implicit assumptions if appropriate. For example, it may be relevant to check the following Markov assumptions. Are there (non)-constant transition probabilities? Is the “memorylessness” assumption of the model valid in this case (ie is it correct to assume no memory for previous states)?

Describe the model mechanics: define the cycle length and the follow-up time and comment as necessary. State whether a half-cycle correction has been included or justify its exclusion.

Describe how the model is calculated (eg hypothetical cohort or Monte Carlo simulation).

Results of the modelled evaluation

In addition to the general results to be presented in Section 3.6, present a Markov trace in tabular or graphical form or preferably both forms. Comment may need to be offered on whether this trace makes sense. For each arm (ie for the proposed drug and its main comparator) and after each cycle:

1. identify the proportions of the cohorts in each state;

2. sum the outcomes (eg utilities) and the costs for each cohort (both for each cycle and as cumulative results) - discounted as appropriate (see Appendix L); and

3. calculate the incremental cost-effectiveness (from both arms).

Compare this trace with any corresponding empiric data (eg partitioned survival). Comment on and explain any differences.

APPENDIX N

UNCERTAINTIES WHICH MAY SUGGEST THE NEED FOR MODELLING

REFER: Section 3.1; Appendices O, P and S

Modelling may be needed to address limitations of the preliminary economic evaluation based on the evidence from the randomised trials presented in Section 2.9. The following list of uses of models is intended to help a sponsor decide whether a model is needed in the context of each submission.

(a) To link the surrogate outcomes measured in the trials to final outcomes and to extend the range of outcomes (for instance the number of patients with unhealed peptic ulcers who eventually need surgery). In such cases the trial results may be supplemented by estimates obtained from non-randomised studies, epidemiological data, market research data or an expert consensus. In particular, epidemiologically acceptable extrapolations of clinical differences demonstrated in the trials to more appropriate final outcomes are potentially helpful. Whatever the source, provide information regarding the validity of these estimates (see Appendix P on data from non-randomised studies and Appendix S on expert opinion).

(b) To extrapolate the outcomes measured beyond the duration of the trials and duration of therapy within the trials to the likely duration of use. This overlaps the first reason to model listed above. In many submissions, it has been implicitly assumed that the outcomes measured in the trials are maintained in the longer term. Such assumptions should be considered explicitly.

(c) To examine the impact of differences between subjects enrolled in the trials and patients who would be likely to obtain the drug on the PBS and between the settings of the trials and the community setting of the PBS in Australia. Both affect the generalisability of the trials to the PBS context. Important patient factors which may affect outcomes are identified in (c) of Appendix E. There may also be important differences in the mix of patients who will receive the drug on the PBS. Two concerns of the PBAC here are that there may be patients in the community who have disease which is less severe than that of subjects who participated in the randomised trials. There also may be patients in the community for whom the main comparator can be expected to perform better than in the trials. Both could diminish the difference in effectiveness between the proposed drug and main comparator and, therefore, increase the incremental cost-effectiveness ratio. Factors relating to the setting include extrapolating results of trials conducted

in hospitals to use outside the hospital and the effect of more rigorous follow-up, which may swamp important differences in the convenience and acceptability of the drug compared with alternative treatments, with resulting effects on patient compliance and thence response to treatment.

(d) To modify resource use patterns measured in the trials to reflect more closely those in Australia (and/or to add likely changes in resource use patterns not measured in the trials). Randomised trials performed overseas are an acceptable basis for an economic evaluation relevant to Australian practice. Although the overall estimate of the change in a final or surrogate outcome may be transferable to Australia, estimates of the costs of resources provided (drugs or other interventions eg investigations, procedures or operations) are often not readily transferable. It is easily apparent that the unit costs are usually quite different. Less apparent, but also important, the frequency or patterns of use of resources may not be relevant to Australia because of major differences in medical practice or different incentives in different economies and health care systems. Sometimes assumptions will have to be made during the adaptation of overseas randomised trials to create a modelled economic evaluation which is relevant to the Australian context. This is particularly important when the main comparator is a non-pharmacological therapy.

(e) To include any relevant differences in resource provision not measured in the trials and to exclude "protocol-derived" resource provision. On the one hand, the trials may not measure provision of all relevant resources and these may need to be added in a model. On the other hand, the trials may require more resources to be provided than would be typical in normal management of the condition (such as extra blood tests to demonstrate safety or effectiveness) and only resources provided or saved in actual practice need be included in a model. If any "protocol-derived" resource provision is to be excluded in a model, consideration should be given to the extent to which these additional resources may have impacted on the results of the trials (eg high intensity screening for deep vein thromboses in trials being associated with lower rates of pulmonary embolism than in usual care).

