Scottish Medicines Consortium

Guidance to Manufacturers for Completion of New Product Assessment Form (NPAF) (Revised June 2007)

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Part A

General Guidance to Manufacturers for Completion of New Product Assessment Form (NPAF)

The New Product Assessment Form (NPAF) provides a template for the evidence required by the Scottish Medicines Consortium (SMC) to make recommendations to NHS Boards and Area Drug and Therapeutics Committees. This form should be used for all new licensed products, indications and formulations (except where abbreviated submission to be completed). Information provided will be treated as confidential and will only be available to members of the SMC and its New Drugs Committee (NDC).

The guidance notes relate to each section within the submission form. A description of the expected content to be submitted within each section of the form will be described and where appropriate the expected source that the information should be drawn from and the style of presentation of that information. General points regarding completion of the submission are detailed below:

Size of submission.
The quantity of evidence to be submitted will vary depending on the product under consideration. A succinct and relevant review of the available evidence is required. Submissions should be concise, but also complete and comprehensive. The required information is stated for each section of the document and applicants should try not to submit any material that exceeds this.

Appendices
The submission should be a stand-alone document. Appendices may be used for information which exceeds the level of detail requested in this guidance but which is considered to be relevant. Appendices should be used sparingly and should not be used to present core information. For example it is not sufficient to attach a key study as an appendix and to complete the efficacy section with 'see Appendix X.' In some cases it will be more appropriate to include data as a supporting document, referenced in the text, than as an appendix.

Formatting
The boxes in the NPAF will expand with the text. When completing the submission it should be clear which text are questions and which are responses, for example, use a different font style for each. Do not shade or highlight text, as this will be removed during the SMC evaluation process. An electronic version of the NPAF should be provided in Word or compatible format, which can be modified (i.e. not as a PDF file).

Commercial-in-confidence data
Indicate that data are “commercial in confidence” (CIC) by underlining the CIC text (not by shading or highlighting). Reasons why the data are CIC and the timescale within which they will remain CIC should be detailed. Information that is CIC will be removed before making the detailed advice document available to the public. SMC will respect confidentiality, but reserves the right to include data which are already in the public domain e.g. as a published abstract or conference poster. In such cases, SMC will not exceed the level of detail in the published source and the submitting company will have an opportunity to review the detailed advice document as part of the routine consultation process. SMC is committed to adhering to the guidelines agreed with ABPI and which appear on the SMC website.

References
The evidence quoted should be referenced throughout the form and references numbered in the order in which they appear in the text. At the end of the submission a list of references should be provided in the Vancouver style. Paper or electronic copies of all references should be provided at the time of submission. Electronic rather than paper copies of references are preferred. SMC requests the opportunity to review in-house clinical trial reports and/or drafts for publication, particularly when pivotal trials are unpublished or published only in abstract form. Clinical trial reports should be provided in sufficient detail to permit a comprehensive understanding of

the trial methodology, conduct and results and to confirm information relating to the trial that is detailed in the NPAF. Generally the information in the main body of the clinical trial report will provide sufficient detail and extensive appendices at the end of the report are usually not required. It is recognised that providing SMC with clinical trial reports and/or drafts for publication may raise issues of confidentiality. However, data from these sources will be treated as CIC and will not be disclosed in any form to persons or organisations out with the SMC and NDC committees, SMC clinical and economic assessors and secretarial staff. These data will be annotated to indicate that they are CIC in paperwork provided to the SMC and NDC committees. Members of these committees, SMC clinical and economic assessors and secretarial staff are bound by confidentiality prohibiting them from disclosing confidential information, including CIC data, viewed during the course of their work for SMC to persons or organisations out with SMC. CIC data are removed from the SMC detailed advice documents that are issued to the NHS and posted on the SMC website.

Front page

The NPAF should be given a title that includes the approved and proprietary name of the product, the indication under review and the name of the company making the submission.

The name and position of the person responsible for compiling the submission should be entered, and this person should sign a master copy to be submitted in hard copy.

A contact person and contact details should be given. This need not be the person making the submission. The purpose is to identify a single contact point for enquiries about the submission. It need not be someone who can directly answer enquiries, but the contact person should have sufficient knowledge to be able to relay enquiries to the appropriate person within the company.

Second page: Patient interest groups

The SMC wishes to involve patient representative groups in the decision making process. The main focus of such involvement would be on the needs and priorities of patients with the condition, and in building up a picture of what it means to be affected. However representatives of those groups may wish to obtain information from the manufacturer about the treatment(s) under consideration.

If companies wish to provide a patient/public friendly version of their submission they can do so following the standard “Summary Information for Patients” available on the SMC website:
http://www.scottishmedicines.org.uk/updocs/Summary%20Information%20for%20Patients%20-%20template%20(Industry).doc.
The SMC secretariat will forward upon request to any patient group making a patient interest group submission in connection with a new product submission.

Third page: Freedom of Information

The Freedom of Information (Scotland) Act 2002 came into force on 1 January, 2005, and enables any person to obtain information from Scottish public authorities, giving legal right of access including all types of recorded information of any date held by Scottish public authorities.

SMC is not a "Scottish Public Authority" for the purposes of Freedom of Information (Scotland) Act 2002 and thus is not subject to the terms of that Act. The 15 Scottish NHS Boards who form the Consortium are the public authorities listed in the Act.

However, the SMC acknowledges the benefits of fostering greater transparency in carrying out its functions and, to that end, has adopted a culture of openness wherever possible in its dealing with information and wishes to act within the spirit of the legislation by providing a response to information requests.

As such all information received may be subject to disclosure under the Freedom of Information (Scotland) Act 2002.

On receipt of a request for information, the SMC secretariat will contact your designated company representative to confirm that information being released is not deemed as commercial in confidence.

Fourth page:

Checklist for Completion of New Product Assessment Form

Before submitting the New Product Assessment Form (NPAF) please ensure the following checklist is complete:

All sections of NPAF completed	
Electronic copy of full NPAF and appendices sent	
Signed hard copy of full NPAF and appendices enclosed	
Summary of product characteristics enclosed	
Copies of all references enclosed	

Guidance notes:
All tasks in the above checklist should be completed before the NPAF is submitted to SMC. Failure to complete any of these may delay processing of the submission.

Part B

Guidance to Manufacturers for Completion of New Product Assessment Form Clinical Sections (Sections 1-5)

1. Registration details

a) State the indication(s) for the product, which are detailed in the submission, as described in the summary of product characteristics.

Guidance notes:
Provide details of the indication(s) detailed in the submission, as described in the summary of product characteristics (SPC).

b) State any other indication(s) for the product, which fall within the remit of SMC. If these have not been reviewed by SMC, provide details of timelines for provision of submissions to SMC for these.

Guidance notes:
If the product is licensed for other indication(s), which fall within the remit of SMC, please indicate this and state the indication(s). If these have not been reviewed by SMC, please provide details of timelines for provision of submissions to SMC for the indication(s).

A separate NPAF for each indication is preferred and facilitates the development of a coherent case for each indication. However this may not be appropriate when indications are closely related e.g. a product licensed for different grades of severity of the same disease.

c) Provide details of the licence status of the product for the indication(s) detailed in the submission, including dates of granted or expected marketing approval.

Guidance notes:
Provide details of the licence status of the product for the indication(s) detailed in the submission, including dates of granted or expected marketing approval.

d) Has the product been designated an orphan medicinal product for the indication(s) detailed in the submission?

Guidance notes:
Provide a statement to indicate whether the drug has been designated an orphan medicinal product for the indication(s) detailed in the submission and when appropriate include the date on which this occurred.

e) Provide details of a potential or the actual UK launch date for the product in the indication(s) detailed in the submission.

Guidance notes:
This information may be used in order to prioritise SMC workload and therefore even an estimated time period for launch would be useful. The launch date should be the date that the product first becomes available for prescribing in the UK. It may be different (earlier) from the launch of a promotional campaign for the product. For a submission relating to a new indication for a product already marketed in the UK, a launch date is not required.

f) Provide details of the formulation(s) of the product which are or will be licensed for the indication(s) detailed in the submission and their actual or anticipated list price(s).

Guidance notes:
Provide details of the formulation(s) of the product, which are or will be licensed for the indication(s) detailed in the submission and their actual or anticipated list price(s).

g) Advise if the product or any of the relevant active comparator(s) are scheduled for or are currently subject to any other form of health technology assessment in the UK and provide details of these.

