1 - PHARMACO-ECONOMIC STUDIES : WHY DO THEM ?

"Pharmaco-economic" studies (or economic evaluations of therapeutic management strategies) are a useful complement to studies which evaluate only the medical aspects of the strategy.

The pharmaco-economic approach also takes into consideration costs and benefits of management strategies and helps to improve health care resource allocation.

Determining cost-effectiveness or cost-utility ratios for different types of medical interventions may help to achieve this for different levels of budget.

2 - GUIDELINES FOR GOOD EVALUATION PRACTICE : WHY

Achieving a consensus view among the different agencies involved in formulating these recommendations is designed to standardise methodological practice in order to provide:

- **credibility** for results, by transparent methods and sources of information, and through sensitivity analysis,

- **quality** studies, by choosing and using the most appropriate methods for each case,

- **comparability** of the results obtained through the choice of cost and outcome indicators used and results which are described in detail.

specific interests and the associated financial limits placed on each.

In any event, the results of these studies must be seen in the context of being an aid to decision making, which by its very nature is multi-factorial, and not as a single exclusive criterion in itself. It is clear to the committee that even by harmonising methods, these studies cannot represent a "press-button" approach and must not in any way bind the decision-maker who commissions the study.

These recommendations are not intended to turn economic evaluations of management strategies into a global optimisation tool for all resources available for the drug. Their objective is less ambitious; one of "local" optimisation, in order to improve resource allocation in the setting of a disease, a group of patients or a given class of drugs.

Recommendation n°1

Given that there are different ways of measuring cost for each of the points of view concerned, it is important that the point(s) of view from which the study is performed is described for a study: impact on budgetary requirements for the Assurance Maladie or hospital etc, or the impact on total health expenditure and on public health for the society. Regardless of the context used, this should be justified.

2 - TIMING OF STUDIES OVER THE LIFE OF A PRODUCT

Pharmaco-economic studies may be performed at different stages in the life cycle of a product, but are usually performed during phases II to IV. Results obtained in France may be used in different contexts: to make a strategic decision in product development, for the initial application for reimbursement and/or re-inscription on the list of reimbursed products.

As knowledge about a product and its setting will change over time, the methodology used must take these different factors into account.

In the case of an application for renewal on the listing of reimbursed products, public bodies pay great attention to confirmation or up-dating of pharmaco-economic results which were obtained before the product was registered.

The evaluation criteria used in these different cases may themselves be different: pre-marketing studies are by necessity based on phase II and III clinical trials, whereas for re-registration, an evaluation is based primarily on the wider use of the product in medical practice.

Recommendation n° 2

The stage of product development and limitations which arise as a result of this and which affect the study should be described.

3 - THEORETICAL FRAMEWORK

Pharmaco-economic studies are defined by the fact that they take into account both medical criteria relating to clinical epidemiology, and cost criteria. This association may be achieved either formally as in the economic theory of welfare and utility, or in a multi-disciplinary methodology which may be qualified by "decision analysis". In the former case, social utility must be defined using extremely rigorous conditions which are often difficult to satisfy. In the latter, operation of

Pharmaco-economic evaluation studies of management strategies may be complemented by an assortment of additional approaches, including the cost of the disease and budgetary requirements. This approach is described in paragraph 15.

Studies based on cost of the disease come before pharmaco-economic evaluations. They provide general descriptive information about the treatments studied for a given disease.
They generally provide an overview of the information available, including descriptive epidemiology of the disease (incidence, prevalence, natural history, morbidity, handicap and mortality), traditional management approaches in the health system and associated costs (direct and indirect). Evaluation of the repercussions of the disease may include quality of life studies (see paragraph 10.2).

Measurements of cost in these studies may encounter the same type of problems as those which are seen in the evaluation analysis *per se* (see paragraph 9).

Recommendation n°:4

It is recommended that a pharmaco-economic evaluation includes a preliminary descriptive section which provides an overview of the major information available (descriptive epidemiology and types of management) on the disease concerned, both in terms of public health and in terms of health expenditure. This section may be as detailed as necessary.

