

« A basis for drugs policy: therapeutic efficacy and fair price »

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INTRODUCTION

All the reforms considered up to now for controlling the increase in health care costs have been motivated primarily on economic grounds. These include making consumers more responsible, sharing costs through co-insurance, capitated payments for providers, reforming physician reimbursement and global budgeting. Consideration of the impact on the health status of patients has been limited, contradicting the ethics of medical practice.

The increased burden on consumers would be more acceptable if medical providers exhibited less variation in diagnosis and treatment decisions reducing the lack of confidence in the health care system¹. It has become increasingly evident that certain medical decisions are tainted with arbitrariness. The variability in diagnoses, prognosis and treatment provide evidence of the fragility of individual reasoning.

Eddy² gives the example for four cardiologists arriving at different diagnoses in 60% of cases when asked to review radiographic evidence of anterior interventricular stenosis. When the same cardiologists were asked to review the same films two months later, 8 to 37% of the cases resulted in different diagnoses.

The probability of success of particular treatments is the determining element for making a medical decision since it orients the choice of diagnostic or therapeutic attitudes. One can observe in certain of these cases considerable divergence of opinion. For example, for colon cancer³ some doctors believe that the recourse to hemocultures and to sigmoidoscopy would permit a 95% reduction of the specific mortality rate. According to others, the predicted decrease in the mortality rate would not be more than 5%.

Physician decision making is dependent on both personal experience and statistical evidence but many give preference to the former and are skeptical of the latter. It is alleged that physicians do not understand the concepts of probability well. As an example, Casscells⁴ asked 60 doctors at Harvard University to solve the following problem : if the prevalence of a disease is 1 in 1 000, if the rate of false positives is 0.05, what is the probability that any patient presenting with the symptoms is affected by the disease ? The correct answer of 2% was given by only 11 (18%) physicians.

These types of disparities explain the large variability in diagnostic and treatment options for patients with the same medical condition. Wennberg⁵ retrospectively divided patients who had been hospitalized in 30 Maine hospitals into 445 groups, depending on their diagnosis and treatment. The number of patients belonging to each group as a function of the number of inhabitants in their place of residence varied considerably. The rate of intervention was similar for inguinal hernia, but it was different for conditions in which indications for an operation ceased to be clearly defined and widely adopted by the profession. The differences were moderately noticeable for appendicitis (variations of 1 to 2.5); they were considerable for discal hernias (from 1 to 8) or for tonsillectomies (1 to 12).

One way to decrease this variation and improve quality of care would be to introduce at a minimum, regulations designed to eliminate irrational choices and non-beneficial treatments. Uncertainty, however, is inherent in medical practice and precludes physicians from making choices using techniques such as linear programming. But given the scarcity of resources, should we continue to resist the introduction of economic criteria in making medical choices ?

1. MEDICAL REGULATION “A MINIMA”

The preceding examples show that one cannot trust individual medical judgement and that it is necessary to establish guidelines. All the proposed definitions in this area converge.

- 1) The most pedagogic is the one proposed by Gilles Johanet⁶ when he distinguishes between useful care, non-useful care and harmful care. The law of diminishing returns applies to medicine as well as other things: maximal gains from interventions are produced initially, progressively tapering off and eventually having no effect on health or possibly creating harm to the patient (for example nosocomial infections).
- 2) Claude Béraud⁷ gave a more precise meaning to these notions by distinguishing the three realities that they encompass: the efficacy of a treatment under experimental conditions; the validity of indications under normal conditions of practice; and finally the usefulness for the patient. A procedure is efficacious when an experimental study demonstrates statistically that it is capable of improving the outcome of an illness. A treatment is justified when a doctor prescribes an efficacious treatment for a defined indication. A treatment is useful for a patient when he considers that his state of health has been improved by it.
- 3) Bernard Avouac⁸ goes further by advocating the principle of relative efficacy versus absolute efficacy: the evaluated drug should not only be efficacious but more so than the competing drugs. Too often, a diagnostic or therapeutic technique is adopted in view of its potential, rather than observed benefit. The Office of Technological Assessment has estimated that 80% to 90% of procedures utilized had not been validated by randomized trials⁹.