Guidance notes:
Provide details of any other health technology assessments, such as those performed by the National Institute for Health and Clinical Excellence (NICE) or Scottish Intercollegiate Guidelines Network (SIGN), which include the drug or a relevant comparator in the indication(s) under review. Details should include the organisation conducting the review, title of the review and expected date of publication. If available, also summarise details of the scope of the review or any initial recommendations of the assessment relating to the product, which is the subject of the SMC review, or any relevant comparator(s).

2. Summary

*In **no more than one page** describe the context within which the submission is being made.*

Guidance notes:

The summary should include:

- Brief overview of the disease
- Brief overview of current treatment options within Scotland which may include non-drug treatment options
- The rationale for the development of the new product, indication or formulation, including perceived gaps in therapy and the underlying pharmacological and/or pharmacokinetic principles
- The suggested place in therapy for this treatment with respect to treatments currently available

3. Comparative Efficacy

a) Provide details of studies, which provide evidence of the clinical benefits with the drug in the indication(s) under review relative to active comparator(s) used in clinical practice. The most relevant are active-controlled trials. However, if active-controlled trials are not available, details of placebo-controlled or uncontrolled trials should be included. Placebo-controlled and uncontrolled trials can also be included if they provide evidence of relevant clinical benefits not demonstrated in active-controlled trials.

Guidance notes on types on trials to be included and sources:
The efficacy section should include details of randomised controlled trials (RCTs), meta-analyses and other studies, which provide evidence of the clinical benefits of the drug in its licensed dose within the indication(s) under review relative to active comparator(s) used in routine clinical practice. The most relevant are active-controlled trials. However, if active-controlled trials are not available, details of placebo-controlled or uncontrolled trials, which provide evidence of the clinical benefits of the drug in its licensed dose within the indication(s) under review, should be included. Placebo-controlled and uncontrolled trials can also be included if they provide evidence of relevant clinical benefits not demonstrated in active-controlled trials.

Details of these studies should be taken from complete published reports of the trials. However, if a published report of the trial is not available, details should be taken from clinical study reports. These references should be provided with the submission to SMC. Where data have been taken from a clinical study report, these should be clearly highlighted in the text by underlining and will be treated as CIC.

Abstracts and posters are NOT appropriate sources for descriptions of the study methodology or primary outcomes of studies. However, if adequately detailed, they may be references for some relevant additional data, for example:
- updates of data subsequent to the primary analyses
- analyses of secondary outcomes not detailed in the published report.

If the studies have been described in publications produced by regulatory authorities this should be noted. These publications include the European Public Assessment Report (EPAR) produced by the European Medicines Agency (EMEA) and Medical reviews produced by the American Food and Drug Administration (FDA).

Where data for a single study have been taken from more than one source this should be made clear. Examples of this include:
- a clinical trial report and a published paper
- an open-label extension to a trial,
- additional analyses (e.g. interim or post-hoc)

Guidance notes on the description of the trial methodology:
For each trial the following details should be included. It is not sufficient to state that there is a description of the study in an accompanying document or an appendix.

Title and/or study number: details of study title from published paper or clinical study report and/or study number

Trial design: brief description of trial design, including details of blinding and randomisation.

Inclusion criteria: details of inclusion criteria including any definitions, especially for potentially ambiguous terms (e.g. “treatment-resistant”), and any assessments used in recruitment.

Exclusion criteria: details of exclusion criteria including any definitions, especially for potentially ambiguous terms, and any assessments used in recruitment.

Study drugs: details of study drug and comparator(s), with dosing information, including routes of administration and titration schedules where appropriate. Where dosing schedules are unlicensed this should be stated.

Permitted and disallowed concomitant medications: provide an overview of concomitant medications permitted and disallowed during the study.

Primary outcome: definition of the primary outcome, including details of the methods of collecting this data and timing of assessments. If the primary outcome is measured on a scoring system, brief details of this should be provided, including an indication of the relevance of the score (e.g. higher scores=better quality of life).

Population included in primary analysis of primary outcome and methods for handling missing data: details of the study population included in the primary analysis of the primary outcome and methods to take account of missing data.

Statistical test in primary analysis of primary outcome: details of the statistical test used in the primary analysis of the primary outcome.

Primary hypothesis under investigation and power calculation: details of the primary hypothesis or hypotheses under consideration and statement about the power of the study including assumptions in the sample size calculation.

Relevant secondary analyses of primary outcome and analyses of relevant secondary outcomes: for any relevant secondary analyses of the primary outcome (e.g. analyses in a subgroup within which the drug is licensed) or analyses of relevant secondary outcomes (e.g. survival when primary outcome was tumour response), provide details of details of the study population included in these analyses, methods to take account of missing data and details of the statistical tests used. If any of these analyses were designed post-hoc, note this and provide details of the rationale supporting these post-hoc analyses.

Guidance notes on the description of the trial outcomes:
For each trial the following details should be included. It is not sufficient to state that outcomes of the study are detailed in an accompanying document or an appendix.

Study patient disposition: details of the number of patients randomised, treated and discontinued from the study and the number of patients who completed the study or are ongoing in the study.

Baseline demographics: details of baseline demographics, including age, sex and relevant variables describing disease duration/severity and, if appropriate, previous treatments. If there are any significant differences between study groups, these should be noted.

Results of the primary analysis of the primary outcome: details of results from the primary analysis of the primary outcome with a measure of variance, preferably 95% confidence intervals. Graphical presentation of data may be appropriate, but should be a supplement to text and tabulated data NOT an alternative. Complex graphics, which markedly increase the size of the document should not be included.

Results of relevant secondary analyses of the primary outcome and analyses of relevant secondary outcomes: details of results of relevant secondary analyses of the primary outcome and any analyses of relevant secondary outcomes in the format described previously for the primary analysis of the primary outcome.

Additional information: details of any relevant additional information.

b) Provide details of ongoing studies or updated analyses of trials described previously, which would provide additional evidence within the next 6 to 12 months for the drug in the indication(s) under review.

Guidance notes:
Provide details of ongoing studies or updated analyses of trials described previously, which would provide additional evidence within the next 6 to 12 months for the drug in the indication(s) under review. For drugs designated as orphan medicinal products for the indication(s) under review provide details of ongoing studies, which could extend the indication(s) to a larger patient population (e.g. current indication for use in severe disease and ongoing studies in moderate disease). For each trial provide a brief description of:
- the trial design, including details of blinding and randomisation;
- the main inclusion criteria, which define the patient population included in the study;
- the primary and/or other relevant outcome(s) measured in the study and likely timescale for reporting of these.

4. Comparative Safety

a) Provide details of studies, which provide evidence of the clinical adverse effects with the drug in the indication(s) under review relative to active comparator(s) used in clinical practice. The most relevant are active-controlled trials. However, if active-controlled trials are not available, details of placebo-controlled or uncontrolled trials should be included.

i) For trials primarily designed to investigate differences between the drug under review and a placebo- or active-comparator in a safety outcome as the primary endpoint, provide complete details of the trial, as described above in section three.

ii) For active-controlled trials, which primarily assessed an efficacy outcome, provide details of any analyses, indicating significant differences in adverse event rates between the drug under review and an active comparator.

iii) For placebo-controlled and uncontrolled trials, which primarily assessed an efficacy outcome, provide details of the type and frequency of adverse effects that might be expected in clinical practice with the drug in the indication(s) under review.

Guidance notes:
For (i) to (iii) details of these studies should be taken from complete published reports of the trials. However, if a published report of the trial is not available, details should be taken from clinical study reports. These references should be provided with the submission to SMC. Where data have been taken from a clinical study report, these should be clearly highlighted by underlining and will be treated as CIC.

b) Provide details of any additional safety issues for the drug in the indication(s) under review compared to relevant active comparator(s), which were not identified in the trials described previously.

Guidance notes:
This section should include a brief summary of additional safety issues for the drug under review compared to relevant comparator(s), which were not identified in the trials described previously and would include, but not be limited to, the following:

- Details of any additional safety issues identified by the regulatory authorities, e.g. requirements for post-marketing surveillance of theoretical but rare potential adverse effects.

- Details of adverse effects not yet identified with the drug under review, which have been observed with comparator(s). Similarly details should be provided of adverse effects identified with the drug under review, which have not been observed with relevant comparator(s). Any limitations of available data for these comparisons should also be stated.