5 - TARGET POPULATION

The target population is the population which may benefit from the treatment as indicated in its product licence. In a broader sense it is the population which may potentially benefit from the treatment. The actual population used is the population which receives the treatment in normal medical practice. This may or may not be similar to the target population.

Recommendation n° 5

The population affected by the product evaluation must be clearly described. For an application for re-listing, the population which is actually being treated by the drug should be described.

6 - TREATMENT ALTERNATIVES AND CHOICE OF COMPARATOR

As an economic evaluation is comparative, the comparator should be a likely alternative to the use of the treatment being evaluated: a drug with the same product licence indication, alternative technology (e.g. surgery) or the "do nothing" approach where there is no alternative. The best

Recommendation n°6

The diversity of methods for prescribing and treatment should be taken into account; several management strategies may be considered. The comparator must be chosen with this in mind, and the reasons for the choice must be explained.

7 - TYPES OF STUDIES

Compliance with good practice for the economic evaluation of drugs should improve comparability of pharmaco-economic studies *inter alia*.

Conventionally, 4 kinds of pharmaco-economic evaluation studies may be identified:

- the cost minimisation study
- the cost-effectiveness study
- the cost-utility study
- the cost-benefit study.

Two other more descriptive kinds of studies exist, although these are not evaluations in the strict sense of the term (cf. paragraphs 4 and 10.2).

Evaluation methods differ from each other in their specific objectives, the context in which they are applied and the economic and medical indicators which they use, particularly to express results. These may be expressed in monetary terms, where we refer to "benefits", or physical units. Choosing the most appropriate evaluation method for the problem to be answered assumes that prior knowledge is available as early as possible about the objective of the evaluation, the context in which it is situated and the information available to perform the evaluation.

7.1 - Cost minimisation studies

Cost minimisation studies are used in situations where the strategies compared differ only in the costs which they incur. Where two strategies are similar in therapeutic efficacy and produce the same consequences (medical and social, for the patient), but at different cost, the least expensive strategy needs to be identified.

7.2 - Cost-effectiveness studies

Cost-effectiveness studies are used to determine the strategy which provides maximal effectiveness for a fixed cost, or conversely to obtain a given medical objective at least cost. These also provide the decision-maker with information about the additional efficacy obtained for

it includes all costs and consequences of the strategy being evaluated, expressed in monetary terms. The monetary values of health results, however, raise many problems, particularly in terms of effects that cannot be substitued.

Recommendation n°:7

Each of the evaluation methods has its own field of application and its own limits. The type of study chosen should be clearly described and justified with respect to the question being asked and must be described at the start of the study. The author should also provide a definition of the type of study used.

8 - TIME FRAME AND EXTRAPOLATION TO OTHER COUNTRIES

8.1 - Time frame

There are several possible time frames. The impact of treatment may be considered over the entire life of the individual (particularly in the case of chronic diseases) or may alternatively be limited to a more restricted period of time.

Although it is determined by the natural history of the disease, the choice of the time frame of the study is often limited by the data available (particularly data from clinical trials). A model may, however, be used to estimate the long-term consequences, both in terms of health costs and results (cf. paragraph 12).

Recommendation n° 8

The time frame of the pharmaco-economic study must be justified in terms of the natural history of the disease and the availability of information.

8.2 - Extrapolation to other countries

Epidemiological information and, in particular, methods of medical and social management processes may vary considerably from one country to another. Similarly, methods for collecting data, costs and their allotted values, are highly dependent on the national context in which the study is performed.

Recommendation n° 9

Where international data on epidemiology, effectiveness or resources consumed are used, extrapolation of such data must be justified.

• The term cost in economics refers to the concept of opportunity cost and takes account of the fact that the cost of resources used to perform a given health intervention equals the value of the health results which would have been obtained if the same resources had been used to perform other procedures.
•Price is, in the strict sense of the word, the result of an offer and a bid, freely expressed in the market place.
• Tariffs are administrative prices, i.e. those fixed by public bodies or negotiated with the administration system.

