HEALTH TECHNOLOGY ASSESSMENT GUIDELINES

DRUG SUBMISSION GUIDELINES FOR NEW PRODUCTS, NEW INDICATIONS, AND NEW FORMULATIONS

Outcomes Based Formulary
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Updated September 2008
OUTCOMES BASED FORMULARY

REFERENCE DOCUMENTS


WellPoint, *Health Technology Assessment Guidelines: Drug Submission Guidelines for Re-Evaluation of Products, Indications, and Formulations (Updated September 2008)*

WellPoint, *Health Technology Assessment Guidelines, Evidentiary and Analytical Standards in Health Technology Assessment, Version 1.0 (forthcoming)*
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INTRODUCTION

In an effort to communicate our recommended evidentiary and analytical standards for the evaluation of drug products to manufacturers, two guidelines have been developed. In preparation for review of a product by the Clinical Review Committee (CRC), Outcomes Advisory Committee, and Value Assessment Committee (VAC), we will request that the manufacturer submit data addressing the areas covered in these companion guidelines. The evidentiary and analytical standards proposed here for formulary submissions to us may become mandatory in the future.

This guideline is intended for manufacturers who are responding to a request for data supporting the evaluation of a new product, or a new indication or formulation of an existing product. This guideline should also be followed if a product is being re-evaluated by the CRC and VAC but data has not been previously submitted using this format. In this case, manufacturers should also ensure that they address the evidentiary and analytical standards detailed in the companion guideline for product re-evaluations, Drug Submission Guidelines for Re-Evaluation of Products, Indications, and Formulations in their submission.

These guidelines should be consulted by manufacturers for dossier preparation in the following situations:

1) New product
2) New indications for an existing product
3) New formulations of an existing product
4) Re-evaluation of an existing product when our previous review was performed without data prepared using these guidelines (the Drug Submission Guidelines for Re-Evaluation of Product, Indications, and Formulations should also be consulted in this case)

This version of the guidelines supersedes the document issued in September 2005. Four important changes in emphasis are listed below. In order to better support our formulary decisions, manufacturers should demonstrate the following:

1) The potential for medical cost offsets following formulary listing of their product. This should be expressed in terms of the total direct costs of care and the impact in per member per year costs.
2) The potential productivity impacts of introducing patients to the new product, where appropriate.
3) The impact on patient reported outcomes, including patient satisfaction as well as quality of life. Where appropriate, health outcomes should be expressed in terms of cost per QALY.
4) The need for manufacturers to submit claims for product performance and cost-effectiveness, appropriate to the short and medium term (a recommended time horizon of 3 years). All such claims are to be expressed in terms that allow for monitoring and verification.
1. OUTCOMES BASED FORMULARY

1.1 Guidelines

We are committed to optimizing patient outcomes through the application of the principles of the Outcomes Based Formulary. In the case of new products, new indications, and new formulations for existing products, this is achieved by requesting manufacturers and others making submissions for formulary evaluation meet certain evidentiary and analytical standards in their submission. As well, manufacturers should be aware that product claims will be subject to an ongoing process of review over the balance of the life cycle of the product. Hence it is important to present product impact claims in terms that allow them to be monitored, validated, and reported to us.

The purpose of this document is to communicate information that we value. While one may find the requested evidentiary and analytical standards demanding, the information requested is necessary if we are to meet our objectives. Manufacturers should note that the information requested is not outside that which is requested by other formulary submission assessors and health technology assessment groups. In preparing this document, we acknowledge the availability of other health technology assessment guidelines.


Where our requirements differ is in our recognition of the need to monitor and validate claims made and to link these to our program of product reviews. Linking product claims to outcomes achieved is an essential part of our commitment to developing the Outcomes Based Formulary. It is anticipated that the guidelines will be reviewed every 3 years and updated versions released.
1.2 Evidentiary and Analytical Standards

Evidence presented in support of an application to us for formulary evaluation should meet accepted standards in both evidence-based medicine and health technology assessment.

Meeting the evidentiary and analytical standards proposed in these guidelines represent a key input to our commitment to evidence-based medicine. This commitment is seen in the recommendation that the clinical assessment and product claims presentation should meet standards for high quality systematic reviews and meta-analyses. Claims for cost-effectiveness should be firmly grounded in the clinical data. Where a modeled case for cost-effectiveness is presented it should meet accepted standards in health technology assessment, be free from any bias in incorporating estimates of relative treatment effectiveness, and be completely transparent. Models should not only be plausible and replicable, but they should be appropriate to our health plan member population.

In focusing on the modeling of cost-effectiveness claims, standards set for such models reflect our commitment to the Outcomes Based Formulary. This commitment is supported over product life cycles by our program of ongoing disease area and therapeutic class reviews.

1.3 Health Technology Assessment Process

The timeline for the appraisal will be made available. Typically, manufacturers will have approximately 45-60 days to prepare a submission.

There is no rigid formula for a technology appraisal. Manufacturers will be asked if they wish to submit data to support an appraisal of their product. Depending on the product, the appraisal may include only that product (a single agent review), a group of similar products (a therapeutic class review), or all therapies used to treat the disease or condition in question (a disease state review). The timeline for the appraisal will be made available. Typically, manufacturers will have approximately 45-60 days to prepare a submission. After an initial review, we may ask the manufacturer for further evidence and analysis to review.
2. PRODUCT DESCRIPTION AND INDICATION

In making a health technology assessment submission to us, the first step should be to present a comprehensive clinical profile of the new product, new indication for an existing product, or new formulation.

2.1 Product Description

A detailed product description is a key element in a formulary submission evaluation. It is recommended that manufacturers ensure that data element requests are answered as comprehensively as possible, following the sub-headings given.

Provide a description of the product (including details of all current indications and formulations) in terms of the following data elements:

a. A copy of the official product labeling / literature
b. Generic name, brand name, and therapeutic class of product
c. List of all dosage forms, including strengths and package sizes*
d. FDA approved indications*
e. Other studied indications or uses for non-approved indications
   • Including a breakdown by percentage of use for each labeled indication as well as key off-label uses
f. Pharmacology*
g. Pharmacokinetics*
h. Contraindications*
i. Warnings / Precautions*
j. Adverse events / reactions*
k. Interactions (drug / drug, drug / food, drug / disease)*, with suggestions on how to avoid them
l. Dosing and administration*
m. Length of course of treatment, and frequency of repeat courses expected (due to therapy failure)
n. Average Wholesale Price (AWP)
o. Confirmation of ability to supply anticipated demand for product at proposed price
p. Comparison with the pharmacokinetic / pharmacologic profile of comparator products on the WP formulary (tabular form)
q. Patent life expectancy

*The FDA-approved package label may suffice for these items.
2.2 Future Indications

*In assessing the potential system-wide impact of the product, manufacturers should provide details of planned or anticipated future new indications and/or formulations of the product.*

In evaluating the future impact of a product, manufacturers should provide details of potential new indications and/or new formulations that are being considered as part of the product development process. Specifically, manufacturers should provide information on the following:

(i) New indication(s) anticipated/sought;
(ii) New formulation(s) anticipated/sought;
(iii) The anticipated date of new indication/formulation approval by the FDA.

Where a new indication is being sought, manufacturers should provide an estimate of the anticipated market share for the product and the number of patients likely to move to the product in a population representative of our system. For new formulations, manufacturers should provide evidence of unmet need and rationale for new formulations.
A clinical, cost-effectiveness, and budget impact assessment of a new product, new indication, or new formulation should rely on an appreciation of the underlying epidemiology of the disease state, an estimate of the number at risk within our system, treatment patterns, and the anticipated place of the product in therapy.

3. TARGET POPULATION, TREATMENT PATTERNS, AND OUTCOMES

3.1 Epidemiology and Burden (Clinical, Economic, and Quality of Life) of the Disease State

In providing an epidemiological and treatment pattern profile, it is important that this reflects the indication approved by the FDA for the product. If the product is restricted to a sub-group of the population in a disease or therapeutic area, this should be identified.