This information may be taken from publications produced by regulatory authorities, including SPCs, published papers and clinical study reports.

5. Clinical Effectiveness

a) Describe any limitations of the trial methodology and conduct affecting the quality of the evidence of clinical benefits and adverse effects with the drug in the indication(s) under review relative to relevant active comparator(s).

Guidance notes:
Provide details of any limitations of the trial methodology and conduct affecting the quality of the evidence it provides relating to clinical benefits and adverse effects with the drug in the indication(s) under review relative to relevant active comparator(s). Examples of this would include, but are not limited to, the following:
- open-label design for measurement of subjective outcomes, such as quality-of-life and adverse events
- non-random assignment to treatment
- effect of high dropout rates on study power

b) Describe the relevance of the outcomes assessed in clinical trials to clinical benefits and adverse effects expected in practice.

Guidance notes:
Provide details of whether trials have directly measured health outcomes such as mortality, survival, incidence of disease, morbidity, functional performance, quality of life or whether surrogate markers have been measured e.g. reduction in blood pressure. Provide details of any association between surrogate markers and health benefits or disadvantages to patients.

For drugs designated as orphan medicinal products for the indication(s) under review, provide a detailed explanation of the relevance of surrogate markers and the theoretical basis for this selection. This should also be related to quality of life data.

Provide relevant details from guidance, such as that from regulatory authorities or professional bodies, on preferred outcome measures for the condition under review.

c) Describe any factors which may influence the applicability of study results to patients in routine clinical practice in Scotland.

Guidance notes:
Provide details of differences between the patient populations included in the studies, which provided evidence of clinical benefits and adverse effects compared to the Scottish population likely to receive the drug in clinical practice. Examples of this include, but are not limited to, the following:
- differences in baseline demographics, such as age, performance status, previous treatments, severity of disease
- differences in clinical management, such as the dose schedule of comparator(s) or permitted/disallowed concomitant drugs, monitoring or assessment frequency.

The following questions should be completed to provide a balanced account of the advantages and disadvantages of the drug in the indication(s) under review relative to relevant active comparator(s).

d) Provide details of the main alternative treatments used for the indication(s) under review within Scottish clinical practice.

Guidance notes:
Provide details of main treatments, including non-pharmacological therapies, used in current clinical practice in Scotland for the indication(s) under review. Licensed products used out with the terms of their UK licence can be included if relevant. However, unlicensed medicines should not be included. If no other treatments are licensed for the condition under review, this should be stated.

e) Provide details of relevant guidelines and protocols relating to the indication(s) under review, including previous SMC guidance for drug(s) which may also be used for the indication(s) under review.

Guidance notes:
Provide details about relevant clinical guidelines, including those from national organisations such as the NICE and SIGN and professional bodies such as the Royal Colleges. If the guideline development was supported by a grant (e.g. from a pharmaceutical company) this should be noted. The following information should be included:
- the organisation responsible for the guideline
- the title of the guideline
- the date the guideline was published-
- brief details of recommendations within the guideline for the drug and relevant comparator(s) within the indication(s) under review.

Provide full details of the final recommendation paragraphs for previous advice from the SMC for drugs, which may also be used for the indication(s) under review.

f) State whether data on the clinical benefits and adverse effects with the drug in the indication(s) under review relative to relevant comparator(s) were available from active-controlled trials. If these were, please omit questions (g) to (j), unless an indirect comparison has been used in the economic model.

Guidance notes:
Make a brief statement (i.e. one or two sentences) about whether data on the clinical benefits and adverse effects with the drug in the indication(s) under review relative to relevant comparator(s) were available from active-controlled trials.

g) Provide details of any indirect comparisons used in the economic model to define clinical benefits and adverse effects to be expected in practice with the drug and relevant comparator(s) in the indication(s) under review

Guidance notes:
Make a brief statement (i.e. one to two sentences) detailing any indirect comparisons used in the economic model to define clinical benefits and adverse effects to be expected in practice with the drug and relevant comparator(s) in the indication(s) under review.

h) Provide details of the search strategies or rationale for identification of data sources used in the indirect comparison to provide evidence of clinical benefits and adverse effects.

Guidance notes:
Provide details of search strategies undertaken to identify data sources used in the indirect comparison to provide evidence of clinical benefits and adverse effects, including criteria for inclusion and/or exclusion of trials from the evidence base. If a search has not been performed, provide details of the rationale supporting the choice of data sources to provide clinical evidence.

i) Provide details of the data sources used in the indirect comparison to provide evidence of clinical benefits and adverse effects.

Guidance notes:
Provide details to identify the data sources used in the indirect comparison to provide evidence of clinical benefits and adverse effects, e.g. for clinical trials, provide the study title and/or clinical study report number. This list of data sources should be referenced and the references supplied with the submission to SMC.

j) Provide details of any relevant differences between the data sources providing evidence of clinical benefits and adverse effects with the drug in the indication(s) under review and those providing evidence for indirect comparator(s). These would include, but not be limited to, differences in terms of (a) patient populations; (b) drug treatments; (c) methodology; (d) study limitations; and (e) results.

Guidance notes:
Provide details of any relevant differences between the data sources providing evidence of clinical benefits and adverse effects with the drug in the indication(s) under review and those providing evidence for indirect comparator(s). These would include, but not be limited to, differences in terms of:

(a) patient populations, by comparing inclusion/exclusion criteria, baseline demographics, including defining relevant variables such as disease severity and previous treatments;
(b) drug treatments, by comparing dosing schedules of study drugs and concomitant study medications, which were allowed and disallowed;
(c) methodology, by comparing trial methodologies;
(d) results, by comparing results;
(e) study limitations, by comparing limitations in methodology and application of results to practice.

k) Provide details of any advantages or disadvantages, other than clinical benefits and adverse effects with the drug in the indication(s) under review compared to usual clinical practice with the relevant active comparator(s). These would include, but are not limited to, differences in terms of: (a) tests or investigations for selection or monitoring of patients; (b) routes or schedules of administration; and (c) service changes.

Guidance notes:
Provide details of any advantages or disadvantages, other than clinical benefits and adverse effects with the drug in the indication(s) under review compared to usual clinical practice with the relevant active comparator(s). These would include, but are not limited to, differences in terms of:

(a) tests or investigations for selection or monitoring of patients. Provide details of any additional tests or investigations needed for selection or monitoring of patients over and above usual clinical practice with the relevant active comparator(s). For example, in terms of efficacy to establish eligibility for treatment (e.g. measure a pre-specified severity of disease for which the product is licensed) or monitor effect (e.g. assess response necessary for continuation of treatment). In terms of safety, to identify patients in whom the treatment is contra-indicated and/or who are particularly at risk from known adverse effects or monitoring to detect potential adverse effects. If the recommended testing/monitoring regimens are extensive, these may be included as an appendix.

(b) routes or schedules of administration. Provide details of any differences in routes or schedules of administration compared to usual clinical practice with the relevant comparator (s). For example, fewer visits to hospital for administration of infusion.

(c) service changes. Provide details of any service changes that would be associated with use of the drug in the indication(s) under review, compared to usual clinical practice with the relevant comparator(s). For example, increase or reduction in healthcare facilities.

Part C

Guidance to Manufacturers for Completion of New Product Assessment Form Ecominic Sections (Sections 6 and 7)

6. Pharmaco-economic Evaluation

This section should be completed by reporting the design, methods and results of the economic evaluation. Section 2 of this document contains more detailed guidance on all of the relevant aspects. It can either be pasted in to this section or attached as an appendix to the submission. In either case, the checklist contained in this section must be completed to denote where in the submission each of the aspects has been covered.

7. Resource Implications

The purpose of this section is to provide an estimate of the potential budget impact in a way that an NHS board could identify, for example, how much money they might have to find if the new treatment replaces existing therapy. It should include acquisition costs of the new treatment, and any direct effect on the use of other resources e.g. on changing from parenteral to oral therapy. However, a full economic analysis is not required here, since cost-effectiveness is considered in the previous section.

Where data are not readily available, estimates in this section may have to be based on assumptions.

Where assumptions are made in this submission, they should be stated and, if possible referenced.

a) *Please give an estimate of the total number of patients in Scotland who have the condition relating to the indication under consideration (current prevalence) and an indication of the source of estimated numbers.*

b) *Please give an estimate of the number of newly diagnosed patients each year over the first five years after introduction (yearly incidence), and an indication of the source of estimated numbers.*

c) *If appropriate, please give an estimate of the net number of patients in each of the first five years after introduction*

(net number = prevalent cases plus incident cases less patients who recover or die).