In a non-market system, however, the prices used may be quite different from opportunity costs. There is no real price, as such, in the field of health, rather there are tariffs which take into account factors which are independent of actual costs and the market place. As an example of this, we see that the tariffs for medical procedures listed in the Nomenclature Générale des Actes Professionnels (Relative Value Scale) represent the result of the interaction between health professionals, paying bodies and public authorities, rather than the result of allocating values to community's own preferences about health.
In the ideal situation, public decisions on the allocation of community resources should be made with reference to the opportunity costs for each project. Insofar as these are difficult to establish in the field of health, however, it is useful to be able to refer to conventional tariffs or to costs which are as close as possible to the concept of an opportunity cost.

9.1 - Direct costs

These costs represent the value of all the resources consumed which are associated with the management of the disease (these include benefits if some costs are avoided as a result of a given treatment).

9.1.1 - Definition

Two types of direct costs may be distinguished :

• Direct medical costs, which cover different aspects including consumption of drugs and use of medical resources (admission to hospital, outpatient appointments and medical consulting visits, laboratory tests and investigations, the costs of treatment of side-effects etc).
• Direct non-medical costs, which are involved in transporting the patient for the purpose of his medical management, for home care assistants and for care provided by voluntary workers etc.

Recommendation n° 10

des Actes Professionnels (Relative Value Scale) and tariffs for each key letter, which are published by public bodies, in addition to other tariffs and prices used (drugs, prostheses etc), which are adjusted to take account of the specific reimbursement figure for the procedure. This practice is valid for direct outpatient costs: laboratory tests and diagnostic investigations, medical consulting visits and outpatient appointments (general practitioners and specialists, nursing and physiotherapy procedures etc), although there may be some discussion as to how these are applied (the difference between the procedure tariff and the true value of the procedure which depends on the time consumed and the level of expertise required). It is conventional to apply the factors used by the Régime Général[1] in calculating reimbursement rates. When, however, a study applies to a specific population, it is useful to take into account changes in tariff rates offered by the different regimes and, where applicable, to apply individual weighting factors. Also, where necessary, the individual situation of insured patients should be considered, in terms of exemption from paying costs.

• From the point of view of the patient, other adjustments are usually made based on the frequency and size of fee over-expenditure (practitioners with the right to exceed budgetary expenditure or who are practising in sector II, in receipt of private fees) and additional insurance coverage. In most cases, information about additional insurance coverage is not available in sufficient detail and tehe payment attributed to individuals generally includes all that part which is not reimbursed by the compulsory National Health Insurance.

• From the society point of view, the value applied should ideally be expressed in terms of opportunity costs. This value is often, however, obtained by adding the reimbursable costs to the costs borne by the patient, including additional coverage.

- Public hospital costs

In order to measure hospital costs, it has until recently been conventional to use the daily cost applicable to the type of institution and the specialty concerned, multiplied by the length of the hospital admission period in days.
Analytical accounting now enables us to come closer to the concept of actual cost rather than tariff cost.
The Programme de Médicalisation des Systèmes d'Information (PMSI) database provides information about analytical accounting which is listed by diagnostic related group (DRG). This type of approach is now becoming widely used to allocate values to admissions to public hospitals. This provides average inclusive costs divided into 14 components (medical staffing, nursing, consumables, medical/technical procedures, kitchen services, linen services etc) which are based on a sample of more than 40 hospitals and a total of more than one million admissions. This type of information is only currently available, however, for short-stay public hospital admissions. No

For short-stay public hospital costs, it is recommended that, wherever possible, analytical accounting data are used and are listed by diagnostic related group (from the PMSI database) using inclusive costs. Until this process becomes more widely applied to all domains in the public and private sectors, billing information and/or conventional tariff data may continue to be used.
It is recommended that the sources of data used are described in all cases. For reimbursement rates, those used by the Régime Général should be applied. Adjustments may be made depending on the characteristics of the populations being studied. From the point of view of patients it is recommended that all of the costs not reimbursed by the Assurance Maladie (including additional cover) are taken into account.