APPENDIX O

RELATIONSHIP BETWEEN SURROGATE AND FINAL OUTCOMES

REFER: Sections 2.8, 2.9 and 3.5; Appendices F (a), H and I

Outcome indicators used in randomised trials

Appendix F asks for a definition of the outcome indicators used in the randomised trials. These are often "surrogate" outcome indicators (see below). Arguably, the closer a surrogate outcome indicator is to the final outcome (see table below), the more useful it is, but generally the more difficult it is to measure accurately.

Final outcomes of therapy

Section 3.5 asks for a definition of the principal intended final outcomes which are expected to change with therapy. In general terms, this is the improvement in health which will result from the therapy. For instance this may be "prevention of death and suffering from stroke" in the case of a new anti-hypertensive medication, not the reduction in blood pressure which is an "surrogate" outcome indicator (see below). Another more simple example of a "final" outcome might be "cure of an uncomplicated urinary tract infection", in the case of an antibacterial agent. For many drugs the intended final outcome is the improvement in quality of life through alleviation of distress. Where the final outcome of the drug therapy is a change in quality of life, a quality of life measure should be considered (see Appendix H). The main therapeutic benefit being measured with a quality of life measure is a change in the health state. Thus return to normal daily functioning through relief of symptoms is a valid outcome. However, return to normal productive capacity with the associated "economic" gains should not be regarded as a final outcome (see Appendices I and L for further discussion of the analysis of indirect benefits).

Use of surrogate outcome indicators to estimate final outcome indicators

Section 3.5 asks for a model to estimate the likely change in the final outcome from the changes in the surrogate indicator. As suggested in Appendix N, applicants should therefore consider the final intended effects of the proposed drug in terms of the ultimate change in health state brought about by therapy. For instance the ultimate aim of lowering moderately elevated blood pressure is to prevent death and impaired quality of life from

a stroke or possibly a myocardial infarction. The ultimate aim of treating a patient with severe asthma is to prevent death, to prevent hospitalisation and to return the patient to a normal level of functioning. However, few trials of drug therapy are large enough to measure changes in final outcomes. Typically, only relatively small trials will be available at the time a drug is considered for marketing approval or Pharmaceutical Benefits listing. The response measures used in these trials will usually be readily measured physiological variables. For the two examples given above this would be blood pressure and spirometry. These are "surrogate" outcome indicators. In a few instances, relationships have been established, or have been proposed, between surrogate and final outcome indicators. Examples include blood left ventricular ejection fraction and survival after myocardial infarction; or serological liver function tests and cure of viral hepatitis. The form of the relationships which have been established between these variables may vary according to whether the data were derived from longitudinal studies or randomised trials. For a very few risk factors (eg blood pressure and blood cholesterol), predictive models are available which estimate events, including deaths, prevented by specified reductions in these variables.

For most drugs the ultimate outcome of therapy is to improve quality of life and/or survival, and in theory all outcomes could be expressed as quality-adjusted life-years (QALYs). In practice few trials have measured the impact of drug therapy on QALYs and in most economic evaluations it will be necessary to employ surrogate outcome indicators. Unfortunately, there has been no attempt to reach agreement on sets of surrogate clinical outcome indicators for use in economic evaluations. It is hoped that this situation will be remedied in due course. The accompanying table is **not** a list of recommended outcome indicators but simply provides examples to illustrate what can be done. For each clinical indication a hierarchy of indicators can be developed. In the left hand column is the final intended outcome and to the right, arguably in descending order of validity, are other possible surrogate outcome indicators. It must be stressed again that these are only provided as examples for a limited selection of clinical indications. However, outcomes which are expressed as proportions (eg proportion of patients in whom blood pressure was "controlled") are easier to incorporate into an economic evaluation than a difference in means for a physiological variable.

At present it is difficult to give categorical advice. Sponsors are encouraged to consider which outcome indicators are most appropriate, and most feasible, given the data available to them. The clinical relevance of the outcome indicators should be established and if necessary supported with data. Where possible the results of randomised trials should be analysed as the proportions achieving specified targets (eg target blood pressure, target Hamilton depression rating scale) rather than the mean change in the variable for the group. This may necessitate some re-analysis but generally the data will be available to the sponsor. When models are used their origins

should be specified, eg longitudinal population studies. Describe the extent to which the models have been modified to provide estimates which are relevant to the Australian population and provide any data that would add to the external validity of the model used. Consider providing a technical document or an attachment to the submission to give the details of the methods and be prepared to demonstrate any computer model if called upon by the Pharmaceutical Evaluation Section.