Clinical

In order to judge the potential impact of a new product for its approved indication, it is important to understand the epidemiology of the underlying disease state. The following elements of the epidemiological profile should be addressed:

(i) Definition/classification of the disease state/therapeutic area;
(ii) Characteristics of the target patient population;
(iii) Characteristics of clinically distinct or prospective sub-populations within the target patient population;
(iv) Criteria for identifying sub-populations;
(v) Annual prevalence/incidence;
(vi) Annual treating/prevalence incidence;
(vii) Risk factors for the disease.

The definition/classification of a disease state should be in terms of current clinical coding schemes (ICD-9-CM). These codes may need to be supplemented by other coding criteria (e.g., CPT, NDC codes). Agreement on the definition of a target disease state is important if we are to gauge the potential impact of a new therapy and the appropriateness of the epidemiological profile presented by the manufacturer. This applies in particular to the situation where administrative claims data are the principal source of data for an epidemiological profile. In some circumstances we may undertake a separate assessment of medical and pharmacy claims within our system to assess the potential for the product and to confirm manufacturer summaries of treating incidence/prevalence, treating patterns and estimates of resource utilization and treatment costs.

In providing an epidemiological and treatment pattern profile, it is important to reflect the indication approved by the FDA for the product. If the product is restricted to a sub-group of the population in a disease or therapeutic area (or sub-groups are expected to respond differently within a wider approved indication for the product), such a group should be identified and their relation to the wider treating population in the disease or therapeutic area detailed.

Further, it is important that the elements of an epidemiological profile are addressed from the perspective of our system. Manufacturers would be expected to provide estimates of
prevalence/incidence and treating prevalence/treating incidence of the disease state for populations similar to those expected to be found in our system.

In providing details of the target population characteristics it is important to identify, not only demographic markers, but also a co-morbidity profile.

It is also important to profile the natural progression of the disease and the risk factors for progression through the stages of the condition.

**Economic**

A description of the economic burden of the disease, both direct and indirect costs, should be provided for the underlying disease state(s). If possible, it would be preferable to describe the burden of disease within the context of a population representative of our health plan members. Whenever possible, it would be preferable to present the information using the following structure:

1. Direct Medical Costs
   a. Hospitalization
   b. Emergency Room
   c. Outpatient Costs
   d. Pharmacy
   e. Other
2. Indirect Costs
   a. Productivity
      i. Days of work missed (absenteeism)
      ii. Cost due to presenteeism (cost of suboptimal productivity while at work)
   b. Other

**Quality of Life**

Clinical and economic outcomes may not necessarily capture all of the important aspects of a disease from a patient’s perspective. Health-related quality of life (HRQOL) is a multi-dimensional measure that encompasses the physical, mental, social, emotional, and functional domains of a disease from the patient’s perspective. HRQOL measures usually incorporate the disease symptoms, complications, functional impairment, clinical efficacy of treatment, and adverse effects of treatment.

Where appropriate, information about the product’s effect on HRQOL should be provided. Both generic and disease-specific instruments should be used to measure the product’s effect on HRQOL, if appropriate. However, the instruments should be well-validated, with documented reliability and validity among patients with the disease state of interest. The results of the HRQOL studies should be clearly interpretable.

The different types of HRQOL instruments capture different aspects of a patient’s HRQOL. Disease-specific instruments are generally more sensitive to specific dimensions of the disease or treatment. These instruments may be better able to capture a product’s effect on a particular
symptom of the disease. In contrast, generic instruments are more generalizable; they better allow for comparison across different diseases or medical interventions. Generic instruments are further subdivided into health profiles and health indices. Generic health profiles (e.g., SF-36, SIP, NHP) generate scores for individual health status dimensions, allowing for determination of differential effect. Generic health indices (e.g., EQ-5D, SF-6D, HUI) generate a single index score for quality of life or utility, which can be incorporated into cost-effectiveness or cost-utility analyses. Therefore, data from all types of HRQOL evaluations should be presented, as appropriate for the disease of interest.

3.2 Treatment Patterns

In establishing the place of a new product, new indication, or new formulation in therapy, it is important to quantify, if necessary by disease stage, current treatment patterns for the target population within our system.

We are interested in understanding current treatment patterns. When patients are newly diagnosed, how are they typically treated with first-line, second-line, third-line, and adjunctive therapies? Once treatment is initiated, please provide the following metrics:

- Medication compliance
- Treatment persistence (how long the patient was on therapy over a defined time period, such as one year)
- Dosage titration (the proportion of patients titrated to goal)
- Switching / augmenting rates
- Discontinuation rates (hazard curve for rates of discontinuation)

A clear understanding of treatment options and therapy sequences by disease stage (whether it is acute or chronic) can be a key input to identifying comparator products and procedures as well as modeling the impact of competing therapies. In providing such a description, a submission should include:

(i) A description of the principal treatment pathways characterizing the disease state
(ii) A description of therapy interventions by disease stage
(iii) A description of the common first and second-line treatments
(iv) A description of treatment adherence and persistence with each of these therapies
(v) A description of the dosing used for each of these treatments

Such a description should be appropriate to the approved FDA indication and applicable to a target population representative of our system.

In order to fully evaluate the potential impact of a new indication or a new formulation of an existing product, details should be provided about its current indication and possible off-label use and utilization.

Where a product has been previously approved for another indication by the FDA, information should be provided on the extent of utilization for that indication in terms of aggregate script/unit
sales in the United States and, where known, the extent of utilization within our system. If data are available, it would be helpful if details could be provided on the formulary status and tiered position of the product in managed care (e.g., number of managed care formularies where the product has a preferred status).

Manufacturers should also provide information on the extent of off-label use for the product. This should detail the principal therapeutic or disease states in which off-label use occurs and the proportion of total annual prescription sales that fall into these categories.

| Utilization measures and treatment patterns should be stratified by business type (Commercial, Medicare, and Medicaid). |

3.3 Treatment Guidelines

Please provide a description of accepted treatment guidelines based on clinical and cost-effectiveness data where available. Please reference the guidelines.

3.4 Place of the Product in Therapy

In evaluating the impact of a new product, new indication, or new formulation it is important to understand the place of the new product in therapy.

Please provide a description of the appropriate place in therapy for the product.

Claims as to the place in therapy of a new product, new indication, or new formulation should reflect its approved indication(s). Given the approved indication, manufacturers should explicitly describe the new product’s place in therapy in the context of existing treatment options and treatment sequences experienced by the target population. In making such claims, manufacturers should consider the following questions:

- Is the product indicated for a specific disease stage?
- Is the product indicated as first line or second line therapy?
- Is the product indicated as monotherapy or combination/adjuvant therapy?
- Is the product to be administered by specialists in an office or outpatient environment?
- Is the product prescribed by specialists or by primary care?

3.5 Comparator Therapies

Comparator therapies or procedures are those that may be able to substitute for the product in clinical practice. The comparator(s) should be relevant to clinical practice for that disease state. If the new product is expected to be used in combination with existing products or procedures, the comparator therapy should include the existing product or procedure when used alone.
Health technology assessment of a proposed new product, new indication, or new formulation of an existing product is driven by the identification of the appropriate comparator product(s) or procedure(s) (including generic alternatives) in the target population. Choice of comparator(s) should be clinically relevant and should reflect current treatment practices, patterns, and patient characteristics appropriate to our population. If there is any concern as to the choice of comparator products, this should be reviewed with us. The choice of comparator should not be limited to those products currently on our formulary.

If a product is intended to be used in combination with existing products, details should be provided on the extent to which the product is expected to be utilized and the extent to which any existing products in combination therapy are expected to be displaced.

3.6 Comparator Clinical Descriptions

Once comparator products and/or procedures have been identified, manufacturers should provide a complete clinical description and justification for their choice (to include systematic reviews and meta-analyses of treatment effect). The description should follow the template described in Section 2.1 above. Copies of package inserts for all comparator products should be included with the submission. Summary comparator descriptions may be presented in the form of evidence tables.

3.7 Comparative Effectiveness Trials and Treatment Effect Claims

For us, the ‘gold standard’ in outcomes claims are those based upon randomized, active comparator, controlled studies with outcomes expressed in comparative effectiveness terms. The outcome claims should be appropriate to our target population and should be in a form that supports our health care decisions.

We are aware that there is often a limited amount of high quality outcomes evidence that is relevant to the information needs of clinical and health system decision makers. Systematic reviews/meta-analyses often point to the fact that evidence quality is questionable with an undue reliance on indirect clinical comparison and treatment effect claims. As such, it is often difficult, not only to provide definitive recommendations for care interventions but to also make decisions, from a reimbursement perspective, as to the long term benefits and risks of competing products.