1.1 The search for medical appropriateness

In medicine, one cannot always demonstrate the superiority of one treatment compared to another within the framework of tests that are directly governed by protocols. Thus, one is obliged to resort to other techniques such as consensus conferences or decision analysis.

The first opinion is to utilize expert judgement to define a standard reference. The Rand Corporation¹⁰ attempted to define appropriate indications for coronary angiography, coronary bypass, endoscopy, colonoscopy, gall bladder ablation, and carotid endarterectomy. The expert panel we asked to assess the validity of utilization of these techniques based on their judgement, clinical experience, and published literature. A scale ranging from 1 to 9 was used. A score of 1 for example, signified inappropriate use, 5 was assigned when use was considered ambiguous, and a score of 9 indicated appropriate use. The researchers defined a disagreement when at least one of the 9 members of the panel assigned a score between 1 and 3, and at least one another chose a score between 7 and 9. A consensus was reached when the difference between scores was no more than 3 points for all the panelists. The study found that there was disagreement among experts in 30% to 81% of the cases.

Though consensus conferences are a step in the right direction they are not without problems. First, often contradictory and inconsistent data is presented to be synthesized in a short time, the conclusions drawn do not have the requisite precision, and they can be highly subjective. Second, the effects of the recommended indications are not considered. Finally, the adoption of these recommendations by the medical profession is likely to be tempered by the fact that they may not be applicable to every individual patient.

The second solution is to incorporate patient preferences in the decision making process. Decision analysis enables one to integrate information on the prevalence of disease, efficacy of treatment, adverse effects and the benefit perceived by the patient¹¹. The reliability of the conclusions obtained will be dependent on the quality and sensitivity of the analysis.

By incorporating the patient's opinion on the benefits of the treatment rather than just objective clinical criteria in the analysis, we are validating the concept of informed consent. Therefore, we should allow norms to emerge from the diversity of individual preferences so long as patient attitudes are sufficiently homogenous. Three such cases can be distinguished. When a favorable opinion is given on an efficacious treatment by a unanimous consensus of patients, this treatment can be considered as a reference (standard) and should be administered systematically. However, when patients' opinions are more divided, and the majority remain favorable towards an efficacious treatment, the application of this treatment should be advised first (guidelines). In all other cases, when the patients' opinion is very divided, or they are indifferent, one should resort to good clinical sense.

1.2 Demonstration of drug efficacy

In the drug industry, evaluation methods are more rigorous and the efficacy has to be demonstrated by experimental research. Randomized trials (called Phase IIIa) demonstrate the efficacy of a new molecule compared to a placebo or a referent treatment, and are mandatory for authorization to market the product. The trials should demonstrate the efficacy and "maximal" tolerance under ideal conditions. It thus optimizes the benefit expected from the treatment when indications are most favorable.

In order to be reimbursed, the product must demonstrate an improvement in medical care based upon its efficacy, tolerance, acceptability, and effectiveness under "natural" conditions¹². These are the guidelines for Phase IIIb trials. The distinction between these two stages of the administrative procedure corresponds to the distinction between efficacy and effectiveness¹³. Phase III trials covers efficacy and tolerance. Phase IIIb introduces the ideal of effectiveness, the improvement in medical service rendered in a natural setting, as well as therapeutic usefulness.

The determination of the reference norms should not pose a problem, as the indications are defined by the "Autorisation Mise sur le Marché" (AMM), on the basis of available evidence from randomized trials. However, recent controversies have shown that they are not devoid of ambiguity. For example, the investigation of statins by the National Health Insurance Fund in November 1990 concluded that there was a lack of precision on the part of the AMM and raised the question whether the AMM missions should be enlarged.

2. THE NEED TO CONFRONT THERAPEUTIC COSTS AND BENEFITS

2.1 The absence of economic criteria results in an impasse

One can well see that such a discussion about a minima of medical regulation excludes a priori the consideration of costs. In order to avoid any conflict between medical logic and economic logic, only proven therapeutic regimens should be provided and useless care should be eliminated. Thus, as long as only efficacious treatments are used, they should be made available regardless of their costs.