Where possible, the data in this section should be specific to Scotland. Where this is not possible, UK data may be adapted based on Scottish population statistics. Population estimates based on the 2001 census are now available from the General Register Office for Scotland www.gro-scotland.gov.uk

The net number should, where appropriate, take account of changing patterns associated with the condition under consideration. In some cases, the prevalence may remain constant from one year to the next. In others, it may

be likely to change e.g. because of changes in incidence and/or prognosis and survival. There may be assumptions that some of these changes will be influenced by the new treatment.

d) Give an estimate of the number of people in Scotland currently treated for this condition.

There may be direct evidence but this may have to be based on epidemiology and assumptions about the proportion of patients who are currently treated.

e) Give an estimate of the number people likely to be prescribed this treatment and the basis for calculation.

This may be based on assumptions about the proportion of patients with the condition who will receive the new treatment as newly treated patients or as a result of being switched from existing treatment.

It may involve making assumptions about market share and uptake changing with time e.g. an analysis of each of the five years after introduction.

f) For the product under consideration in this submission, and for the principal alternative treatments, give the direct cost associated with treatment over a defined time period.

For the product under consideration and each of the principal alternative treatments identified in section 1e, give the cost of treatment over a defined time period e.g. the acquisition cost of 28 days' chronic treatment, annual costs or cost per treatment episode.

- Include average length of treatment (or range)
- Include average dose anticipated (or range)
- Include whether or not treatment is continuous, one-off or given cyclically but for a finite time
- Estimate cost per patient per year, or other appropriate time period, stating any assumptions made

g) For the product under consideration in this submission, identify any direct savings over a defined time period.

In general, direct costs and savings refer only to the acquisition cost of the product and the costs involved in the process of providing the treatment e.g. administration sets and diluents for a parenteral preparation. Other costs and savings should be considered in the economic analysis.

h) Provide a summary of the net resource implications for Scotland in each of the first five years following introduction. This should take account of acquisition costs associated with the new treatment and with other therapy whose uptake may be influenced by its availability.

This should combine the data on acquisition costs/savings with the data on the number of patients likely to be treated to give an appropriate estimate over the time periods for which the data are available.

CONTENTS

Summary

- It is the responsibility of the manufacturer to clearly demonstrate the case for the cost-effectiveness of medicines submitted to the SMC. If the manufacturer does not submit economic evidence according to the principals and standard outlined in the guide the SMC will not recommend the medicine for use in Scotland.

- The perspective adopted on costs should be that of the NHS in Scotland and social work.

- The evidence submitted must be assembled systematically and synthesised in a transparent and reproducible way.

- All data used to estimate clinical and cost-effectiveness must be presented clearly in tabular form and include details of data sources.

- Clinical and cost-effectiveness needs to be considered over an appropriate time horizon relevant to Scottish practice and patients and all relevant treatment options for the specific patient groups should be compared.

- In general, cost-utility analysis is the preferred form of economic evaluation, with health effects expressed in terms of quality-adjusted life-years (QALYs).

- The SMC considers modelling a relevant framework within which available evidence can be synthesised and estimates of clinical and cost-effectiveness generated.

- The annual discount rate recommended for both costs and benefits is 3.5%.

- Uncertainty surrounding the estimates of cost-effectiveness needs to be included.

- The process applied to orphan drugs submissions is the same as all other drug submissions.

1. Introduction

This document sets out the SMC Guidance to Manufacturers for the economic assessment of medicines included in the New Product Assessment Form.

The first section summarises the background and general principals of the guidance with section two looking specifically at the design requirements for economic evaluations. Sections three and four address the approaches for synthesis of the evidence and valuing health effects; section five covers evidence on cost; section six covers discounting and section seven modelling methodology; section eight covers a key area, that of presentation of data and results; with the final section outlining the SMC approach to orphan drugs.

To help manufacturers meet the SMC's requirements, the guidance includes specific advice supported by additional commentary in italics. A copy of the economic checklist used by the SMC to judge the quality of economic submissions is appended to this guidance.

1.1 SMC Remit

The remit of the Scottish Medicines Consortium (SMC) is to provide advice to NHS Boards and their Area Drug and Therapeutics Committees (ADTCs) across Scotland about the status of all newly licensed medicines, all new formulations of existing medicines and any major new indications for established medicines. The review of medicines containing devices will be confined to those licensed as medicines by the MHRA/EMEA. The remit of SMC excludes the assessment of vaccines, branded generics and devices. The SMC aims to make a recommendation soon after the launch of a medicine.

1.2 Guidance Development

This guidance was developed by health technology assessment experts from the SMC, the pharmaceutical industry and research centres. The principals and content of the guidance were agreed following extensive discussions and consultations. The guidance will be reviewed and updated at regular intervals.

1.3 Remit and Exceptions to the Guidance

The SMC will recommend the use of a medicine based on an economic evaluation of that medicine within the NHS in Scotland. If the manufacturer does not submit economic evidence according to the principals and standard outlined in this guide the SMC will not recommend the medicine for use in Scotland.

There is only one exception to the requirement for an economic evaluation and this applies to those medicines that fulfil the SMC criteria for an abbreviated submission. Part of the rationale for an abbreviated submission is that they have a minimal economic impact on NHS Scotland, no economic evidence is required.

1.4 Responsibility of the Manufacturer

The SMC makes recommendations to NHS boards and prescribers in Scotland on the use of new medicines and new indications for existing medicines based on an assessment of the likely clinical and cost-effectiveness. The principle source of evidence for this judgement is the submission made by the manufacturer of the medicine. **The onus to clearly demonstrate the case that their medicine is cost-effective in the role they propose is thus upon the manufacturer.** To achieve this, the manufacturer must provide a clear, concise, unbiased and robust case to support the application. Robustness will be judged on the basis of the methodological quality of the case submitted. The application needs to show that the medicine will:

(i) provide additional health benefits that are valued by patients compared to current Scottish practice and that this is at a net cost to the NHS that offers acceptable value in relation to other uses of the same resources,

or

(ii) offer equivalent levels of health benefit to patients at an equivalent or lower net cost to the NHS.

While the SMC requires manufacturers to comply with the SMC Guide, it has not defined a single reference case which must be submitted. Should manufacturers wish to use a reference case approach, then SMC recommends that set out by NICE (see Annex 1).

1.5 Consistency of Requirements Across the UK

The SMC recognises that the pharmaceutical industry is facing a growing number of organisations performing similar roles, notably the National Institute for Clinical Excellence (NICE) and the All-Wales Medicines Strategy Group (AWMSG). A key theme in developing this SMC Guide was consistency with existing, authoritative guidance; in the UK context this means the NICE document, "Guide to the Methods of Technology Appraisal"[1] (henceforth "the NICE guide"). This document was drawn up by experts, following extensive discussions and consultation and many of the principles can be accommodated within the SMC Guide. However, there is some divergence between this guidance and that advocated by NICE, for several valid reasons:

(i) the two organisations have slightly different remits and thus are not carrying out identical tasks - SMC critically appraises the manufacturer's submission whereas this is only one component of a NICE health technology assessment.

(ii) SMC generally reviews medicines at an earlier stage of the product cycle than NICE do with consequences for data availability.

(iii) the two groups of decision makers place a different weight on some aspects of the economic evaluations.

The main areas of difference are in respect of probabilistic sensitivity analysis, measurement of utilities and the need for a reference case.

1.6. Guiding Principles

1.6.1 Clinical and Cost-effectiveness

In order to inform the SMC's decision makers, the analytical framework within which evidence is synthesised to estimate clinical and cost effectiveness needs to include a number of important features.

- Consistency between the methods used in submissions is needed to assist the SMC in making consistent appraisals of different medicines and over time.
- All relevant comparators for the medicine being appraised need to be included in the analysis.
- All relevant evidence needs to be assembled systematically and synthesised in a transparent and reproducible manner.
- The costs that are most relevant are those of the NHS in Scotland and local government social work departments.

[1] Available on-line at http://www.nice.org.uk/pdf/TAP_Methods.pdf

- Measures of health-related benefits used should be comparable to promote consistency between appraisals and to allow comparison with the benefits from other medicines that may be displaced if new medicines are adopted.
- The time horizon should be sufficient to reflect important cost and benefit differences between the medicines being compared.
- The uncertainty surrounding the estimates of cost effectiveness needs to be explored.