In evaluating competing therapies we consider three decision criteria first. These are (i) effectiveness; (ii) efficacy; and (iii) safety. Claims for each of these basic elements should be supported by reference to the appropriate clinical trial data and systematic reviews/meta-analyses. From our perspective, the ‘gold standard’ input for health care decisions is the well-conducted, active comparator, randomized, controlled effectiveness trial conducted in a real-world setting. Like efficacy trials, these studies should have hard, rather than surrogate, primary endpoints, as appropriate. Combining this type of evidence with efficacy trials and systematic reviews/meta-analyses provides both the proof of cause and effect as well as a robust assessment of the magnitude of the difference between products in a real world setting.
Comparative effectiveness trials explore the risks, benefits, and costs of competing interventions in everyday clinical practice. Comparative effectiveness trials are distinguished from efficacy trials (e.g., placebo controlled Phase IIIA trials) in that they:

- Select and compare, through active comparator trial designs, relevant or viable clinical intervention strategies;
- Recruit a diverse yet relevant population of study participants that reflect everyday clinical practice;
- Recruit patients and physicians from a representative cross-section of practice settings;
- Focus on treatment outcomes that are relevant to our patients, physicians and decision makers; and
- Report on the resources used to support therapy over a time frame that is sufficient to capture the relevant treatment effects.

It is critically important that in evaluating clinical and cost-effectiveness claims in the framework of comparative effectiveness clinical trials that this is done over an appropriate time frame, reflecting the course of the disease. Trial design should reflect an ability to quantify final outcomes and to provide meaningful and evaluable claims on the differences in treatment effect for competing interventions.

Traditionally, health technology assessments have recommended that outcomes be reported in intention-to-treat terms. While this rule should still be followed in reporting on efficacy trials and in systematic literature reviews, it could be argued that in comparative effectiveness trials, intention-to-treat measures could overstate expected outcomes. If manufacturers, in reporting on naturalistic trials, believe this is the case, then they should justify the relevant measure.

3.8 Productivity

In addition to clinical claims for treatment effect and safety, we are also interested in the impact of new products, new indications, and new formulations on workplace productivity. This aspect of product impact is of particular interest to employers. We would expect that for all products with the potential to impact workplace productivity (including absenteeism), manufacturers would be in a position to present evidence, ideally from comparative effectiveness trials, to support such claims. Even if evidence is not available for their product at the time of making a formulary submission, manufacturers would be expected to present a case for potential productivity benefits (including a systematic review of the literature) and to detail how claims might be evaluated once the product has been listed on formulary (e.g., prospective study design and techniques/instruments for measuring productivity impact). Manufacturers should ensure that they differentiate their specific product from comparator products in terms of the potential productivity impact of treating patients within a disease area (i.e., alleviating symptoms).
3.9 Grading of Clinical Evidence

The key to presenting a clinical case for a new product is to ensure that each study included as support meets minimal quality standards and is generalizable to our treating population.

Given our commitment to evidence based medicine and developing the Outcomes Based Formulary only high quality data supporting treatment effect claims are judged sufficient for use in making health care decisions for our population. This evidence can be in the form of individual clinical studies (effectiveness and efficacy-based), systematic reviews, or treatment guidelines. We will critically review all such information to determine its usefulness in health care decision-making. In judging a study or review to be ‘useful’, the design and conduct of the study is a critical input. In applying a usability scale, studies are judged at four grade levels:

Grade A: Useful – The evidence is strong and appears sufficient to use in making health care decisions – it is both valid and useful.

Grade B: Possibly Useful - The evidence is potentially strong and might be sufficient to use in making health care decisions.

Grade B-U: Possible to uncertain usefulness - The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty.

Grade U: Uncertain – There is sufficient uncertainty so that caution is urged regarding the use of the information in making health care decisions.

This grade is further sub-divided into:

- Grade UV: Uncertain Validity – perceived methodological weaknesses.
- Grade UU: Uncertain Usefulness – methodology appropriate but applicability of the results is uncertain.
- Grade UVU: Uncertain Validity and Usefulness – combination of the above.
- Grade UA: Uncertainty of Author – the author is uncertain about their findings.

Grade X: Not Useful - studies that are so poorly done and so potentially misleading that the strongest caution is urged about their quality.

We believe that, other things being equal, that high quality randomized controlled trials and meta-analyses have the greatest evidentiary claim to proving cause and effect. High quality effectiveness trials of similar design and scientific method build upon this and provide robust information about how products work in a real world environment. These are the type of trials preferred for formulary decision-making, especially when they are designed to make comparisons between products (comparative effectiveness trials). Additionally, high quality treatment guidelines add further information about how the products are being positioned in the clinical practice setting at a national level. A combination of these different types of information provides a sound basis for monitoring and validating claims for product performance.

3.10 Target Population
Manufacturers should be clear as to the target population for the indication approved by the FDA and the number of patients in our target population that are expected to begin the new therapy.

Estimates of the anticipated impact of a new product, new indication, or new formulation, are in large part, due to:

(i) The number and characteristics of the target population anticipated within our system; and
(ii) The number and characteristics of patients in our system who are expected to begin the new product following formulary listing.

Manufacturers should be clear concerning the target population for their product in order to ensure that it is consistent with the indication approved by the FDA.

Manufacturers would be expected to detail the number and characteristics of patients expected to move to or initiate the new product (indication or formulation) in each of the first three years following the listing of the product on our formulary.
4. CLINICAL ASSESSMENT AND OUTCOMES CLAIMS

The purpose of our clinical assessment is to produce an unbiased estimate of the clinical efficacy, safety, and effectiveness of the product against comparator therapies.

In order to properly evaluate the clinical evidence for a new product, new indication, or new formulation, it is important that we have access to (i) comprehensive clinical assessments of the proposed product (including new indications for an existing product and new formulations) and (ii) comprehensive clinical assessments of the comparator products or procedures for the indication sought, at the dosage and formulation approved by the FDA.

We recognize that in numerous disease areas, the number of relevant clinical studies can be numerous. We do not want manufacturers to provide study summaries at this level of detail. Rather, manufacturers should always focus first on published high-quality systematic reviews/meta-analyses of both the manufacturer’s and comparator products and then supplement those analyses with individual studies published subsequent to the systematic reviews/meta-analyses. Assessing the weight of these latter studies may require a reworking of published systematic reviews.

Manufacturers should:

- Prepare a summary statement of clinical advantage and appropriate place in therapy
- Identify potential clinical subgroups within the target population
- Report on the generalizability of the outcomes reported
- Provide reprints of the literature used in the preparation of the clinical assessment
- Report on the literature search procedures undertaken to identify subsequent systematic reviews/meta-analyses and clinical studies not included in previous systematic reviews/meta-analyses
- Report on the criteria applied for excluding reviews/studies which are not considered relevant to the assessment
- Identify relevant high quality systematic reviews/meta-analyses of the product (if appropriate) and its comparators
- Undertake a systematic review/meta-analysis of the relevant studies, and
- Prepare systematic review/meta-analysis and individual study summaries.

We approach the clinical assessment of products using the principles of evidence-based medicine. As such, only clinical evidence of high quality is considered in efficacy and effectiveness assessments. However, lower quality evidence may be considered during assessment of product adverse effects and harms; any such studies should also be included in the safety section of the submission. All reports, summaries, and systematic reviews/meta-analyses included in the submission are expected to follow these same principles. It is important for manufacturers to provide transparency in the process used for evaluating the literature to determine its quality. Studies with significant threats to validity should not be included in clinical reviews; however, these studies should be listed as excluded with the reason for exclusion. For systematic reviews/meta-analyses, studies with significant threats to validity should not be included unless the appropriate sensitivity testing proves that they do not adversely affect the analysis.
In addition to reporting on existing systematic reviews/meta-analyses and individual clinical studies, new meta-analyses may be undertaken when appropriate. These analyses provide a key link to the treatment effect assumptions underpinning the modeling of cost-effectiveness and budget impact claims. Meta-analyses undertaken by manufacturers will be subject to the same quality assessment as published studies. Therefore, it is important for manufacturers to provide significant detail as to their methodology, data analysis, the magnitude of the treatment effect, the precision of the treatment effect, and assessment of potential biases.