9.2 - Indirect costs

9.2.1 - Definition

These costs mostly refer to productivity losses on a macro-economic scale. Productivity losses affect both the patient and the patient's close contacts. In addition to productivity losses associated with loss of work, the leisure time lost by the patient and by the patient's close contacts should also be taken into account.

Although short or long-term loss of work due to partial or total handicap, and also premature death have, for many years, been accepted to represent a loss of production for the society, there are now several arguments to suggest that it is not appropriate to include these costs. Firstly, productivity values are dependent not only on human or equipment resources but also on demand. In a setting of high unemployment, the long-term unemployed will effectively make up for some long-term patient absenteeism. Flexible internal working practices in a company (overtime, job sharing) and external factors (locum replacements) do, to a large extent, make up for short-term absenteeism.

Recommendation n° 12

Indirect costs (benefits) may appear in a study where the management strategy or disease being considered justifies this. In all cases, the reasons for including and methods of calculating these costs should be justified and costs should be presented separately from direct costs.

9.2.2 - Measurement

Conventionally, indirect costs are measured using the so-called "human resource" concept, which measures losses of productivity by loss in gross salary associated either with the disease or with a treatment. In this situation, the productivity value of a person is calculated from his income and it is conventional to multiply the number of days lost by the average national income, expressed either as the mean added value or mean salary.

From the point of view of the society, it is recommended that estimates of loss of productivity are expressed in physical units without allocating values (number of working days lost, number of school days lost etc).
Nevertheless, if the study is being performed from the point of view of the Assurance Maladie, the magnitude of payments given out from the public funds must be included in the calculations.

9.3 - Intangible costs

These costs relate to the loss of a patient's well-being and that of the patient's close contacts due to the disease. These are the human psychological costs of the disease (suffering, pain, loss of life). These costs are implicit and may even explicitly be taken into account in studies which include quality of life concepts, using for example the willingness to pay approach, and in cost-benefit studies.

Recommendation n° 14

Intangible costs (benefits) are by their very nature entirely different from direct and indirect costs and it is inappropriate to add these costs together. Intangible costs may nevertheless, be considered in a separate study (quality of life, willingness to pay etc).

10 - OUTCOMES DEFINITION AND MEASUREMENT

As the principle of pharmaco-economic studies is to compare the costs of a treatment with the outcomes produced by that treatment, it is crucial in the evaluation process that these outcomes are both defined and measured. The outcomes of a treatment may be defined in many ways. They may also be measured in many ways.

The range of outcome indicators which may be used depends on the objective of the study, the type of study, the nature of the information available and the indications for the product as they appear in its product licence.

Four major variants of the concept of an outcome will be considered, together with their specific indicators: effectiveness, quality of life, utility and willingness to pay. We shall then examine their use in combined indices.

10.1 - Effectiveness

10.1.1 - Definition of effectiveness

Measurement of the effectiveness of a treatment raises several questions of definition.

Wherever possible in pharmaco-economic studies, effectiveness in actual use is to be preferred to efficacy. If efficacy is used, however, attempts should be made to convert this to actual effectiveness using an appropriate approximation.

S*urogate end-points* and *final end-point*

The use of surrogate end-points (for example a fall in blood pressure or cholesterol concentration) raises two types of problems in an economic evaluation:

- The first is a comparison problem: only treatments which lower blood pressure or cholesterol levels may be compared. How do we then consider other treatments which act on other parameters but which have, nevertheless, an impact on the incidence of, for example, cerebrovascular accidents or of myocardial infarction?

- The second is a difficulty in interpretation : what is the significance of the costs associated with a 20% reduction in one of these parameters?

These difficulties can only be resolved if a valid relationship can be found between the surrogate end-point and the final end-point.

Recommendation n° 16

It is recommended that final end-points are used in preference in pharmaco-economic studies. If only surrogate end-points are available, the relationship between these end-points and the final end-points should be estimated as best as possible by modelling.

10.1.2 - Choice of indicators relevant to final effectiveness

- One or more indicators?

A treatment may have many effects and expression of effectiveness by several indicators raises problems of interpretation. Combination of end-points into a single, global indicator raises the well-known methodological difficulties of data aggregation and weighting.