Examples of outcome indicators

Condition being treated	*Final outcome indicator*	*Surrogate*	*Outcome*	*Indicators*
Coronary thrombosis (thrombolysis)	Quality-adjusted survival	Number surviving	Number with specified level of left ventricular function	Number achieving coronary reperfusion
Unstable angina (various interventions)	Quality-adjusted survival	Number surviving	Number with myocardial infarction	Number with adequate relief of pain
Stable angina (various interventions)	Quality-adjusted survival	Number with acceptable quality of life	Number who can walk a specified distance	Number with adequate relief of pain
Asthma (various drugs)	Quality-adjusted survival	Number surviving	Number with adequate control of bronchial hyperreactivity	Number achieving a target level of airways function
Depression (various drugs)	Quality-adjusted survival	Number avoiding suicide	Quality of life (may be improved by drugs)	Number achieving a target Hamilton or Montgomery-Asberg Depression Rating Scale
Hypertension (various drugs)	Quality-adjusted survival	Number avoiding stroke	Quality of life (may be worsened by drugs)	Number achieving a target blood pressure

APPENDIX P

USES OF DATA FROM NON-RANDOMISED STUDIES

REFER: Sections 2.2 and 3.5; Appendices N, Q and R

Non-randomised studies include classical observational designs such as cohort studies (with concurrent controls) and case-control studies. They also include quasi-experimental designs such as "before and after" studies, case series with historical controls and a comparison of the results of two or more single-arm studies.

Use of data from non-randomised studies to estimate comparative clinical performance when data from randomised trials are not available (see Section 2.2)

Classical community-based epidemiological designs, such as controlled cohort and case-control studies, can be used to estimate the comparative clinical performance of therapy if randomised trials are not available. However, it has been repeatedly shown that such studies are subject to a range of biases that frequently lead to over-estimation of the true benefit of the treatment given to the intervention group. Consequently claims about the comparative clinical performance that are based solely on data from such sources will be treated with some scepticism.

Data from the other types of quasi-experimental non-randomised designs, for instance "before and after" studies, case series with historical controls; and comparisons of results of two or more single-arm studies are subject to major and (often) non-quantifiable biases. This topic is dealt with in Appendix R. Consequently claims about comparative clinical performance that are based solely on data from these types of analysis will be treated with scepticism.

Some criteria that should be used to assess the scientific rigour of non-randomised studies are provided in Appendix R. However these are for general guidance only and may have to be adapted to particular situations. The interpretation of the results of such studies is difficult and expert epidemiological guidance will be helpful if data of this type are central to the submission.

If data from non-randomised studies must be used to estimate comparative clinical performance, follow the advice on how to present the methods and the results of the studies that is given in Appendix Q. Present the studies in the main body of the submission and attach a report of each study presented to the main body of the submission. Provide clear cross-references between the presentation of the studies and the reports.

Based on the results presented in answer to Appendix Q, state the category from Section 2.8 which best describes the proposed drug. As discussed here and in Appendix R, these results are likely to be biased, so their interpretation should be conservative. Having selected the category, return to Section 3 to present the modelled economic evaluation.

Use of data from non-randomised studies to modify or extrapolate beyond the evidence from randomised trials in a modelled economic evaluation (see Section 3.5, Appendix N)

Although the estimation of comparative clinical performance from non-randomised studies is a questionable exercise, it is accepted that data from non-randomised studies must sometimes be used in order to extrapolate beyond the results of a randomised trial. This is because the trial may have been of insufficient size or duration to capture the full impact of therapy on the outcomes of the disease, and/or the typical resource provision measured in an overseas trial may need adjustment to reflect patterns of use observed in Australia (this is particularly important for resource estimates where the main comparator is a non-pharmacological therapy). Given that the data from non-randomised studies are subject to bias, assumptions based on these data made during a modelling exercise should be conservative.