The clinical assessment of efficacy and effectiveness should assess all relevant published studies that have been undertaken as part of the product development process and include only those of reasonable quality. Those that are not of sufficient quality should be listed separately with a brief description of their limitations. Any meta-analyses performed by a manufacturer should only include those studies of reasonable quality unless the appropriate sensitivity analysis proves that those of lower quality do not significantly affect the results. The clinical assessment of safety section may include studies of lower quality as discussed above. Unpublished studies may be included in the submission but should be clearly separated from those that are published. Sufficient detail about unpublished data should be provided to allow these data to be evaluated.

Manufacturers should provide a list of all trials undertaken for the product (or new indication or formulation) which have been submitted to the FDA as part of the marketing approval process.

### 4.1 Literature Reviews

In undertaking a systematic review of the clinical literature and reporting on the individual trials, it is important to include those studies that are relevant to the indication(s) approved by the FDA and our target population.

Reporting on a systematic review of the clinical literature in a disease or therapy area is a major step in establishing the case for a new product, new indication, or new formulation.

- As well as describing the search procedures and the databases/agencies included in the search (see Section 4.2 below), it is also important to focus on those clinical studies that are relevant to the approved indication(s) and our target population. It is just as important, in the assessment process, to understand why a particular study has been excluded from the systematic review. It is recommended that all studies and systematic reviews (both published and unpublished) that have been excluded be identified and that a brief summary of their limitations be included in the submission.
- In cases where there is relevant literature reviewing off-label uses, this data should be included in a separate section but be subject to the same assessments as mentioned above.
- It is suggested that literature searches to identify the relevant systematic reviews/meta-analyses be restricted to the last ten years, or as appropriate given the relevance to current clinical practice.
4.2 Literature Searches

Whenever a literature search is undertaken it is important that it is not only comprehensive and transparent, but that we can replicate and validate it as part of the technology assessment. We request that manufacturers provide reprints of important studies identified by their literature search.

In reporting on the epidemiological, clinical, and technology assessment literature for a new product, indication, or formulation, it is important that the literature search and reporting strategy are as comprehensive and inclusive as possible. Early in the life of a new drug there may be relatively few data in the peer-reviewed literature. In this case, manufacturers may want to submit sections from the Integrated Summary of Efficacy and Safety (the same document which was furnished to the FDA) as a supplement to sparse literature sources. In making a submission, details of the information retrieval process should be presented together with the criteria adopted for the selection of literature supporting the clinical evaluation, systematic reviews/meta-analyses, and the pooling of outcomes data for product assessments and cost-effectiveness modeling.

We will consider unpublished data during our clinical appraisal of products only if sufficient detail about the study is available to evaluate the scientific method used. Unpublished data will be subjected to the same scientific standard and critique process as published data. If a manufacturer chooses to include such information, it should be clearly noted as ‘unpublished’ and kept separate from published information. Any additional information necessary to fully evaluate this unpublished data should be included.

In making the submission, manufacturers should detail for each search undertaken:

- All databases and other sources searched (to include Internet address)
- Search criteria
- Time period for the search
- Any restrictions on the literature search
- Inclusion/exclusion criteria

Exclusion and Inclusion Criteria

In undertaking a literature search, it is important not to be too restrictive. It is recommended that when a provisional list of clinical studies and associated materials has been assembled, a further review be completed to exclude those items that are not pertinent to the dossier.

The review criteria employed to identify those clinical studies and associated materials that are excluded from evaluation and reporting should be detailed.

The exclusion criteria for a trial might include one or more of the following factors:

- Serious methodological flaw
- Trial subjects are not those in the indicated target population
Dosage regimen or formulation of the product in the trial is not consistent with the product label
- Inadequate duration of follow-up
- Outcome measures are not relevant to the submission
- High-drop out rates or missing data, with no sensitivity analysis
- Use of post-hoc analysis to draw cause and effect conclusions
  - Subgroup analysis where subgroups were not determined in advance.
- Non-significant findings or power calculation is not clear
- Non-ITT analysis (>5% of patients excluded from the primary outcome analysis)
- Inadequate dosages
- Use of non-validated scoring methods
- Disease oriented outcomes only (BP lowering vs. CV mortality)
- Unclear quality assessment methods for meta-analysis studies
- Study duration too short for endpoint (e.g. 6 weeks HbA1c)
- Use of other medications that may influence or confound the effect of the primary drug on outcomes

In our appraisal of products, we will only consider trials that represent good quality evidence. Each trial will be critiqued and those that are determined to represent evidence that is not useful or of uncertain usefulness will be excluded from consideration. We recommend that where there is a substantial and long-standing clinical literature, the literature search should initially focus on the most recent high quality systematic reviews/meta-analyses.

We recommend that in addition to searches of the major public databases, searches should also be undertaken of the major health technology assessment internet sites. These would include (in particular) the National Institute for Health and Clinical Excellence (NICE) site, the Canadian Agency for Drugs and Technologies in Health (CADTH) site, and the Agency for Healthcare Research and Quality (AHRQ) site.

4.3 Clinical Study Summaries

Once the relevant clinical studies have been identified, a summary should be prepared for each. These summaries form the basis for subsequent meta-analyses, the overall claim for the product, and the cost-outcomes modeling.

Summaries of all relevant quality clinical trials for the product and its comparators should be presented. These summaries should primarily include published (and peer reviewed) studies that are considered appropriate in supplementing and updating high quality systematic reviews/meta-analyses. Clinical trial summaries from unpublished data for the product may be included, but should be clearly identified and separated from the published literature. In addition, sufficient details about such unpublished data should be provided to allow us to critique the studies. A 1-2 page summary of each study is proposed.
While the actual form of presentation is left to the discretion of those preparing the health technology submission, it is recommended that the clinical study summary address the data elements listed in Table 1 below:

**TABLE 1: PROPOSED DATA ELEMENTS FOR CLINICAL STUDY SUMMARIES**

<table>
<thead>
<tr>
<th>Data Element</th>
<th>Study Details and Reviewer’s Critique</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Study Reference and Summary</td>
<td>Published Studies: Full bibliographic citation with a copy of the abstract</td>
</tr>
<tr>
<td></td>
<td>Unpublished Reports: Reference (to include agency name and website address) and copy of executive summary if available</td>
</tr>
<tr>
<td>2. Study Funder</td>
<td></td>
</tr>
<tr>
<td>3. Regimens studied</td>
<td></td>
</tr>
<tr>
<td>4. Indication(s) studied</td>
<td></td>
</tr>
<tr>
<td>5. Hypothesis</td>
<td></td>
</tr>
<tr>
<td>6. Inclusion and Exclusion criteria</td>
<td></td>
</tr>
<tr>
<td>7. Basic description of study methodology</td>
<td></td>
</tr>
<tr>
<td>8. Outcome measures (primary and secondary)</td>
<td></td>
</tr>
<tr>
<td>9. Known confounders</td>
<td></td>
</tr>
<tr>
<td>10. Randomization achieved</td>
<td></td>
</tr>
<tr>
<td>11. Comparability of baseline characteristics</td>
<td></td>
</tr>
<tr>
<td>12. Blinding Achieved</td>
<td></td>
</tr>
<tr>
<td>13. Concealment of Allocation</td>
<td></td>
</tr>
<tr>
<td>14. Potential Biases (e.g., selection bias, performance bias, follow-up bias, assessment bias)</td>
<td></td>
</tr>
<tr>
<td>15. Patient adherence results</td>
<td></td>
</tr>
<tr>
<td>16. Duration of study</td>
<td></td>
</tr>
<tr>
<td>17. Number randomized</td>
<td></td>
</tr>
<tr>
<td>18. Number analyzed</td>
<td></td>
</tr>
<tr>
<td>19. ITT achieved</td>
<td></td>
</tr>
<tr>
<td>20. % Loss to follow-up</td>
<td></td>
</tr>
<tr>
<td>21. Imputation method for ITT/loss to follow-up</td>
<td></td>
</tr>
<tr>
<td>22. Assessment of quality of results analysis</td>
<td></td>
</tr>
<tr>
<td>23. Other problems identified</td>
<td></td>
</tr>
<tr>
<td>24. Study Results (or refer to table below)</td>
<td></td>
</tr>
<tr>
<td>25. Safety Assessment (or refer to table below)</td>
<td></td>
</tr>
<tr>
<td>26. Study Quality Assessment</td>
<td></td>
</tr>
<tr>
<td>27. Rationale for Assessment</td>
<td></td>
</tr>
</tbody>
</table>

**Results Table (copy rows as needed)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study %</th>
<th>Control %</th>
<th>ARR/ARI</th>
<th>NNT/NNH</th>
<th>Time Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.4 Systematic Reviews/Meta-Analyses

In making a submission to us, manufacturers are encouraged to present a systematic review/meta-analysis for both their product and comparator products and to link these to modeled parameters for the cost-effectiveness case.