Where a single indicator is used, this assumes that efficacy has only one dimension; this must be justified or at least explained.

- Events avoided or disease-free survival?

Many studies have chosen to express effectiveness in terms of specific critical events avoided (e.g. fractures, ulcers or deaths avoided).

several indicators are used, the means by which these may be combined should be stated.
If the indicator describes a number of events avoided, the time period over which the result has been obtained should be stated. A number of years of life saved or increased life expectancy is to be preferred to the number of deaths avoided. These life years saved may or may not be discounted, although the final solution must be justified wherever possible.
Similarly, quality of life during the years gained should be described by an appropriate indicator.

10.1.3 Measurement of effectiveness

The major question which arises in estimating effectiveness is the availability of the necessary information.

- Obtaining data from clinical or clinico-economic studies

Ideally, an experimental study should be used to establish the clinical benefits of a treatment, both in terms of effectiveness and of tolerance.
These clinical trials therefore represent the gold standard in clinical evaluation. They compare patients who are randomised either to an intervention group or to a control group, in order to test hypotheses of efficacy and safety according to rules of Good Clinical Practice, which are now well established.

It is well-known that these results are valid internally, although their major weakness arises from the fact that in general they refer to theoretical clinical efficacy and not to effectiveness as observed in actual practice, as they are artificial in nature and have limitations imposed by the protocol (low external validity).
Various approaches may be used to solve these difficulties: clinical trials which are closer to real situations, retrospective case-control studies, intervention trials, cohort studies, analysis of patient databases, modelling etc.

Wherever a non-experimental method has been used, there are significant risks of selection and interpretation bias. Nevertheless, various statistical processes (multivariate analysis etc) may be used to limit any identifiable confounding variables.

Development of patient databases over a period of years is a useful means of comparing the actual conditions under which the products are used to their theoretical conditions, and thereby indirectly, but only qualitatively, to evaluate their actual effectiveness.

- Overview of clinical findings (meta-analyses)

Where several clinical trials have been performed in the same type of intervention, literature reviews or meta-analysis of these studies may provide useful information.

Measurement of the quality of life associated with a state of health is a further way (and occasionally a substitute) of evaluating effectiveness. It is often essential to compare treatments which affect not only the duration of life but also its quality. This is particularly appropriate in the context of chronic or recurrent diseases.
It enables the patient's point of view to be taken into account (or that of the patient's representative), and enables functional criteria such as physical, social, mood etc to be added to the purely medical end-points (laboratory results, clinical findings - often surrogate end-points). This provides the patient's view (or that of the patient's representative) about the different consequences of the disease and/or its treatment.

The concept of quality of life must be distinguished from that of utility. The former refers to psychometric scales which are often multi-dimensional in nature. The latter refers to an individual's choice or preferences and is expressed using combined indices. These choices and preferences may, however, refer to states of health which have been defined via quality of life measurements.
Measurement of a single index of effectiveness, which combines both clinical judgement and quality of life measurement criteria, is not a true indicator of utility.

Recommendation n° 19

In an economic evaluation it is often important to measure the patient's quality of life - this information may not be provided by conventional measurements of clinical efficacy. Measurement of quality of life is particularly appropriate in the case of chronic or recurrent diseases.

10.2.2 - Measurement of quality of life

Quality of life may be measured :

- either from clinical trials,
- or from trials of actual use in a strict methodological setting,
- or from descriptive studies.

Several types of measurement instrument or quality of life scales are available, mostly in the form of self-administered questionnaires.The following may be used to measure quality of life :

- a generic health scale alone,
- a disease specific scale alone,
- a generic health scale and a disease specific scale.

Generic measurements evaluate the patient's condition, regardless of the disease. These measurements are favoured by those who make decisions in health matters as they enable groups of patients suffering from different diseases to be compared. Their psychometric qualities are often

their consequences to be placed in order.

• **In a comparison between products** : generic instruments may be used to compare products with each other and with other treatment options, both for a disease and for other purposes : specific instruments only permit comparisons to be made in the limited context of the disease concerned.