If data from non-randomised studies are used in a modelled economic evaluation to modify or extrapolate beyond the evidence from randomised trials, follow the advice on how to present the methods and the results of the studies in Appendix Q. Present the studies in a technical document or an attachment to the submission. Provide clear cross-references between the presentation of the studies and the main body of the submission. If a technical document is used, attach a report of each study to this document. If an attachment is used, provide the report of each study separately, along with any other supplementary references.

As requested in Section 3.5, indicate which results from the evidence from randomised trials are being modified or extrapolated. Explain how the modifications and extrapolations are achieved by the model. In particular, if non-comparative data are used, it is necessary to make an assumption about how the comparator arm will change. The usual practice, in the absence of empirical evidence to the contrary, is to assume that the comparator arm will change so that the relative rate between the two arms measured in the randomised trial(s) will remain constant. Justify the use of this (or any other) assumption in the model presented in the submission.

PRESENTING NON-RANDOMISED STUDIES

REFER: Appendices O and R

Categorise the studies into the study type(s) defined in Appendix R. Then, for each methodological topic listed for the relevant study type in Appendix R, choose the description that best fits each study. If the submission includes a number of studies of the same type, tabulate the responses.

Present the following characteristics of each study (tabulate the responses if more than one study):

(a) the comparability of the study subjects with patients who are likely to receive the drug on the PBS;

(b) the dosage regimens of the drugs; and

(c) the definition of the patient-relevant outcomes measured and their natural units of measurement.

NOTES: see Appendices E and F for definitions of the above characteristics.

Present the results of all patient-relevant outcomes measured (see (a) in Appendix F), together with their respective 95% confidence intervals. In general, the results will be in the form of a proportion, a difference in proportions, an odds ratio, a relative risk, or a hazard ratio. Occasionally the results will be in the form of a difference in some other response variable (eg forced expiratory volume).

APPENDIX R

MEASURES TAKEN BY THE INVESTIGATORS TO MINIMISE BIAS IN NON-RANDOMISED STUDIES

REFER: Appendices P and Q

This appendix is designed as a useful guide to help the PBAC and the sponsor review the scientific rigour of the evidence by assessing the measures taken by the investigators to minimise bias. It is not intended to discourage the presentation of data.

Categorise the studies into the study type(s) defined below. Then, for each methodological topic listed for the relevant study type, choose the description that best fits each study. If the submission includes a number of studies of the same type, tabulate the responses.

As for the assessment of randomised trials in Appendix D, the purpose of these assessments is to provide the sponsor and the PBAC with a clear idea of which studies are of greater scientific rigour. There is no minimum standard, but the PBAC is most likely to be persuaded by the data of the highest scientific rigour. Submissions should therefore be particularly careful to justify using the results of studies with less scientific rigour in an economic evaluation in place of trials with greater scientific rigour.

There may be other aspects of particular non-randomised studies which may affect the results of such studies and their comparability with different studies of the same type. If these aspects are likely to be important, they should also be identified.

CLASSICAL OBSERVATIONAL DESIGNS

Controlled cohort studies

In this study type, assignment of the groups of individuals to treatment is not random. However, individuals receiving the proposed drug and control individuals are followed forward in time from first exposure. Cohort studies can be concurrent or historical. In the former, the study is planned and conducted prospectively. In the latter, existing records are used to define treatment status and determine the outcomes.

Possibility of confounding: it is important that there are no substantial differences at baseline between treated and control subjects in respect of factors that could influence the outcome(s) being studied. Which of the following best describes the differences in baseline factors?

1. There were significant differences in baseline factors between treated and control subjects that have been shown to influence the study outcome(s), and these were not adjusted for in the main analysis.

2. There were significant differences in baseline factors between treated and control subjects that might have influenced the study outcome(s), and these were not adjusted for in the main analysis.

3. There were no differences in baseline factors between treated and control subjects that might have influenced the study outcome(s), or any differences were adjusted for in the main analysis.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

Adequacy of follow-up: it is important that an attempt is made to summarise the study outcomes for all subjects who were included in the study. Which of the following best describes the adequacy of follow-up in the study?

1. There were significant numbers of drop-outs with no assessment of study outcome(s) in the subjects who dropped out, and drop-out rates differed between treated and control groups.

2. There were some drop-outs with no assessment of study outcome(s) in the subjects who dropped-out, and drop-out rates were (approximately) equivalent in treated and control groups.

3. Study outcome(s) were assessed in all or nearly all treated and control subjects.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

Blinding of outcomes assessment: it is important that the observer responsible for measuring the study outcome is unaware of whether the subject belongs to the treated or control group. Which of the following best describes the blinding of outcomes assessment?