Meta-analyses can be a bridge between clinical trial evidence for a new product, new indication, or new formulation and the modeled cost-effectiveness case. Meta-analyses have the potential to provide the justification for parameter values in decision model specifications. Meta-analyses should include a quality assessment of each individual study. Clearly, meta-analyses produced by groups such as the Cochrane Collaboration, NICE in the UK, and the US Evidence-based Practice Centers will potentially have the greatest weight.

We are interested in two types of meta-analyses;

- Evaluations which systematically combine the available quality trial data for the product and comparator products; and
- Evaluations of existing meta-analyses of the product and comparator products

In the former case, in undertaking a meta-analysis, it is recommended that the following points are addressed:

- Statement and justification of the inclusion/exclusion criteria for the study trials included within the meta-analysis;
- Justification for the inclusion/exclusion of trial data in terms of the outcomes selected for the meta-analysis;
- Tabulation of the results of individual trial outcomes data as point estimates with associated 95% confidence intervals;
- Plotting the results (where appropriate) in terms of both relative and absolute risk reductions as point estimates with associated 95% confidence intervals;
- Assessing the extent to which heterogeneity is present and provide an explanation for heterogeneity;
- Combining the results using either a fixed or random effects model and justifying the choice of modeled summary outcome for the cost-effectiveness analysis.

Where published systematic reviews or meta-analyses are available, they should be summarized addressing the data elements listed in Table 2:

### TABLE 2: PROPOSED DATA ELEMENTS FOR SYSTEMATIC REVIEWS/META-ANALYSES

<table>
<thead>
<tr>
<th>Data Element</th>
<th>Study Details and Reviewer’s Critique</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Study Citation and Summary</td>
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<td>3. Regimens studied</td>
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<td>4. Indication(s) studied</td>
<td></td>
</tr>
<tr>
<td>5. Hypothesis</td>
<td></td>
</tr>
<tr>
<td>6. Outcome measures (primary and</td>
<td></td>
</tr>
</tbody>
</table>
4.5 Outcome Claims

*Claims for treatment effect should be presented in the form of clinical outcome claims as well as in terms of patient reported outcomes (including quality of life.)*

Manufacturers are expected, in undertaking systematic reviews/meta-analyses, to identify studies which report on clinical as well as patient reported outcomes. Measures of treatment effect – as clinical outcomes – should reflect agreed-upon standards for reporting within the disease area. A similar justification should support the choice of instrument in patient reported outcomes. Even so, manufacturers should be aware that many patient reported outcome instruments have poor psychometric and measurement properties. Care also has to be taken in (i) reporting on patient reported outcome claims which have minimum clinical significance and (ii) the form of the claim. Claims for quality of life, for example, should be based upon instruments which have the appropriate interval measurement properties. Cost per QALY claims should be based on generic instruments that generate absolute utilities (e.g. EQ-5D, SF-6D, etc.) Utilities from disease-specific instruments should be cross-walked to a generic utility-generating instrument.

If there are concerns with likely patient adherence to medication over the forecast period for clinical impact claims, manufacturers should present assumptions about likely medication possession patterns and factors these assumptions into such claims. Claims made for comparative medication possession should be amenable to monitoring and verification.
4.6 Statement of Clinical Advantage

Claims for clinical advantage should be based upon the results of the clinical assessment of the relevant literature for the proposed product and comparator therapies as discussed in previous sections.

In describing a new product, new indication for an existing product, or a new formulation, it is recommended that the manufacturer identify the clinical category which best describes the product. The following categories are proposed:

(i) The drug has a significant clinical advantage over its comparator(s) in terms of its effectiveness/efficacy and/or adverse event profile;
   
   (a) The drug is more effective/efficacious with similar or fewer adverse events reported;
   (b) The drug is equally effective/efficacious but has fewer adverse events reported; or
   (c) The drug is more effective/efficacious with more adverse events reported.

(ii) The drug is similar to its comparators in terms of its effectiveness/efficacy and adverse event profile;

(iii) The drug is less effective/efficacious, but has a more favorable adverse event profile.

Claims for clinical advantage, including claims based upon patient reported outcomes (e.g., quality of life claims) should be presented in terms that are amenable to monitoring and validation over the balance of the product’s life cycle.

4.7 Sub-Group Analyses

If there is a prior clinical expectation of a differential sub-group treatment effect for a product in a target population, this should be identified. Manufacturers would be expected to show that such an effect has been recognized in protocol design and that it has been incorporated into the cost-effectiveness and budget impact case for the product, if statistically significant.

It is desirable for both formulary and patient management to identify groups within a target population that might be expected to respond differently to a drug or treatment intervention. If there is a prior belief that sub-groups within a target population would be expected to respond differently, then it is important to document the clinical case and the evidence for a differential response. If a sub-group effect is presented, then the manufacturer should demonstrate that the appropriate statistical test was performed to detect this. Identifying a subgroup effect may impact trial design and the criteria used in patient selection for pivotal trials.
4.8 Generalizability

Unless there is evidence to support a more broadly based claim for clinical outcomes, WP will only consider evaluating claims for clinical impact and cost-effectiveness that are limited to the indication approved by the FDA.

As well as identifying potential subgroup effects, manufacturers should ensure that clinical and cost-effectiveness claims that extend beyond the patient population identified in pivotal trials are substantiated. As well as demonstrating internal validity, more broadly based claims extending to wider populations (e.g., persons over 65 years of age) should demonstrate external validity. Unless there is evidence for external validity, we would expect that the overall clinical and cost-effectiveness claims would be limited to the indication approved by the FDA (or the population identified in the pivotal trials). If the manufacturer believes that there is evidence to support a more general claim for the product, this should be demonstrated. However, it is understood that there may be additional high quality clinical information available beyond FDA approved indications for a product especially in the situation where such indications are being targeted for future FDA submission. In this case, although the current product claims may not include off-label uses it is expected that any high quality clinical studies would be included in the submission.

4.9 Pharmacovigilance

Claims for product safety and proposed methods for pharmacovigilance are of particular interest to us. Manufacturers should detail the anticipated adverse event profile for their product and comparator products.

The manufacturer’s statement of clinical advantage for their product should be supported by a summary profile of the anticipated safety/adverse event profile for the manufacturer’s product and comparator products. Manufacturers are on notice that we expect to be kept regularly informed as to adverse events attributable to products within a disease area or therapeutic class. An acceptable pharmacovigilance strategy should be seen as an integral part of the monitoring and validation of product claims.
5. COST-OUTCOME ASSESSMENT AND PRODUCT CLAIMS

5.1 Evidentiary and Analytical Requirements

We are only interested in models that generate empirically evaluable claims within a relatively short timeframe relevant to the range of potential comparators within that disease state.

Cost-effectiveness and budget impact claims should be presented in terms that are amenable to monitoring and verification in a relatively short time frame. Modeled cost-effectiveness claims should generate outcomes that accrue to baseline populations or treatment cohorts in no more than 3 years. Lifetime cost-per-QALY models which have been used in other health care systems to support recommendations for clinical guidance and place of product in therapy are not as useful for our formulary decisions. Where a model embodies productivity claims, the requirement for a short-term frame of reference also applies (e.g., reductions in absenteeism).

At the same time, however, the fact that a model has a short term predictive focus does not mean that manufacturers should restrict their claims for cost-effectiveness to one or a few selected comparators. We are interested in assessments which establish the claims for a product’s place in therapy. Short-term modeled claims should include all relevant comparators, together with the appropriate treatment sequences which reflect both established treatment practices and patterns (including clinical guidance recommendations), as the basis for establishing the product’s place in therapy as either monotherapy or as part of a combination/polytherapy intervention.