Recommendation n° 20

It is recommended that only instruments which have been validated should be used to measure quality of life and that a generic scale is combined with a specific scale. It may, however, be appropriate to use only one of these two instruments, providing this is justified.

10.3 - Utility

10.3.1 - Definition of utility

In economic theory, the utility of a good or service to a financing body, which is assumed to act rationally, is the pay-back in return for the benefit which the body agrees to pay. It is different from the concept of medical utility which assesses the sound basis of a given treatment for a patient in defined circumstances.

In the health sector, the utility (in the economic sense of the term) associated with different states of health is a measure of individual preferences (those of the patients or the general population) with respect to these different states, using appropriate indicators. The utility of a drug is not scored in its own right but through value judgements obtained from individuals about the state of health which the treatment produces.

Recommendation n° 21

Measuring utilities is different from the technical measurements of the results of a treatment. Utilities express outcomes from the point of view of the individual (patients or general population) and are a further criterion in making a decision They may be particularly appropriate in certain diseases and/or treatments.

10.3.2 - Measurement of utility: methods used to identify preferences

There are many methods and different combinations available to identify preferences. Three major methods are available to allow the individuals concerned to express their preferences about different states of health.

- Classification methods using visual analogue scales

The standard gamble method uses expected utility theory and choices under uncertainty as the assorted states of health which are offered as an alternative to the current state are weighted by the probabilities by which they may occur. This system is difficult to use as interviewees do not find it easy to base their opinions on probabilities and the choices offered are frequently unrealistic.

- Time trade-off

This involves expressing the number of years of survival in a given state of health which the individual would be prepared to exchange for a fixed number of years in perfect health (or better health). This trade-off does not account for the utility of these years of life in good health, nor does it relate the trade-off to the probability of the event occurring.
In contrast, the time trade-off method is relatively straightforward to perform.

Recommendation n° 22

Of the different methods available to identify preferences about states of health characterised by their quality of life and duration, visual analogue scales should be used with caution because of the problems which arise in interpreting them. The standard gamble and time trade-off methods would therefore appear to be more appropriate, although each has its own qualities and limitations. The reasons used to select one method over another should therefore be explained in evaluation studies.

10.4 - Willingness to pay

Willingness to pay may be used to estimate the value which individuals attribute to a good or service from the financial sum which the individuals concerned would be prepared to pay in order to benefit from the good or service. This method enables individual preferences to be combined in a cost-benefit analysis and an overall opinion to be expressed about the result (the state of health obtained following a treatment) in financial terms.

The willingness to pay method, which is still in its experimental stages, is subject to two types of bias;

- answer bias: due to an inadequate description of the scenario resulting in the *cost-(value) being under-estimated by the respondent, or influenced by the respondent's strategic behaviour*;
- selection bias: due to a failure to include non-responses or conflicting responses in the statistical analysis.

Recommendation n° 23

Recommendation n° 24

Where the result of a treatment is expressed through a combined index of both efficacy and quality of life, the latter should preferably reflect individual preferences.
Depending on the context of the study, these preferences may be those of the general population (social perspective) or of the patients who are directly involved (patient perspective).
They may take the form of utility coefficients, which are applied to states of health, or may be obtained from quality of life indicators, which take account of these factors implicitly in the way they are constructed. Regardless of the method chosen, it is essential that the method by which these combined indications are calculated and the status of individuals who express their preferences are described and that the underlying assumptions are validated.

11 - DISCOUNTING COSTS AND BENEFITS

The time frame of different therapeutic strategies may be short or long, depending on the situation. In studies which are based on time frames over several years or more, the problem of discounting arises. This involves taking into account individual preferences as they apply in real time.

The problem of discounting is characterised by three questions :

- whether or not to include individual preferences at different times;
- what level to use;
- whether or not benefits are discounted and the legitimacy of so doing.

If we consider existing guidelines at an international level, it is broadly accepted that a discount rate of 2.5 and 5% may be used for costs The problem of discounting benefits is still controversial as future depreciation (with reference to lives saved) is not yet fully accepted.