1. There was no attempt to blind the observer(s) to the treatment or control status of the study subjects, or any attempt made was inadequate to keep the observer(s) fully blind to the treatment or control status of the study subjects.

2. The observer(s) were kept fully blinded to the treatment or control status of the study subjects.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

Case-control studies

In this study type, subjects are defined by the presence (cases) or absence (controls) of the study outcome, and their prior use of the proposed drug is compared.

Selection of cases: it is most important that cases are selected independently of their treatment status. Which of the following best describes the selection of cases?

1. The process of referral and selection of cases was likely to have been influenced by the subjects' prior use of the drug and knowledge of the association between use of the drug and study outcome (eg a woman of child-bearing age with a painful swollen leg is more likely to be referred for investigation if she has been using an oral contraceptive).

2. The process of referral or selection of cases was not influenced by the subjects' prior use of the drug or knowledge of the association between use of the drug and study outcome.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

Selection of controls: the purpose of the control group is to provide an estimate of the odds of exposure in subjects who are free of the disease in question in the source population. Which of the following best describes the selection of controls?

1. The controls were not drawn from the same source population as the cases.

2. The controls were drawn from the same source population as the cases (community controls).

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

Possibility of confounding: it is important that there are no substantial differences between cases and controls in respect of factors that could influence the outcome being studied other than the risk of exposure to the drug. Which of the following best describes the comparability of cases and controls?

1. There were significant differences in factors between cases and controls that have been shown to influence the study outcome, and these were not adjusted for in the main analysis.

2. There were differences in factors between cases and controls that might have influenced the study outcome, and these were not adjusted for in the main analysis.

3. There were no differences in factors between cases and controls that might have influenced the study outcome, or any differences were adjusted for in the main analysis.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

Possibility of measurement bias: it is important that assessment of treatment status (or exposure) is made in an unbiased way. Which of the following best describes the assessment of treatment status?

1. The measurement of prior drug use (or exposure) was made using an unstructured interview or questionnaire by an observer who was aware of the case/control status of the subject.

2. The measurement of prior drug use (or exposure) was made using a structured interview or questionnaire by an observer who was aware of the case/control status of the subject.

3. The measurement of prior drug use (or exposure) was made using a structured interview or questionnaire by an observer who was unaware of the case/control status of the subject, or the definition of exposure preceded the outcome (eg based on a computerised prescription record, as in a case-control study "nested" in a larger cohort).

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

QUASI-EXPERIMENTAL DESIGNS

"Before and after" studies

In this type of study, subjects are observed before and after an intervention (eg a new drug) is introduced. It is really only possible to use this design if the manifestations of the illness being treated are both chronic and reversible. Typically this will be an opportunistic study, rather than planned. In addition to the sources of bias that affect the previously mentioned observational designs, this study type has particular problems

related to time (or order) effects, resulting from the subjects being observed over a period, and the lack of a contemporaneous control group. There may be changes in disease severity or symptomatology or resource use that are occurring independently of any treatment, and it is impossible to assess these properly without a contemporaneous control group. It is highly likely that subjects will be switched to the new therapy because they have not been doing well on the old therapy, and thus their symptoms will tend to be most severe at the time of switching. Regression to the mean will make the new drug seem better than the old one, both in terms of apparent treatment responses and resource provision.

Selection of subjects:

1. The subjects were selected retrospectively from case-notes, and the investigators were probably aware of the responses to the old treatment at the time of selection.

2. The study was planned, and prospective data collection was undertaken in both study periods, and selection of the subjects was made without knowledge of the treatment responses.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

Possibility of confounding:

1. There were within subject differences in factors between the two study periods that were likely to influence the study outcome(s), and these were not adjusted for in the main analysis.

2. There were no within subject differences in factors between the two study periods that were likely to influence the study outcome(s), or any differences were adjusted for in the main analysis.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

Adequacy of follow-up:

1. Drop-out rates differed between the "before" and "after" study periods with no assessment of study outcome(s) in the subjects who dropped-out.

2. There were no drop-outs in either study period (this implies prospective data collection in both periods), or study outcome(s) were assessed in all subjects who were commenced on treatment.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

Blinding of outcomes assessment:

1. The observer(s) responsible for outcome assessment were aware of which treatment the study subjects had been receiving.