5.2 Model Transparency

Transparent and simple models are strongly preferred. The model complexity will vary according to disease state. However, models should only be as complex as necessary to arrive at reasonable conclusions.

5.3 Trial-Based Evaluations

We will attach the greatest weight to modeled claims for cost effectiveness that are based directly upon one or more well-conducted, controlled, active comparator, clinical effectiveness/efficacy trials.

The importance of modeled claims for costs and benefits based directly upon well-conducted clinical trials cannot be understated. The ‘gold standard’ in cost-effectiveness modeling for WP is data from one or more comparative effectiveness trials that allow for:

- A direct comparison and quantification of treatment effects and other relevant patient reported outcomes (including quality of life);
- An assessment of patient and community preferences for alternative therapies;
- A quantification of costs and benefits over the natural course of the disease;
- An assessment of the resources used to support alternative therapies; and
- An evaluation of the impact of uncertainty on the claims made for alternative therapies
We recognize, however, that the majority of cost-effectiveness claims will be synthetic in nature with models utilizing data from a number of sources. Even so, we would encourage manufacturers to consider undertaking active comparator trials to support the case for their product over the natural course of the disease.

5.4 Literature Searches

In developing a modeled claim for a new product, new indication, or new formulation, we recommend manufacturers report all literature searches that have been undertaken to assess the health economics claims that have been made for comparator products and other products (to include procedures) within the disease area. Literature searches should include publicly available health technology assessments for the disease or therapy area undertaken by technology assessment groups (e.g., NICE) as well as online database searches.

When reporting the results of the literature search, manufacturers should present 1-2 page summaries of the studies that are considered relevant for the modeled cost-effectiveness case presented to us. It is also important that manufacturers identify those studies that are not considered relevant for a detailed assessment, with the reason(s) for exclusion.

The data elements that should be considered when summarizing health economics studies are detailed in Table 3.

<table>
<thead>
<tr>
<th>Data Element</th>
<th>Scope to include information on:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Study Citation</td>
<td>Published Studies: Full bibliographic citation with copy of abstract Unpublished Studies: Reference (to include agency name and website address) and copy of executive summary if available</td>
</tr>
<tr>
<td>2. Study Objectives</td>
<td>Statement of hypotheses tested</td>
</tr>
<tr>
<td>3. Study Design</td>
<td>Classification as cost-effectiveness, cost-benefit, cost-utility, cost minimization, or cost-consequence study</td>
</tr>
<tr>
<td>4. Model Structure</td>
<td>Type of model: simple decision model, Markov model, econometric modeling of unit data, discrete event simulation; therapies evaluated; treatment pathways</td>
</tr>
<tr>
<td>5. Model Assumptions</td>
<td>Comment/justification of the assumptions used in the model</td>
</tr>
<tr>
<td>6. Model Timeframe</td>
<td>Modeled duration of treatment</td>
</tr>
<tr>
<td>7. Model Population</td>
<td>Indication; sub-groups within disease area</td>
</tr>
<tr>
<td>8. Model Location</td>
<td>Country; treatment location</td>
</tr>
<tr>
<td>9. Model Outcomes: disease specific</td>
<td>Surrogate; final outcomes</td>
</tr>
<tr>
<td>10. Model Outcomes: generic</td>
<td>Quality of life instrument</td>
</tr>
</tbody>
</table>
11. Modeled claims for cost-effectiveness | Confidence ellipses, scatter plots, CE acceptability curves, probabilistic sensitivity analysis

12. Modeled claims for system impact | Patient moving model, pharmacy and total costs

13. Treatment of uncertainty | Sensitivity analysis; simulation analysis

14. Data source(s) | Trial based; synthetic model construct

15. Rigorous evidence-based process used? | Was a systematic review was conducted; Were acceptable methods for critical appraisal of the literature employed

16. Potential biases | Address potential bias of study, including possible effect of model assumptions

17. Study results

18. Quality score (e.g., Evidence and Usability Grade)

5.5 Defining the Decision Problem

Claims for cost-effectiveness are typically made in the context of a decision model. Manufacturers should be prepared to justify the modeling approach used and the model structure, as well as ensuring that it is consistent both with the indication approved by the FDA and our target population.

In the absence of controlled, active comparator, clinical effectiveness/efficacy trial data that meet our evidentiary standards, modeled claims for cost-effectiveness of competing therapies will typically be based on synthetic constructs. In presenting a synthetic decision framework, manufacturers should justify not only the structure of the decision model, but the values claimed for model parameters. In developing such a framework, manufacturers should remember that ultimately claims should be expressed in effectiveness terms, with the impact of model structure and model parameter uncertainty taken into account. The decision framework should reflect the approved indication for the product and the product’s proposed place in therapy for our target population.

Specifically, situations where a modeled synthetic approach may be considered appropriate would include situations where:

- Only surrogate or intermediate endpoints are reported from systematic reviews and meta-analyses, and the analyst needs to link these outcomes to final outcomes or subsequent outcomes for patients who fail to respond to first-line treatment;
- There is a need to extrapolate beyond the end-point of a clinical trial to capture treatment interventions and cost consequences over a longer observation period;
- The characteristics of the population in the trial do not match the characteristics of the target population and indication sought within our population (characteristics could include: age, gender, disease severity, treatment setting);
• Trial results lack an active comparator and the analyst has to bring together data from placebo controlled trials in order to structure a direct comparison in the decision model; or
• Resource utilization reported in the trial is not appropriate to our population (to include claims for the cost of treatment)

All of these factors introduce additional uncertainty into modeled claims for a new product. It is for these reasons that we recommend probabilistic sensitivity analyses in addition to traditional univariate analyses whenever a modeled cost-effectiveness claim is presented, even if the modeled claim is based directly on controlled, active comparator, clinical effectiveness/efficacy trial data.

Manufacturers should ensure transparency in developing and presenting a modeled cost effectiveness claim. All assumptions should be justified and appropriately referenced to trial data and systematic reviews/meta-analyses of the clinical and health economics literature.

5.6 Input Variables

When defining the values of the input variables in the model, this should be done from our perspective. Cost input variables should focus on the direct costs of supporting therapy and treatment pathways.

It is critical to identify the appropriate resource utilization inputs and unit costs for the modeled comparison of competing therapies. Our principal interest is in the direct costs of health care delivery. In evaluating the direct cost implications of patients moving to a new therapy, manufacturers should be as specific as possible in defining the resource units employed in the various treatment arms and their unit costs.

Drug inputs should be identified by their NDC code, GPI code, or other commonly-used drug code. Prescription units should match the product label unless a case can be made for average units. If average units are claimed (e.g., number of inhalers per month), then the distribution of inhaler units should be specified as well. Drug costs should be in average wholesale price (AWP) per unit.

All resource units should be specified in terms of commonly-used medical billing codes. Choice of medical billing code may be justified by prior evaluations of treatment patterns from administrative claims data. If considered appropriate, manufacturers should detail the distribution of resources appropriate to each therapy intervention stage (to accommodate parameter uncertainty). Manufacturers should also identify each resource unit by its relative value unit.

In translating resource units to costs, manufacturers should apply a relative value unit multiplier. Unless otherwise justified, the dollar value of the multiplier should be the current Medicare fee schedule multiplier.

If manufacturers wish to extrapolate resource utilization to generate estimates of the costs of care over a 3 year timeframe, this should be justified. Similarly, if manufacturers consider that
indirect costs (including time loss due to loss of productivity) are relevant to the cost-effectiveness case; their inclusion also should be justified. If there are concerns about likely patient adherence to medication over the forecast period for cost-effectiveness claims, manufacturers should present assumptions regarding likely medication possession patterns and factor these into claims for cost-effectiveness. All of these claims should be amenable to monitoring and verification.

5.7 Outcome Measures

*Outcome claims should, as far as possible, be expressed in effectiveness terms and should reflect outcomes that are relevant to both the patient and the physician. Outcome estimates should be presented in intention-to-treat terms.*

In making the case for differential treatment effects of a new therapy, the outcomes measures chosen should include those that are relevant to both the patient (e.g., survival, quality of life) and the physician (e.g., achieving clinical targets). When selecting the outcomes variables to capture direct health effects, these should be justified in terms of patient preferences and linked to the results of systematic reviews/meta-analyses.