1.6.2 Synthesis and Modelling

The process of assembling evidence needs to be systematic. Evidence must be identified, quality-assessed and, where appropriate, pooled using explicit criteria and justifiable and reproducible methods. These principles apply to all categories of evidence that are used to estimate clinical and cost-effectiveness, including evidence typically drawn from a number of different sources such as cohort studies for parameters relating to the natural history of the condition, randomised trials for relative treatment effects, and cross-sectional surveys for resource use and costs.

It is necessary that clinical and cost-effectiveness are considered over an appropriate time horizon relevant to Scottish practice and patients and that all relevant treatment options for the specific patient groups are compared. It will be necessary to provide an analytical framework within which the available evidence to estimate clinical and cost-effectiveness relevant to the decision making context can be synthesised. Modelling provides a relevant framework based on decision analytic models using aggregated data or statistical models using patient-level data.

1.6.3 Requirements for Evidence

The requirements for evidence of effectiveness include the quantification of the effect of the medicines on the course of the disease, the effect of the medicines on patients' health related quality of life (HRQoL) and the valuation of those effects in a way that reflects the preferences of the general population.

Data are required to quantify the effect of the medicines on use of resources in terms of physical units (for example, days in hospital and visits to a GP) and valuing those effects in monetary terms using appropriate prices and unit costs.

Despite limitations or deficiencies in the evidence base, decisions still have to be made concerning the use of medicines. For example, small sample sizes may result in some parameters being estimated with a low degree of precision or evidence on effectiveness might come from outside the UK healthcare system or relate to subgroups of patients other than those of principal interest for the appraisal. Therefore, analyses should use the best evidence available, be explicit about data limitations and any attempts to overcome these and quantify as fully as possible how the limitations of the data are reflected in the uncertainty in the results of the analysis.

1.6.4 Analysis of Uncertainty

It is important for the SMC to understand the uncertainty associated with the clinical and cost-effectiveness information. This requires the appropriate use of rigorous methods to quantify the implications of parameter and methodological uncertainty for the results of an analysis. This assessment of decision uncertainty enables the SMC to make decision regarding further research.

Commentary

The SMC recognises that estimating cost-effectiveness of a medicine at launch is not easy, but its recommendations will commit scarce NHS resources so an economics submission is essential. This applies to all medicines, including those with orphan status. If evidence is only available for part of the indication then any positive recommendation will be restricted to the more limited indication. Where there is uncertainty around the value of parameters this should be addressed within the text and through sensitivity analysis.

A key aim of SMC is to keep its process efficient so that recommendations are issued as close to launch as possible. Manufacturers can help by being concise: experience suggests a typical economic case can be summarised in around twenty pages, provided it is clearly referenced and supported by appendices and accompanied by electronic versions of the original articles that provide the evidence base. Reviewers can request more detail if necessary.

The SMC does not routinely require the manufacturer to submit an electronic copy of a model or spreadsheet of calculations. When further analysis is required the economics reviewer will ask the manufacturer to carry this out. However, the SMC assumes the model or spreadsheet is readily available and may ask to see a copy at any point.

2. Design of the Economic Evaluation

The design of the evaluation is one of the crucial aspects and manufacturers must give it very careful attention. If the design of the economic analysis submitted does not meet the basic points set out in this section then the submission has little chance of success.

2.1 Defining the Decision Problem

Estimating clinical and cost-effectiveness should begin with a clear statement of the decision problem. This will require a definition and justification of the medicines being compared and the relevant patient group(s). If the submission applies only to a sub-set of the indication then this should be stated. The SMC recommendation will be limited to the sub-set of the indication for which evidence is submitted. Patient groups/indications for which there is no economic evaluation will be explicitly excluded from SMC recommendations.

2.2 Comparator

Comparator medicines must be specified as precisely as the medicine being appraised. There are frequently several potential comparator medicines as, for example, practice is not necessarily consistent across Scotland or the UK and between the UK and elsewhere. All relevant comparators must be identified, although a full comparison will not always be appropriate for every one of these comparators.

The comparator the SMC is interested in is the one that will most likely be replaced if the medicine under consideration is accepted by the SMC for use in Scotland. This may be different to the comparator in the clinical trials programme for the medicine; if so the manufacturer must carry out an indirect comparison. The service replaced might also involve no active treatment of the condition.

Flow diagrams can be helpful to show how patients were managed before the medicine became available and the proposed patient pathway if the medicine is accepted by SMC.

Commentary

The SMC's recommendations to NHS Scotland are based in part on the likely additional costs (or savings) and health benefits of using the medicine in question. For this reason, the appropriate comparator is the medicine or care that will be replaced by the new medicine.

This aspect of the design is critically important: cost-effectiveness is a relative concept so if the comparator is inappropriate, then the resultant net costs and benefits will be unsuitable for decision-making purposes and lead to the SMC failing to recommend a medicine.

Some potential difficulties include:

- *the current treatment involves the use of a medicine that has a licence but this does not cover the specific indication in question (so-called "off-label" use). In this case, the manufacturer must make a judgement about what the most appropriate comparator is. The SMC recognises that manufacturers have strong reservations about comparing with "off-label" medicines. However, in judging the comparator to use the manufacturer must also bear in mind that some "off-label" medicines are so widely used that any economic comparison that did not include them would have neither relevance nor credibility for the NHS in Scotland.*

- *current practice is highly variable - in this case, the SMC's preferred solution would be to obtain Scottish treatment or audit data showing what the most common treatment is and use that as the comparator. Information of the volume of prescriptions by general practice is available at the Prescribing and Dispensing section of the Scottish Health Statistics website (www.isdscotland.org) although this does not show the indication the medicine was prescribed for.*

- *current practice is not "best practice" for example, where SMC or NICE guidance has been issued but not implemented. If data on prescribing trends suggest the SMC/NICE recommended medicine is likely to become standard practice in the very near future (e.g. next twelve months) then it should be selected as the comparator; this will be a matter for judgement and the rationale for the approach used should be set out. However, if there is no such evidence then current Scottish practice is the preferred choice as comparator.*

2.3 Perspective

The perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on costs should be that of the NHS in Scotland and social work (referred to as Personal Social Services (PSS) in England). If the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, these should be reported in a sensitivity analysis. They can also be included in a discussion although this may limit their impact on the decisions.

This is consistent with an objective of maximising health gain from available resources. Some features of healthcare delivery that are often referred to as 'process characteristics' may ultimately have health consequences – for example, the length of waiting lists for elective surgery. When there are significant characteristics of healthcare medicine that have a value to individuals that is independent of any direct effect on health, these should be noted. These characteristics include the convenience with which healthcare is provided and the level of information available for patients.

2.4 Type of Economic Evaluation

In general, cost-utility analysis is the appropriate form of economic evaluation, with health effects expressed in terms of quality adjusted life years (QALYs). Cost-minimisation analysis may be appropriate if the proposed medicine is demonstrated by trials to be therapeutically equivalent to the relevant comparator(s), as assessed using an adequately designed and powered non-inferiority or equivalence or superiority study.

Alternative approaches can be considered in those circumstances in which the QALY may not to be the most appropriate outcome measure. For example:

- The QALY does not capture the main health benefit of the medicine – contraception is one example. In this situation, cost-effectiveness analysis is acceptable.

- The QALY does not capture the main benefit of the medicine where this is something other than health. For example, the main advantage of a new medicine might be patients prefer the delivery system. However, manufacturers need to be cautious because the SMC may ask whether this preference translates into better concordance and whether this translates in turn into health gain. The manufacturer must make a careful argument for not using a QALY in these circumstances.

- Utility values used in QALYs appear to lack sensitivity in circumstances where other measures suggest health improvements or disease reductions. Again, this should be demonstrated and not simply asserted. SMC would need to be assured that the changes in alternative outcome measures are valued by patients.

- Utilities used in QALYs cannot be adequately measured for the main health states generated by the condition in question (e.g. this may be the case with some mental health states).

- Where cost-minimisation analysis using non-QALY outcome measures can be demonstrated to be appropriate.

Manufacturers are urged to think carefully before deciding not to use QALYs as the SMC regards this methodology the most appropriate to make comparisons of value across health care interventions. If manufacturers present other methods (e.g. willingness to pay studies or a discrete choice experiment) these must be fully described and the uncertainty in results fully explored.