2. The observer(s) responsible for outcome assessment were kept fully blinded to the treatment being received by the study subjects.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

Case series with historical controls

Typically this type of study is carried out by a clinical department that has introduced a new management procedure and wishes to compare the results with those of patients treated previously in the department using the old management procedure. Thus, this type of study shares the same problems of order effects as "before and after" studies but does not involve the same individuals in both arms.

Selection of subjects:

1. The subjects were selected retrospectively from case-notes, and the investigators were probably aware of the responses to the old treatment at the time of selection.

2. The study was planned, and prospective data collection was undertaken in both study periods, and selection of the subjects was made without knowledge of the treatment responses.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

Possibility of confounding:

1. There were differences in factors between subjects in the two study periods that were likely to influence the study outcome(s), and these were not adjusted for in the main analysis.

2. There were no differences in factors between subjects in the two study periods that were likely to influence the study outcome(s), or any differences were adjusted for in the main analysis.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

Adequacy of follow-up:

1. Drop-out rates differed between the two study periods with no assessment of study outcome(s) in the subjects who dropped-out.

2. There were no drop-outs in either study period, or study outcome(s) were assessed in all subjects who were commenced on treatment.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

Blinding of outcomes assessment:

1. The observer(s) responsible for outcome assessment were aware of which treatment the study subjects had been receiving.

2. The observer(s) responsible for outcome assessment were kept fully blinded to the treatment being received by the study subjects.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

Comparison of the results of two or more single-arm studies

In addition to all the problems noted earlier with "before and after" studies or case series with historical controls, this approach has the added disadvantage that the outcome assessments were made by different investigators in different settings. It is not possible to compare the results of such studies with any confidence.

Selection of subjects:

1. In the studies for either or both alternatives, the subjects were selected retrospectively from case-notes, and the investigators were probably aware of the responses to the old treatment at the time of selection.

2. The studies for both alternatives were planned, and prospective data collection was undertaken for all consecutive patients in the study period, and selection of the subjects was made without knowledge of the treatment responses.

NOTES: if there is insufficient information available to classify the studies, assign them to the first category.

Possibility of confounding:

1. There were differences in factors between subjects in the study populations for the two alternatives that were likely to influence the study outcome(s), and these were not adjusted for in the main analysis.

2. There were no differences in factors between subjects in the study populations for the two alternatives that were likely to influence the study outcome(s), or any differences were adjusted for in the main analysis.

NOTES: if there is insufficient information available to classify the studies, assign them to the first category.

Adequacy of follow-up:

1. Drop-out rates differed between the studies for the two alternatives with no assessment of study outcome(s) in the subjects who dropped-out.

2. There were no drop-outs in the studies for either alternative, or study outcome(s) were assessed in all subjects who were commenced on treatment.

NOTES: if there is insufficient information available to classify the studies, assign them to the first category.

Blinding of outcomes assessment:

1. In the studies for one or both of the alternatives, the observer(s) responsible for outcome assessment were aware of which treatment the study subjects had been receiving.

2. In the studies for both alternatives, the observer(s) responsible for outcome assessment were kept fully blinded to the treatment being received by the study subjects.

NOTES: if there is insufficient information available to classify the studies, assign them to the first category.

APPENDIX S

EXPERT OPINION

REFER: Sections 1.2, 1.5, 3.5 and 3.7; Appendix N

Uses of expert opinion

Expert opinion is not a substitute for sound scientific evidence. Therefore it will only be considered if there are no data from randomised trials or non-randomised studies addressing the matter for which expert opinion has been sought. However, when these data are not available, or are unlikely to become available in the near future, expert opinion has been found to be useful in some aspects of preparing submissions to the PBAC:

(a) to help set the context of the economic evaluation by defining the place of the proposed drug in treatment (the main indication and the main comparator, see Sections 1.2 and 1.5 respectively);

(b) to help modify the patterns of resource use and, very rarely, the clinical outcomes measured in randomised trials conducted in different settings, such as in other countries (see Section 3.5 and (d) and (e) of Appendix N); and

(c) to help predict which resources will be used and how often each will be used to manage outcomes reported in the randomised trials but not followed up (see Section 3.5and (e) of Appendix N).

Presenting expert opinion

If expert opinion is used in a submission, this should be presented in a technical document or an attachment to the main submission that has clear cross-references with the main body of the submission.

Justify the need for expert opinion in the opening section of the presentation. Describe the methods used to obtain and collate the opinions by following the structured approach provided below. Then summarise the opinions obtained together with the extent of any variability in the opinions. Indicate how the opinions have been used in the main body of the submission. Justify the approach used in the sensitivity analysis (see Section 3.7) to reflect any variability in the opinions obtained.