5.8 Quality of Life and the Reference Case

*The US Panel on Cost-Effectiveness and the latest National Institute for Clinical Excellence (NICE) Guide to the Methods of Technology Appraisal argue for the pivotal role of a reference case in driving resource allocation decisions within health care systems. We also take this position to emphasize the importance of assessing therapy impact in quality of life terms.*

Where resources are limited, evidence from a comparative cost-outcome assessment can be a critical input in the decision by health systems to support and invest in a new product. Because decisions to invest resources are necessarily comparative and typically involve a number of disease states, claims can be expressed as a generic cost per QALY to help standardize the cost-effectiveness metric.

Although we are not mandating that a generic cost per QALY reference case be presented as part of a formulary submission, several recommendations are suggested when a reference case is being presented. When reporting QALYs gained, manufacturers should ensure that these claims are:

- Based upon health states that are described through a standardized and validated generic instrument;
- Generated from a choice-based method of preference elicitation;
- Reflective of preferences within our population; and
- Generated from an active comparator trial (or trials).
It should be noted that we do not subscribe to establishing cost per QALY thresholds. Rather, each drug product is evaluated on its merits, whether this impact is assessed as part of a new formulary evaluation or a re-evaluation.

Alternatively, if a manufacturer has developed a product reference case claim for other health assessment agencies, (e.g., in order to meet NICE requirements), this should be reported in the submission. If it is possible to translate the reference case to include US-population preferences, this information should also be presented as part of the submission.

5.9 Quality of Life

*Manufacturers are expected to present the case for their product in quality of life terms.*

Even if a reference case argument is ruled out, at least in an initial submission, manufacturers are expected to present the case for their product in quality of life terms. Manufacturers should consider patient reported outcomes and quality of life as the default outcome measures in cost-effectiveness claims. Manufacturers would be expected, as part of their literature review, to review the various instruments that characterize a disease or therapy area and justify their choice of instrument in terms of its technical properties and relevance to our target population. If such a case is presented, manufacturers should show that they are aware of the range of constructs that drive quality of life claims and utilize an instrument that not only meets traditional psychometric standards but also supports cost-per-QALY claims. Instruments should have interval scoring properties and be capable of generating absolute utility scores and cost-per-QALY claims. Claims based upon instruments that don’t achieve these standards will be accepted but the claims made will be accorded a lower evidentiary weight. Quality of life claims should be presented in empirically evaluable terms with scores representing clinically meaningful differences in evaluating alternative treatment interventions. If claims are expressed as patient reported outcomes, they should be expressed in a form that is amenable to monitoring and validation.

5.10 Patient Sub-Group Cost-Outcome Claims

*If there is a clinical sub-group case for cost-outcome claims, this should be presented as a separate analysis.*

In evaluating health technologies, manufacturers should consider whether or not, within the general treating population, the response to therapy and the resources required to support treatment may differ by patient characteristic. It is important to recognize (as noted in Section 4.7 above) that clinically differentiated sub-groups may exhibit quite different cost-outcome behaviors. If this is the case, then manufacturers would be expected to present a modeled cost-effectiveness case for such sub-groups. Parameter estimates for the modeled assessment should be generated from trials (and accompanying systematic reviews/meta-analyses) that have been designed to capture and differentiate sub-group effects.
5.11 Uncertainty

Modeling the cost-effectiveness claim for a product should accommodate uncertainty. In decision modeling, uncertainty can arise through model or structural uncertainty as well as parameter uncertainty. Manufacturers, in evaluating the impact of uncertainty, should address both sources. In the case of parameter uncertainty, our preference is for evaluations that take explicit account of uncertainty through simulation modeling. Probabilistic sensitivity analysis is recommended.

Claims for products that are generated by decision models should take uncertainty into account. Uncertainty can arise from two sources: (i) modeled or structural uncertainty and (ii) parameter uncertainty. In the former, the manufacturer may have a choice of alternative decision or treatment pattern frameworks. If these are expected to impact materially claims made, then this should be explored. Parameter uncertainty has received considerable attention in the literature and there are now established techniques for incorporating such uncertainty into modeled claims for a product.

Traditionally, parameter uncertainty has been addressed through the application of univariate sensitivity analyses to decision models. Although such assessments generate useful estimates of the relative strength of each parameter’s contribution to the overall cost-effectiveness, these analyses also have their limitations. The principal limitation is that univariate sensitivity analyses cannot capture the uncertainty associated with all input parameters. In accounting for parameter uncertainty, probabilistic sensitivity analysis is recommended (i.e., where probability distributions describe uncertain parameters). If probabilistic sensitivity analyses are employed in modeling the inputs to a decision model, it is important to document the assumptions made by source and to link these to the default assumptions underlying the modeled cost-effectiveness claims. Manufacturers are expected to justify the choice of distribution(s) to capture parameter assumptions.

In presenting the impact of uncertainty on cost-outcome claims, we prefer for the results to be presented using simulation techniques that generate cost-effectiveness acceptability curves and a cost-effectiveness frontier to identify interventions with the highest cost-effectiveness. However, the manufacturer should format modeled data in such a way that allows us to assess the contribution of individual parameter uncertainty to overall modeled or structural uncertainty. Claims made using probabilistic sensitivity analysis should be presented in a form that makes them amenable to monitoring and verification within a 3-year timeframe. Manufacturers should propose how these claims are to be evaluated.

5.12 Spreadsheet Modeling

We recommend that, in presenting a cost-outcome case for their product, manufacturers provide an electronic or spreadsheet version of the model. This will allow us to assess the claims made as well as consider the implications of modifications to input assumptions, unit costs, and prices to modeled claims.
The requirement for an electronic or spreadsheet version of the cost-outcomes model that supports a manufacturer’s claims is common practice in health technology assessment and formulary submission guidelines. Access to an electronic or spreadsheet model will allow us to evaluate the robustness of the modeled claims of product impact as well as consider the implications of changes to input assumptions, unit costs, and prices on modeled claims.

If a sub-group case is made for the product, then the spreadsheet model should present a separate analysis for the sub-group or allow the sub-group(s) to be identified within the overall modeling framework.

In detailing the spreadsheet model, manufacturers should take explicit account of uncertainty in the specification of parameter values and in the software used to support the spreadsheet model. The use of a simulation package to account for uncertainty is preferred.
6. BUDGET AND SYSTEM IMPACT CLAIMS

Presenting a cost-outcome claim for a product is only the first step in meeting our information requirements. Manufacturers are also asked to provide estimates, over each of the three years following formulary listing, of the impact of the product on the pharmacy budget, the medical budget, the total costs of treatment, and outcomes for patients in that disease or therapy area.

In evaluating the potential impact of a new product, indication, or formulation, we are concerned with the overall impact on per member per year (PMPY) costs of treating patients in that disease or therapy area. Manufacturers are expected to focus their claims on the total costs (medical and pharmacy). There are two aspects of the total cost impact to be considered: (i) the average annual total cost of treating patients who adopt the new therapy; and (ii) the impact of patients adopting the new therapy on the average total cost of treating patients in that disease area. Estimates of cost impact are to be presented for each of the first three years following the listing of the product on our formulary.

Claims for total cost and system impact should be expressed in terms that are amenable to monitoring and validation. Manufacturers should also present the assumptions that support total cost impact claims in a form that can be monitored and verified (e.g., the characteristics of patients who would be expected to move to the new therapy or the impact on comparator therapies).

6.1 New Start Patients

As the basis for assessing the impact of a new product, claims pertaining to the characteristics of patients who are most likely to begin therapy are paramount. Manufacturers are expected to be explicit as to which patients they expect to adopt therapy once their product is introduced on formulary.