Commentary

It should be emphasised that the SMC's decision making process focuses on patient outcomes. Thus whilst the SMC is interested in claims such as reduced toxicity or greater patient convenience, the key factor is what impact these will have on patient outcomes in terms of reduced illness or higher concordance. The preferred economic evaluation is therefore cost utility analysis.

The focus on cost-effectiveness analysis is justified by the more extensive use and publication of these methods compared with cost-benefit analysis and the focus of the SMC on maximising health gains from a fixed NHS/PSS budget. Given its widespread use, the QALY is considered to be the most appropriate generic measure of health benefit that reflects both mortality and HRQoL effects. It is recognised that alternative measures exist (for example, the healthy-year equivalent) but few economic evaluations have used these methods and their strengths and weaknesses are not fully understood. If the assumptions underlying QALYs (for example, constant proportional trade-off and additive independence between health states) are considered inappropriate in a particular case, then evidence to this effect should be produced and analyses using alternative measures may be presented as a non-reference case analysis.

Manufacturers should note that failure to collect data to measure and value QALY gain in the clinical trial programme is NOT an adequate reason for not using QALYs. Similarly, disease-specific outcomes are not helpful since they do not give comparability of the cost-effectiveness of a medicine against other common health services.

Cost-consequence analysis is not useful to the SMC as the trade-offs between different dimensions of benefit are not made clear.

2.5 Time Horizon for the Economic Evaluation

The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the medicines being compared.

Results (in terms of net cost per QALY gained) need to reported at different time horizons intervals e.g. at end of trial follow-up, at 5 years follow-up and at five-year intervals thereafter.

A time horizon shorter than lifetime is justifiable when there is no differential mortality effect between options and differential costs and HRQoL relate to a relatively short period – for example, in the case of an acute infection.

2.6 Incremental Cost-effectiveness

The incremental cost-effectiveness ratio – typically a net cost per QALY gained - is a summary statistic for the economics evidence. Its appeal is that it is concise and allows comparisons with other health services. Its two main drawbacks are (i) it gives an impression of precision when an indication of the extent of uncertainty might be more appropriate, and (ii) it needs to be set in the context of other factors relevant to decision-making. The SMC does not have a fixed upper limit on willingness-to-pay for a QALY.

In making its decisions SMC notes sections 6.2.6.10 and 6.2.6.11 from the NICE guidance, as follows:

Below a most plausible ICER of £20,000/QALY, judgements about the acceptability of a technology as an effective use of NHS resources are based primarily on the cost-effectiveness estimate.

> Above a most plausible ICER of £20,000/QALY, judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make more explicit reference to factors including:
>
> - the degree of uncertainty surrounding the calculation of ICERs
> - the innovative nature of the technology
> - the particular features of the condition and population receiving the technology
> - where appropriate, the wider societal costs and benefits**.**
>
> Above an ICER of £30,000/QALY, the case for supporting the technology on these factors has to be increasingly strong. The reasoning for the Committee's decision will be explained, with reference to the factors that have been taken into account, in the 'Considerations' section of the guidance.

Commentary

The challenge for decision-making is to strike a balance between decision-making based upon explicit, stated principles and the need to retain some flexibility to respond to the circumstances of any particular case. This section sets out some general principles but in any individual decision it is the responsibility of the SMC to weigh the factors and issue guidance that it feels to be consistent with the full range of evidence (economic and other, quantified and qualitative).

The sections from NICE quoted above are helpful but NICE faces slightly different issues in that it has an independent summary of the evidence commissioned through the NHS HTA R&D programme. By contrast, SMC is interpreting the evidence submitted by a pharmaceutical manufacturer and thus will be facing greater challenges in terms of judging the likely quality of the evidence submitted and the consequences for the uncertainty surrounding the net cost per QALY estimate.

3. Synthesising Evidence on Outcomes

All the relevant clinical literature relating to the medicine under evaluation will be included in Sections 3 and 4 of the manufacturer's submission. NICE describe an approach that will synthesise these data into a point estimate of treatment effect plus the variance around that estimate. This approach is valid but the SMC will also accept an economic evaluation based on a single clinical trial provided,

(i) the patients recruited to the trial are broadly representative of a Scottish or UK population,
(ii) the trial is a “head-to-head” with the relevant comparator

and

(iii) it is demonstrated by the manufacturer that this trial does not have notably different results to the trials that are not used. In other words, the SMC requires consistency of clinical effects between Sections 3 and 6 of the manufacturer's submission and no bias.

3.1 Indirect Comparison

If no head to head evidence is available an indirect comparison is required. This enables the medicine and current Scottish practice to be indirectly compared by evaluating trials where a third treatment (including placebo) was used. To reduce the high risk of bias associated with quoting from single studies in the literature the following steps needs to be followed and clearly demonstrated:

(i) the literature has been searched in a systematic way
(ii) there are clear and plausible rules for including and excluding studies
(iii) the baseline characteristics of the population in each trial alongside the effect sizes to demonstrate homogeneity
(iv) the method for arriving at a point estimate of efficacy should be clear and transparent

and

(v) the value elicited should be a key part of the sensitivity analysis.

3.1.1 Systematic Review

This involves the systematic location, appraisal and synthesis of evidence in order to obtain a reliable overview. Databases searched and literature searching strategies should be reported. There should be a clear rationale for selecting specific studies from those identified.

3.1.2 Study Selection and Data Extraction

In order to reduce the risk of selective use of single studies, manufacturers should demonstrate that a systematic literature search has been undertaken and state the inclusion criteria for studies. Each study meeting the criteria for inclusion should be subjected to critical appraisal.

3.1.3 Meta-analysis

Synthesis of outcome data through meta-analysis is appropriate provided there is sufficient, relevant and valid data that uses comparable measures of outcome. Where such data are not available, the analysis may have to be restricted to a qualitative overview that critically appraises individual studies and presents their results. Forest plots are a useful tool to illustrate the individual study population results. The characteristics and limitations of the data (that is population, intervention, setting, sample size and validity of the evidence) need to be fully reported.

Before any statistical pooling is carried out an assessment of the degree of, and the reasons for, heterogeneity in the study results should be undertaken – that is, variability in the effects between studies that may suggest that individual studies reflect different study circumstances. Statistical heterogeneity of study results can be addressed using a random (as opposed to fixed) effects model. Known clinical heterogeneity (for example patient characteristics or intervention dose or frequency) can be managed by judicious use of methods such as subgroup analyses and meta-regression. For methodological heterogeneity (for example where different trials are of different quality) the results of sensitivity analyses (varying the studies in the meta-analysis) should be reported. If the risk of an event substantially differs among the control groups of the studies included in a meta-analysis, an assessment of whether the relative risk is constant over different baseline risks should be undertaken. This is especially important when the relative risk is to be used within an economic decision model and the baseline rate in the model is very different to the control event rates of the studies in the meta-analysis.

Forest plots should include lines for studies that are believed to contain eligible data even if the data are missing from the analysis in the published study. An estimate of the proportion of eligible data that are missing (because some studies will not include all relevant outcomes) will be needed for each analysis.

3.2 Role of Expert Opinion

Where data from trials are insufficient to provide values for relevant variables, and such values can be obtained from expert opinion, then SMC will consider this as a valid source of evidence. The impact of this evidence will be greater if the submission is transparent on the process used, for example on the selection criteria used to approach potential experts and the range of values provided by the experts. Variables elicited from expert opinion should be tested in the sensitivity analysis.

4. Valuing Health Effects

In order to make clear comparisons of the value of new medicines, the SMC has a preference for cost-utility analyses using QALYs as the primary outcome measure. This should include gains in length of life and quality of life, as well as adverse effects such as toxicity, which should be included as negative impacts on quality-of-life.

The SMC guidance regarding the use of QALYs has largely adopted the NICE guidance (section 5.5 of the Methods of Technology Appraisal Guide to Manufacturers) but specifies this in terms of a preference (rather than a requirement) for utility estimates from a validated generic utility instrument such as the EQ 5D. Given the timing of SMC appraisal in relation to launch, the SMC also allow manufacturers to use alternative well-designed methods of utility measurement if generic utility data are not available or to use non-QALY outcome measures if this is shown to be appropriate and the value of the medicine to NHS in Scotland can be demonstrated. This is reflected in the full SMC guidance for valuing health effects presented below.