Recommendation n° 25

It is recommended that costs are discounted in all cases. Costs may be discounted using conventional rates (2.5 or 5%) but should also be subject to a sensitivity analysis in which these figures are varied. As the issue of discounting benefits has not yet been resolved, these should be presented both with and without discounting. In all cases the non-discounted result should be presented in these studies.

12 - MODELING

A model is a simplified, reasoned and formalised representation of a true situation which the user is endeavouring to evaluate. Models are used in situations too complex to be evaluated directly and where inadequate information is available. They involve reducing situations to their primary components and isolating these components from the many secondary influences which may apply

There are many modelling methods. Some aim to be explanatory, such as multivariate statistical models, which endeavour to link overall changes with those of "explanatory" variables. Others are predictive and attempt to measure the consequences of alternative decisions in an uncertain world, but one which may be defined in terms of probabilities (decision tree, stochastic process, Markov chains etc). The Markov models are particularly well suited to evaluate medical treatments. These are dynamic, stochastic models which follow the changes in a population by the probabilities of different "states", which are each allocated a cost and a measure of the state of health.

Models may be validated both internally and externally. Internal validation questions the correctness of the findings and the coherence of the structure in which they are placed.
External validation examines the comparability of the simulated dynamics with those actually seen in practice.

As information about a model is primarily dependant on the assumptions from which the model is constructed, it is important that robustness is tested by sensitivity analysis.

Recommendation n° 26

Modelling is a perfectly acceptable means of evaluating treatment strategies where information is incomplete or inappropriate for the problem being assessed. It allows both costs and outcomes to be evaluated. The hypotheses and estimates on which the model is based should be explained and documented and their robustness should be confirmed by sensitivity analysis. The model itself must be validated both internally (consistency with findings) and externally (application of results obtained from the model to the changes which are observed in practice).

13 - SENSITIVY ANALYSIS

An economic evaluation is an analysis of an uncertain situation. The parameters used may occasionally be imprecise or be hypothetical. For this reason, thresholds must be provided.
Uncertainty may be measured in two ways: by sensitivity analysis and by a statistical evaluation of the distribution of results:

- Sensitivity analysis involves varying the parameters relevant to the model from the values which were initially used. It does not obviate the need to justify the initial values and the intervals through which values are varied from the baseline in comparable populations, although these may be used to confirm the robustness of the conclusions reached and to identify the key variables in the model.

- Classical statistical distribution tests are performed on costs and outcomes. For effectiveness parameters for example, the distribution of costs and in particular their median, mean, confidence interval, first quartiles and outliers will be examined.

14 - PRESENTATION OF RESULTS

14.1 - General details

Results must be presented in such a way as to make the study transparent. It is essential that people who read the study obtain a precise idea of the way in which results were obtained, particularly where a model is used, and that the reader must be able to follow the reasoning used without difficulty.

Recommendation n° 28

The report should be presented in such a way as to take account of the different points raised in these recommendations.The results of a study should be presented in successive stages, distinguishing the effects of treatment on one hand, from costs on the other. It is recommended that calculations are shown in detail, in order that it is possible for both their accuracy and their relevance to be confirmed.
All clinical, epidemiological and financial data should be provided as these are essential for the study to be validated and be fully understood.
Detailed references should be provided. In particular, sources used to calculate costs must be given.
These details may be provided in appendices in order to make the study easier to read.
The agency which has commissioned the study must also be named for the purposes of transparency.

14.2 - Ratios

Cost-effectiveness (or cost-utility) ratios are designed to provide an overview of the results of a comparative evaluation of different treatmen. This implies that ratios should be presented in a differential format in which the difference in the costs of two treatments is set against the difference in the effects which the treatments may have. The contents of the numerator and of the denominator should also be adequately described to avoid counting something twice (where the same effect is expressed both in the numerator and in the denominator). Life years lost, for example, should not be counted in the costs.

Recommendation n° 29

Cost-effectiveness (or cost-utility) ratios should be expressed in differential format so that they may be used as a criterion to assist decision-making. Variations in use of resources should be shown in the numerator and those which influence the state of health in the denominator, taking care to avoid counting factors twice.
Components of these ratios (costs and results) should also be presented with their statistical distribution (mean, median, confidence interval etc).