Describing the collection and collation of expert opinion

The following details should be provided:

(a) the criteria for selecting the experts;

(b) the number of experts approached;

(c) the number of experts who participated;

(d) whether a declaration of potential conflict(s) of interest was sought from all experts or medical specialty groups whose opinions were sought;

(e) the background information provided and its consistency with the totality of the evidence provided in the submission;

(f) the method used to collect the opinions;

(g) the medium used to collect the opinions;

(h) the questions asked;

(i) whether iteration was used in the collation of opinions and, if so, how it was used;

(j) the number of responses received for each question;

(k) whether all experts agreed with each response, and, if not:

  (i) the approach used to finalise the estimates; and

  (ii) the approach used to present the variability in the opinions.

NOTES:

Tabulate the responses to (b), (c) and (j).

FOR (a) There is a preference for a random or comprehensive set of prescribers likely to prescribe the proposed drug, or for approaching the appropriate medical specialty group. If a small group of experts must be approached, it may help to ask each expert to explain the reasoning behind the expert opinion offered. Including these explanations in the technical document or attachment would allow the opinions to be assessed on the basis of the underlying reasoning, rather than only depending on the authority of the experts.

FOR (d) Provide a signed statement from each expert and specialty group specifying any potential conflict of interest and stating the nature of any contractual arrangement, including how much payment was offered and accepted. Where the collection of expert opinion has been contracted out, the contractor should provide this statement, reporting on both the arrangements made between the sponsor and the contractor and the arrangements made between the contractor and those whose opinions were sought.

FOR (e) Include a copy of any background information provided in the technical document or attachment. If background information has been provided, it may help to ask the experts to define the comparative clinical place of the proposed drug and the main comparator based on this background information. Including the experts' definitions in the technical document or attachment would allow an assessment of the consistency of the background information with the evidence provided in the submission.

FOR (f) For example, were the experts approached individually or was a meeting convened?

FOR (g) For example, was information gathered by direct interview, telephone interview or self-administered questionnaire?

FOR (h) Although the way the questions are asked is an important source of potential bias in obtaining expert opinion, the methods of designing questionnaires or interviews have not developed to the stage where general and prescriptive guidance can be given. Instead two issues require assessment on a question by question basis:

(i) the extent to which each question is neutral or biased; and

(ii) the extent to which each question is open or closed.

To allow an assessment to be made, include in the technical document or attachment an outline of the interview questions or a copy of the questionnaire.

FOR (i) For example, the Delphi techniques use an iterative approach.

FOR (k) (i) For example, a Delphi technique could be applied; or the majority opinion, the median, or the mean could be presented.

FOR (k) (ii) For example, the range or the variance could be presented.

PART IV

ABOUT THESE GUIDELINES

PROCESS OF REVIEW

These *Guidelines* were first released in draft form in August 1990. Initially their use was optional and this period provided valuable experience and feedback. Constructive and detailed criticisms of the *Draft Guidelines* were received from pharmaceutical companies, the Australian Pharmaceutical Manufacturers Association and independent experts. These were reviewed in detail to produce the first revision in August 1992.

In January 1993 it became mandatory for companies making submission to the PBAC to follow these *Guidelines*. Our experience has expanded greatly and the current revision draws on the lessons of over 160 submissions containing economic evaluations.

The pool of experienced evaluators has also expanded. After a preliminary period as a working party, the ESC was formed by the PBAC at the beginning of 1994. This Sub-Committee comprises clinicians, clinical epidemiologists, health economists and clinical pharmacologists and its major task is to review and interpret economic analyses submitted to the PBAC and assess their quality, validity and relevance for the PBAC. As part of its Terms of Reference, the ESC is entrusted with the task of conducting future revisions of the *Guidelines*.

Revision

Overall, the *Guidelines* have stood the test of time. There has been little change in the information sought, but there has been some re-ordering and re-emphasis. This is to enable presentation and evaluation of the best available comparative clinical data as a prelude to the economic evaluation. Features of the revision are summarised below.

Associated Documents

Documents that should be read in conjunction with these *PBAC Guidelines* are the *Manual of Resources and their Associated Costs* and the *Glossary to the Guidelines for Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee*. The *Manual* is revised periodically in the same way as the *PBAC Guidelines* and the *Glossary* is revised during the revision of the *PBAC Guidelines*.