To calculate QALYs for any medicine, it is necessary to use a classification system to describe patients' HRQoL over time. To allow comparisons across interventions, the SMC prefers that health states should be measured in patients using a generic and validated classification system for which reliable and appropriate population preference values, elicited using a choice-based method such as the time trade-off or standard gamble (but not rating scale), are available. Ideally, these data will be generated through randomised controlled trials of the medicine, although utilities derived from observational studies of patients would be acceptable as long as it can be shown that the patients and health states adequately match those in the clinical trials used in the submitted economic evaluation.

It is recognised that different classification systems do not give consistent utility values to the same health states and hence results from the use of different systems cannot always be compared. Given the comparative nature of the SMC's work and the need for consistency across appraisals, the SMC would ideally wish that all appraisals used the same system. Currently, the most appropriate choice in the UK appears to be the EQ-5D. Whilst it is widely used and simple to incorporate into studies, the EQ-5D may not be appropriate in all circumstances. Given the evolving nature of this methodology, the SMC believe it would be inappropriate to require the use of the EQ-5D to the exclusion of any other valid generic utility measures. Those submitting data should provide reasons for their choice of instrument. Manufacturers should also indicate whether they have any evidence that will help the SMC to understand to what extent, and for what reason, their choice of instrument will have impacted on the valuation of the QALYs gained.

If utility data from generic validated instruments is not available, the SMC will, in general, accept utilities from three other sources:

(i) Utilities mapped from a disease specific quality-of-life measure included in a clinical trial - the SMC will want to see well designed and explicit methods of mapping from the disease-specific measure to a generic measure and from there to utilities.

(ii) Specific surveys for direct measurement of utilities for appropriate disease/condition health states. This should use time trade off (TTO) or standard gamble (SG) methods of utility elicitation. SMC will accept values from either public members or patients and places more store by the perceived validity of the utility values when put in the context of utilities for other health states. The SMC need a description of the vignettes of health states used for the valuation and a clear explanation of how the health states were derived.

(iii) Values taken from previous studies reported in published literature. However, the submission must report all of the utility values reported in the literature and the literature selection process, in order that the SMC can see that the manufacturer has not been selective. The submission must also show that the health state valued in the literature reflects the health states in the submitted economic evaluation. For example, if the new medicine is for advanced prostate cancer it is not sufficient to use literature values that are reported for the state "prostate cancer" with no further description.

Use of any other approaches to measuring QALYs will require clear justification in the submission. If appropriate data on utilities/QALYs for carers or other groups other than the patients affected is provided as additional evidence this will need to be presented separately from the primary QALY analysis as this is outside of the perspective adopted by the SMC.

Commentary

Where survival is a factor, life-table data from the following website: http://www.gad.gov.uk/Life_Tables/Life_tables_background.htm are acceptable.

5. Evidence on Costs

5.1 NHS and Social Work Costs

Costs should relate to resources that are under the control of the NHS in Scotland and social work (equivalent to PSS in England) where differential effects on costs between the medicines under comparison are possible. These resources should be valued using costs relevant to the NHS in Scotland and social work. Where the actual price paid for a resource may differ from the public list price, the public list price should be used. Sensitivity analysis should assess the implications of variations from this price. Evidence should be presented to demonstrate that resource use and cost data have been identified systematically.

Where cost data are taken from literature, the methods used to identify the sources should be defined. Where several alternative sources are available, a justification for the costs chosen should be provided. Where appropriate, sensitivity analysis should be used to assess the implications for results of using alternative data sources.

Staffing costs should include all costs incurred by the NHS as an employer, not just the salary. Capital costs should be annuitised. All costs should be updated to the current year using a UK health service price index. Resource use (in physical units) and costs should be reported separately so that SMC can assess each part of the calculation.

Drug costs should be based on unit prices listed in the BNF or MIMS. For the comparator drug cost, the product that represents the product most likely to be replaced should be selected. If a volume-weighted average based on Scottish practice is used, a comparison with the cheapest medicine should be included in a sensitivity analysis. (If the manufacturer believes the generic version is less effective and is therefore not an appropriate comparator this argument and supporting evidence should be set out).

Resource use and costs are two aspects of an economic evaluation that are least likely to be generalisable across countries. For resource use, data from elsewhere in the UK are acceptable. Resource use data from other countries or estimated by a panel of experts should be avoided if possible, or at least validated for the Scottish setting (e.g. by demonstrating that treatment patterns are similar between the country in question and Scotland) and included in a sensitivity analysis.

Value added tax (VAT) should be excluded from all economic evaluations but included in budget impact calculations at the appropriate rate (currently 17.5%) when the resources in question are liable for this tax.

5.2 Non-NHS and Non-social Work Costs

There will be occasions where non-NHS/social work costs will be differentially affected by the medicines under comparison. In these situations, the SMC needs to be made aware of the implications of taking a broader perspective on costs for the decision about cost-effectiveness. When sensitivity analyses include these broader costs, explicit methods of valuation are required. In all cases, these costs should be reported separately from NHS/social work costs.

Commentary

In terms of the costs to value resource use, a first point of reference in identifying such costs and prices should be any current official listing published by the Scottish Executive Health Department, National Services Division, the Department of Health in England and/or the Welsh Assembly Government.

Data on Scottish hospital costs are available on a per diem basis from Scottish Health Service Costs, which can be found at: http://www.isdscotland.org/isd/info3.jsp?pContentID=3098&p_applic=CCC&p_service=Content.show&

NHS Reference Costs from the Department of Health in England (www.dh.gov.uk) are acceptable.

Primary care and community costs from the Unit Costs of Health Care publication by Personal Social Services Research Unit, University of Kent, are also acceptable (www.ukc.ac.uk/PSSRU/). Social service costs are hard to find for Scotland and English data (e.g. from PSSRU) are acceptable. Other sources of cost data should be clearly explained.

6. Discounting

Economic results should reflect the present value of the stream of costs and benefits accruing over the time horizon of the analysis. An annual discount rate of 3.5% should be used for both costs and benefits. When results are potentially sensitive to the discount rate used, sensitivity analysis should vary the rate between 0% and 6%.

7. Modelling Methods

Modelling provides an important framework for synthesising available evidence and generating estimates of clinical and cost effectiveness relevant to the SMC's decision-making process. Situations where modelling is likely to be required include those where:

- patients participating in trials do not match the typical patients likely to use the medicine within the NHS
- intermediate outcomes measures are used rather than effect on HRQoL and survival
- relevant comparators have not been used or trials do not include evidence on relevant
- subgroups are important
- the long-term costs and benefits of the medicines extend beyond trial follow-up.

Providing an all-embracing definition of what constitutes a high-quality model is not possible, however some guidelines are available. In general, all structural assumptions and data inputs should be clearly documented and justified. This is particularly important in the case of modelling to extrapolate costs and health benefits over an extended time horizon. In such circumstances the results of using alternative time horizon scenarios should be reported in order to compare the implications of different assumptions for the results. Scenarios might include that treatment benefit in the extrapolated phase is:

(i) nil
(ii) the same as during the treatment phase and continues at the same level

or

(iii) diminished in the long term.

It is important for models to quantify the decision uncertainty associated with a medicine – that is, the probability that a different decision would be reached if it were possible to ascertain the true cost-effectiveness of each medicine before making the decision. Modelling parameters must be included in a sensitivity analysis.

Commentary

The SMC welcomes the use of models to support the economic case for a medicine. However, modelling is also open to bias and the manufacturer should make efforts to ensure the approach used is transparent in terms of the structure, workings and validity of their model.

Schematic representations of models are helpful. Two areas of weakness in submissions to date have been:

(i) being clear about where the data inputs come from - if they come from Section 3 of the Submission, it is helpful to give a clear reference to a table and preferably a column and/or row and details of any calculations required to move from the clinical data to the model data e.g. moving from annual transitional probabilities to monthly values. If the data estimate comes from the literature the key question for the SMC is whether the context from which it was taken is compatible with the context it is being used in. For example, if a heart disease model to represent the use of a medicine in a Scottish population were being put forward, then including a piece of data on disease progression from a Japanese population (to pick an extreme example) would arouse suspicion. The manufacturer thus needs to provide a brief summary of the context for each data estimate from the literature.