14.4 - Distribution features and equity problems

Any calculation method used to present an overall result or to weight results (data combination procedures, discounting benefit etc) which may obscure problems of equity by favouring or undercounting a group of patients should be discussed. Cumulative life years should in particular be handled with caution. A treatment, for example, which enables a patient to gain 10 life years does not have the same value as one which enables 10 patients to gain 1 year. The overall result for each is, however, identical. Choice of one over the other implies that the author has taken a stance on equity.

Recommendation n° 31

It is recommended that aggregate results are expressed in such a way as to take account of any underlying equity problems in the aggregation method used.

14.5 - Time frame of the evaluation

It is possible that the evaluation may be undertaken under different conditions depending on the time frame of the study. This may, in the first instance, be defined by the length of randomised trials or of observational studies on which the economic evaluation is based. If this observation period is considered to be inadequate, the studies may extend the period by extrapolation or by a more complex model.

Recommendation n° 32

If the study consists of both short-term results from clinical trials and longer-term results based on modelling or on clinical observations, results of these two phases should be presented separately before any aggregation process is applied. Where aggregation is to be used, the aggregation methods and their limits must be justified and discussed.

14.6 - A standard format to present studies

Most of the "*guidelines*" formulated in different developed countries contain a recommended list of points which should be covered in the presentation of the study. Some are relatively demanding in the details they require to be presented. Whilst not wishing to be excessively formal or prescriptive, these recommendations will attempt to list the points which all studies should endeavour to explain.

Recommendation n° 33

Wherever possible, reports showing results of a comparative evaluation of management strategies should make the following points clear to the reader:

•the limits of the evaluation presented.

15 - BUDGETING

An important secondary aim of pharmaco-economic evaluations is to estimate the short- and medium-term (2-3 years) consequences of instituting a new treatment for the different health service agencies involved (Assurance Maladie, additional insurance, patients, public hospitals, private practitioners etc). This type of analysis follows on logically from the studies described above. They may be distinguished in many respects by the choices of methodology used:

- systematically, including tariffs and transfers of financial resource (direct costs and variable costs);
- a short- and medium-term context (2-3 years);
- including the actual financial mechanisms which apply to the structures and agencies involved, combining intrinsic resistance to change with the changes in medical practice which will result from the new practice;
- an approach taking into account the effects of treatment being available on a wider scale (i.e. effects on the entire health service system) including the effects of replacing existing management strategies, allowances for the market where competition exists and the short- and medium-term costs avoided as a result of the effectiveness of the treatment;
- including specific details of the populations who will receive the treatment being evaluated (target population, actual population, defined patient sub-groups etc).

Recommendation n° 34

In addition to pharmaco-economic evaluations carried out on a micro-economic basis, it may be useful to extrapolate the results obtained in order to estimate the budgetary consequences of a treatment studied for the major agencies involved in the short- and medium-terms, in the event that treatment is applied on a wider scale.
These estimates may be more or less complex, depending on the case, and should be described together with the assumptions on which they are based.

methodological progress and in the ways they are actually applied to provide information for making decisions. In addition to up-dating, two major tasks come out of this first work:

1. The formation of a database of all French pharmaco-economic studies. This will require identifying, listing and analysing all studies which have been performed in the last ten years, beginning with those which have been published, but also including those which have not been published.

2. Obtaining comparative data from these French studies for their results (cost-effectiveness, cost-utility or cost-benefit ratios) for the different types of intervention which have been evaluated.

It should be stated from the outset that these lists of ratios ("*league tables*") will only be meaningful if the calculation methods used and their constituent parts (costs and outcomes) have first been checked to ensure that they are consistent, or that they have been adjusted by appropriate mechanisms.

Finally, we should take the opportunity which has been provided by this work to stress the importance of promoting the accessibility of evaluation studies, particularly by authors making systematic efforts to publish their studies in peer-reviewed journals.

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[1] Regime general : National Health Insurance for person on salary.