FOCUS OF THE THIRD REVISION

This revision has focussed on ensuring that the most up-to-date information available to the Industry in relation to submitting a submission is included in the *Guidelines*.

Two new Appendices have been included, consisting of documents that have been officially been endorsed by the PBAC:

Appendix A: Guidelines for consideration of fixed combination products

Appendix G: Hierarchy of sources of evidence for equi-effective doses

THE FUTURE

The *Guidelines* are currently in revision, with focus on the analysis of clinical outcomes and valuation of health outcomes. Further feedback on these *Guidelines* is welcome, and should be forwarded to:

The Director
Pharmaceutical Evaluation Section
Department of Health and Ageing
GPO Box 9848
Canberra ACT 2601
AUSTRALIA

RATIONALE FOR ECONOMIC EVALUATION

The principles on which these *Guidelines* are based are discussed in more detail in the *Background Document on the use of economic analysis as a basis for inclusion of pharmaceutical products on the Pharmaceutical Benefits Scheme* by Evans D, Freund D, Dittus R et al. (1990), which was reprinted without amendment in November 1993, but is now out of print.

Australia, like other countries, is faced with a steady increase in the total cost of pharmaceuticals. Although the drug budget is not "capped" in Australia, choices must be made as to which drugs will have their use subsidised by the Commonwealth Government. Economic evaluation is one factor to be considered when making choices between competing therapeutic modalities.

Recommendations for the listing of drugs on the PBS are made to the Minister by the PBAC. Since January 1993 the PBAC has considered the results of economic analyses in its decision making.

By law, the PBAC has to assess the degree to which new drugs represent "value for money" to the Australian community. It is in the interests of the community, industry and the PBAC that uniformity be maintained in the conduct and evaluation of economic analyses. It is appreciated that the practical aspects of the economic evaluation of the performance of pharmaceuticals are challenging for members of the pharmaceutical industry, the PBAC and the administrative arm of government. For this reason, there will continue to be flexibility in the interpretation of these *Guidelines*. It is hoped that this will assist industry and government to further increase their experience of, and expertise in, the techniques of economic evaluation.

Analysis of the cost-effectiveness of a drug requires ready availability of an array of basic information. Much of this information is available to the sponsor, but the emphasis tends to be different from that of a general marketing application. This is because economic evaluation requires consideration of a more extensive set of outcomes than those which are included in a general marketing application. It is necessary to consider comparative effectiveness and the cost of the proposed drug and the changes in the use of resources that are likely to result from its introduction. This includes changes in the use of other medical services that are not subsidised through the PBS.

Clinical studies conducted to support a general marketing application often will not have collected the necessary data, particularly relating to the use of resources and are seldom of sufficient duration to predict all of the possible outcomes of therapy. It is likely that practice will change and that most of the extra data necessary for economic evaluation will be collected as a

routine part of clinical studies in the future. In the meantime economic evaluations for most drugs will be based on short- to medium-term randomised trials (presented in Section 2) supplemented by a number of assumptions (in a modelled economic evaluation, see Section 3). Often these assumptions about probable outcomes can be made on the basis of the results of other randomised trials, non-randomised studies, or consensus obtained from groups of experts in the field. Section 3 provides an opportunity for estimates of relevant outcomes to be presented rather than confining the evaluation to only those outcomes included in the randomised trials. There is some uncertainty in this exercise and advice is provided in the relevant sections and appendices of the *Guidelines*.

A number of specific points are worth stressing in this section on the rationale for economic evaluation. The results of overseas randomised trials of sufficient scientific rigour are a reasonable basis for economic evaluations relevant to the Australian health care system. However, an economic evaluation performed overseas will often not be suitable because of major differences in unit costs, the patterns of resource use and the way in which health care is funded. Sponsors are encouraged to submit an evaluation which is relevant to the Australian context. Usually the focus of the evaluation is on incremental cost-effectiveness; in other words how much more does it cost to achieve any additional benefit over alternative therapies? Cost-benefit analysis in which outcomes are expressed in monetary terms rather than a change in health state are generally not encouraged by the PBAC. In most evaluations the costs to be included should be those associated with altered use of drugs, medical and other related social services. Costs associated with changes in employment and productive capacity may be incorporated in a separate analysis. Generally, the costs and outcomes will be those associated with the disease under study and not those diseases which, in the fullness of time, patients might be expected to develop if they receive effective treatment for their current complaint.