The first step in evaluating the system impact of introducing a new product is to give estimates of the characteristics and number of patients who are expected to adopt the new product in the disease and/or therapy area. Manufacturers should detail, for each of the three years following the listing of the product on our formulary:

- The characteristics of patients who are expected to transition to the new product from the comparator product(s); and
- The number (or proportion) of new patients who are expected to initiate therapy

When reporting the numbers and characteristics of patients who are expected to adopt the new therapy, manufacturers should indicate how these patients are to be identified from administrative claims data. Manufacturers should provide identifiers (e.g., ICD-9 codes; CPT codes) that will allow us to monitor patient adherence or non-adherence patterns and validate the claims made by the manufacturer.
If there are characteristics of patients that cannot be identified from administrative claims data, manufacturers should suggest how their claims for patients’ therapeutic behavior are to be verified.

6.2 Resource Utilization Impact

Claims about resource sparing or tradeoffs between pharmacy and medical expenditures are a key input to resource utilization impacts. It is important to detail such claims and to propose how these should be audited.

As well as detailing expected patient therapy changes, manufacturers are also asked to forecast, again for each of the three years following formulary inclusion, the impact of introducing the new therapy on the resources used to support treatment in the disease and/or therapeutic area. As a baseline for resource utilization impact projections, manufacturers are encouraged to express projections in a way that is verifiable using administrative claims data.

The resource unit impact should be detailed in terms of common codes and should identify (where appropriate), for the population of patients who switch therapy, the expected distribution elements such as:

- Prescription utilization
- Pharmacy trend
- Market shares of class
- Physician visits
- Urgent care visits
- Emergency room visits
- Duration of hospitalization
- Procedures employed
- Laboratory monitoring

Administrative claims data should be the primary source for verifying claims.

6.3 Budget Impact Claims

Within the disease or therapy area, claims for net budget impact over the first three years following formulary inclusion are expected to be monitored. These claims should be modeled with the analysis in probabilistic sensitivity analysis terms.

Manufacturers are expected to provide estimates of the overall or net budget impact of therapy changes in each of the first three years following formulary inclusion. These estimates should be developed from claimed changes in the patterns of resource utilization (see Section 6.2 above). In making these claims, manufacturers are asked to present a spreadsheet model. Once again, to capture the effect of uncertainty, the model inputs should be specified in probabilistic sensitivity analysis terms. In making a budget impact claim, manufacturers are expected to provide estimates of both pharmacy and medical budget impacts. These estimates should be net of budget
impacts on other products within the therapy area and should indicate whether or not potential increases in the pharmacy budget might be offset by savings in the medical budget. The budget impact is expected to detail the net impact of patients moving from existing therapies, the uptake by new patients, the number of units of the product prescribed for individual courses of therapy, and the impact on prescribing of other pharmaceutical products.

In translating resource utilization projections to cost impacts, manufacturers should identify the relative value unit code and their assumptions regarding the value of the relative value unit multiplier.

### 6.4 Impact on Patient Population Outcomes

The principal reason for adding a product to formulary is acceptance of the claim by a manufacturer that the product yields additional clinical benefits and that, for the cost incurred, we judge the product to be of significant value. Therefore, from an Outcomes Based Formulary perspective, it is important that clinical and quality of life claims are monitored and validated for the population of patients who are introduced to a new therapy.

In making a cost-effectiveness and value case for a new product, new indication, or new formulation, manufacturers should recognize the importance of ensuring that both clinical and quality of life related claims for our target population are capable of being monitored and verified from a health system or patient population perspective. Given our commitment to the Outcomes Based Formulary, it is important to track the treatment experience and the distribution of outcomes for the population of patients who are introduced to the new therapy. While modeled claims are a key input to an initial decision to place a product on formulary, this decision needs to be confirmed and revisited as part of the ongoing product review process.

Given evidence from large-scale, naturalistic, clinical trials, it may be possible to predict the impact of introducing the new product on the distribution of outcomes in a target population. However, modeled claims will still need to be monitored and validated, even when they are expressed in probabilistic sensitivity terms. As patient outcomes cannot be monitored and validated solely from administrative claims data, it is important that manufacturers propose how their claims for patient outcomes should be monitored and validated.

### 6.5 System Impacts for Patient Sub-Groups

Given the competition for scarce health care resources, it is important that manufacturers, in making claims for system impacts, present an impact assessment for clinically differentiated sub-groups.

Manufacturers should present system impact assessments for each clinically relevant sub-group identified in the general treating population. Where a modeled case for cost-effectiveness is made for a sub-group, this is to be matched by a systems impact assessment that addresses for the sub-group:
- New start patients (section 6.1)
- Resource utilization impact (section 6.2)
- Budget impact (section 6.3)
- Impact on patient population outcomes (section 6.4)

### 6.6 Spreadsheet Modeling

*It is recommended that, in presenting a systems impact case for their product, manufacturers provide an electronic or spreadsheet version of the model. This will allow us to verify the claims made as well as consider the implications of modifications to resource utilization assumptions, unit costs, and prices on modeled claims.*

Manufacturers are asked to provide a spreadsheet model to support their resource utilization and budget impact claims. Access to this spreadsheet model will allow us to evaluate the robustness of the modeled claims for systems impact.

If a sub-group case is made for the product, then the spreadsheet model should present a separate analysis for the sub-group or allow the sub-group(s) to be identified within the overall system impact framework.

In detailing the spreadsheet model, manufacturers should take explicit account of uncertainty in the specification of parameter values and in the software used to support the spreadsheet model. The use of a simulation package to account for uncertainty is preferred.
7. MONITORING AND VALIDATING CLAIMS

7.1 Evaluating Product Claims

Manufacturers making a submission to support a new product, new indication, or new formulation, should be expected to monitor and validate claims for their product.

The monitoring and validation of claims are seen as an integral part of an ongoing process of evaluating product impact over its life cycle. Manufacturers are expected, not only to establish a process for monitoring and validating claims, but to present the results, when requested, in submissions to ongoing disease area and therapeutic class reviews. This should occur within a 3 year timeframe.

Accepting a modeled claim for treatment effect, cost-effectiveness, or budget impact, even if a claim has face validity, is only a first step. Manufacturers, as part of the formulary submission process, should not only present claims for cost effectiveness and system impact in empirically evaluable terms, but should also propose how they intend to monitor and validate such claims. This does not have to occur within our treating population. Manufacturers could identify similar populations within other health care systems and monitor and validate claims in those populations.

There are a number of options available in study design and protocol choice. Modeled or trial-based claims for cost-effectiveness could be assessed experimentally through a prospective, active comparator, randomized trial. If the trial is powered for economic endpoints and the resource utilization is not driven by the protocol design, this could be an ideal vehicle for assessing such claims. If claims are expressed in terms of resource utilization impacts, then these could be assessed through non-experimental or observational studies. A retrospective assessment of changing patterns of care supported by econometric modeling could be used to test hypotheses about the impact of patients moving to a new therapy on specific resource units or on the overall costs of care. If predictions regarding the characteristics and number of patients who move to a new therapy are made, then these could be evaluated through administrative claims data.

It is the responsibility of manufacturers to detail the proposed study design and timeframe for each of the claims made for the product. Irrespective of whether or not the claim is for comparative treatment benefit, cost-effectiveness, or budget impact, all claims that are made for the product should be matched to a proposal for individual claim monitoring and validation. Manufacturers are expected to detail when the claims assessment is to begin and to ensure that results are available for possible submission to us no later than 3 years from formulary listing. We may comment on the proposed study design but will not endorse or support a proposed process of monitoring and validation. There is no requirement that monitoring and validation be undertaken within our health system; merely that the results are generalizable to our target population.
7.2 Timeliness of Product Re-Evaluation

Manufacturers should recognize that the entry of a new product onto the formulary and our initial assessment is only a first step to a continuing review of the product and its place in our system. For this process to be meaningful, claims monitoring and validation should occur within a relatively short timeframe.

Monitoring and validating the claims made for the impact of a new product, new indication, or new formulation of an existing product are a key part of our commitment to the Outcomes Based Formulary. As part of its long term strategy, we are committed to an ongoing evaluation of clinical, cost-outcome, and system impact claims made by manufacturers as part of its program of product re-evaluation. For this process to work effectively, monitoring and validation of claims should occur within a timeframe that allows us to respond to study results as part of the formulary cycle of product re-evaluation. We are not interested in proposals for monitoring and validating claims, particularly claims for comparative treatment effect and product safety, that would occupy a significant part of the product’s patent life. Ideally, manufacturers should anticipate a request to report to us within 3 years for clinical, cost-effectiveness, and budget impact claims.