(ii) reporting outputs from the model as opposed to net cost per QALY gained figures. For example, if the manufacturer uses a Markov model then they must include a table that shows the number of patients in each state of the model at the end of trial follow-up, at five years follow-up and at five yearly intervals thereafter. This gives reviewers a better feel for the model and gives the SMC some evidence to judge whether the model behaves in a realistic manner.

8. Presentation of Data and Results

8.1 Presenting Data

All data used to estimate clinical and cost-effectiveness must be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses and measures of precision should be detailed for all variables

Consideration should be given to the graphical representation of clinical and cost-effectiveness data to support its effective communication and interpretation.

Commentary

NICE emphasises the use of tables but the SMC also finds well-designed graphs to be especially helpful and would urge manufacturers to give more thought to this aspect of presentation.

8.2 Presenting Expected Cost-effectiveness Results

The expected value of each component of cost and expected total costs should be presented; expected QALYs for each option compared in the analysis should also be detailed. Incremental cost-effectiveness ratios should be calculated as appropriate.

Standard decision rules should be followed in combining costs and QALYs. These should reflect any situation where dominance or extended dominance exists. Incremental cost-effectiveness ratios (ICERs) reported must be the ratio of expected cost to expected QALY.

8.3 Dealing with Parameter Uncertainty in Cost-effectiveness Analysis

Sensitivity analysis should be used to deal with sources of uncertainty. This includes uncertainty about the clinical and cost-effectiveness estimates, choice of studies to include in a meta-analysis, and the structural assumptions made in a model.

The analysis of the uncertainty in all parameters for decision uncertainty assumes that factors such as a model's structure and data inputs are considered to be appropriate. However, these characteristics of the model are also subject to uncertainty, which should be formally examined using sensitivity analysis.

Common examples of this type of sensitivity would be:

- where there are doubts about the quality or relevance of a particular study in a meta-analysis, in which case the analysis could be re-run excluding this study
- where there is uncertainty about the most appropriate assumption to use for extrapolation of costs and outcomes beyond trial follow-up
- where there is variability between hospitals in the cost of a particular resource or service, or the acquisition price of a particular medicine.

Uncertainty about the appropriateness of the methods used can also be dealt with using sensitivity analysis, but these analyses must be presented separately.

Analyses using alternative methods other than those prescribed in the SMC Guide should be presented separately from those relating to structure and data.

8.4 Uncertainty in ICERs

The SMC require the manufacturer to demonstrate, through the use of sensitivity analyses:

- The robustness of the ICERs.
- Under which circumstances the ICER exceeds £20,000 and £30,000.

8.5 Presenting Sensitivity Analyses

Consideration should be given to one and two-way sensitivity analyses, supported by graphical representation including threshold values. Each alternative analysis should present separate results.

Probabilistic sensitivity analyses may be submitted in support of the application, but are not considered mandatory.

Appropriate ways of presenting uncertainty are confidence ellipses and scatter plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

Commentary

NICE require probabilistic sensitivity analysis to address parameter uncertainty. The SMC recognises the potential benefits of this approach and welcomes research in the area. However, the SMC recognise that the robust well-evidenced data required to inform probability values for each parameter may not be available until the medicine has been in use for some time.

Hence the SMC do not require probability sensitivity analysis but require robust one-way and two-way sensitivity analyses, which explore a range of plausible values for the parameters of interest. The rationale behind the range of estimates explored should be provided.

In addition the SMC require the manufacturer to show under what circumstances the net ICER exceeds £20,000 and £30,000.

8.6 Presenting Analysis of Clinical and Cost-effectiveness for Patient Sub-groups

Given the SMC's focus on maximising health gain from limited resources, it is important to consider how clinical and cost-effectiveness may differ because of differing characteristics of patient populations. Typically, the capacity to benefit from treatment will differ between patients, but this may also impact on the subsequent cost of care. There should be a clear clinical justification and, where appropriate, biological plausibility for the definition of the patient sub-group and the expectation of a differential effect. Ad hoc "data-mining" in search of significant sub-group effects should be avoided. Care should be taken to specify how sub-group analyses were undertaken, including the choice of scale on which effect modification is defined. The precision of all sub-group estimates should be reflected in the analysis of parameter uncertainty. The characteristics of the patients associated with the sub-groups presented should be clearly specified to allow the SMC to judge the appropriateness of the analysis with regard to the decision problem.

An intention-to-treat (ITT) analysis is required to estimate clinical effectiveness because ITT analysis preserves the randomisation of the trial population. However, a particular sub-group analysis that may also be useful is the analysis of per-protocol populations. A per-protocol population can be a pragmatically valid sub-group when such a population would be successfully selected for treatment in the normal care setting.

Commentary

ITT includes data for all participants analysed regardless of whether or not they dropped out of the study crossed over to another treatment or received an alternative intervention and per-protocol population comprises individuals who completed the trial according to the pre-specified trial protocol. While a per-protocol analysis can be presented, this should be confined to a sensitivity analysis. The SMC has a clear preference for intention-to-treat analysis.

8.7 Reflecting Equity Considerations in Cost-effectiveness Analysis

The estimation of QALYs implies a particular position regarding the comparison of health gained between individuals. Thus, an additional QALY is of equal value regardless of other characteristics of the individuals such as their socio-demographic details, or their pre- or post-treatment level of health. This position reflects the absence of consensus regarding whether these or other characteristics of individuals should result in differential weights being attached to QALYs gained.

Commentary

It can be difficult to include equity considerations within an economic evaluation. They can certainly be included in a discussion of the main findings, and the manufacturer may consider summarising these in Section 2 of the submission as well.

9. Orphan Drugs

The SMC issued the following statement in August 2004:

> "The SMC have adopted the European Agency for the Evaluation of Medicinal Products (EMEA) definition regarding orphan medicines - an orphan medicine is one licensed for treating or preventing life-threatening rare diseases affecting fewer than 5 in 10,000 people in the European Union.
>
> SMC requires all submissions to be comprehensive and all sections in the product assessment form completed. This includes orphan drugs, where a meaningful attempt needs to be made to produce robust clinical and economic data. SMC recognises that orphan drugs may have a less well developed clinical trials programme and therefore less information than usual may be available for some sections. On the other hand, more detail may require to be submitted in other areas, e.g. on the relevance of surrogate markers and the theoretical basis for their selection which should then be related to Quality Of Life data.
>
> As with all medicines, the managed introduction and subsequent monitoring of orphan drugs requires to be a joint responsibility with the NHS. If there is a significant lack of data on long term outcome with an orphan drug, this monitoring may include specific Clinical Audit and where relevant a patient registers.
>
> The process applied for orphan drugs submissions is the same as all other drug submissions. However, the submission process may require being more iterative for orphan drugs. In addition, orphan drugs, regardless of the SMC advice, may have an advice review date set. This would allow an additional submission after further clinical trials or the collection of clinical audit data.
>
> Finally, orphan drugs submissions must give an explanation as to the potential extension of use beyond the licensed target group (i.e. those not covered by clinical trials)."

From the economics point of view, this means that while it is essential for the manufacturer to provide an economic case, the SMC will make some allowances for the quality of the clinical evidence available and the resulting uncertainty about the cost-effectiveness. However, this does not mean that the SMC will make allowances on the basic design of the evaluation (e.g.

choice of appropriate comparator) or in ways the health benefit is measured and valued in QALYs.

ANNEXES

Annex 1 The Concept of the Reference Case

The SMC requires manufacturers to submit economic evaluations consistent with its Guidance. Compliance with the SMC Guide is mandatory. The SMC has not specified a reference case which must be adopted as a base case. This reflects the emphasis SMC places on receiving submissions as close as possible to the time of launch: such timing may preclude manufacturers from presenting all the data required for a pre-specified reference case.

However, to assist manufactures, the SMC has judged that the reference case set out in section 5.3 of the NICE Guide is appropriate for use in a submission to the SMC. The key elements of the analysis in the NICE reference case are summarised in Table 1.

Table 1

Element of Health Medicine Assessment	Reference Case
Comparator	Alternative therapies routinely used in the NHS in Scotland
Perspective on costs	NHS in Scotland and social work
Perspective on outcomes	All health effects on individuals
Type of economic evaluation	Cost-utility analysis
Synthesis of evidence on outcomes	Based on a systematic review
Measure of health benefits	Quality-adjusted life years (QALYs)
Description of health states for calculation of QALYs	Health states described using a standardised and validated generic instrument
Method of preference elicitation for health state	Choice-based method, for example, time trade-off