In the area of drug treatment the arguments are a bit less simplistic. First, the prices imposed by the pharmaceutical industry are defined according to reference products, recent or old. Secondly, health

expenditures for drugs are explicitly taken into account by the Commission on Transparency using the following classification system :

1. Major therapeutic advances
2. Important improvement
3. Modest improvement
4. Minor improvement
5. Absence of improvement with a reduction in cost
6. Absence of improvement without a reduction in cost.

However, it is necessary to recognize the ambiguity of these actual classifications¹⁴. On one hand, it is desirable to avoid unjustified expenses for health insurance by affirming that costs can be justified by effectiveness if one takes into account various benefits such as, a reduction in the rate of hospitalizations, leaves of absence from work, or undesirable side-effects that lead to further medical interventions. On the other hand, there is an ethical problem when one refuses to provide a given drug solely on the basis of cost considerations even though the drug makes it possible to gain years of life albeit at a higher price than another drug.

The net economic cost of a treatment is not only the direct therapeutic benefit associated with it. It also includes criteria related to other supplementary costs and benefits. The goal is not to minimize health expenditures but to suppress the most flagrant aberrations of products that are both less efficacious and more expensive (class 6 above).

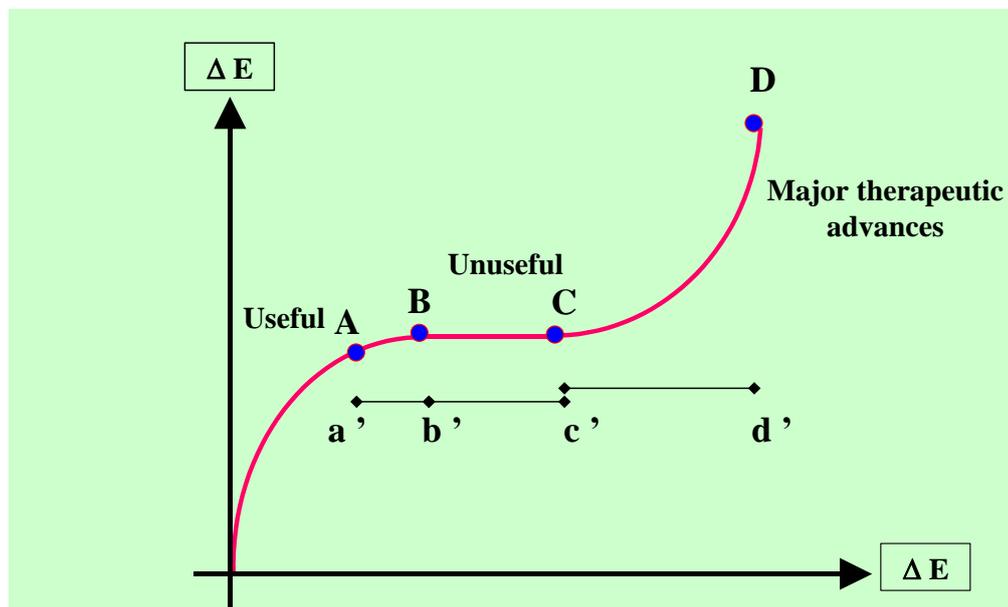
The classification of new drugs to the first four levels of the above series is a function of the clinical benefits provided. The technical advice formulated by the Transparency Commission on the rate of reimbursement is linked to : (a) “the therapeutic interest” of the new drug, which depends on the disease severity and on the available pharmaceutical alternatives and (b) the differential of clinical benefit produced.

When a product corresponds to a therapeutic necessity in a manner that is more efficacious and more innovative than competitive products, it is said to correspond to a need.

In the logic of the classification groups, priority should be given to products than can be ranked higher but this raises two problems. First, will we exhaust all available resources in favor of major innovations at the expense of all other categories? At present there are no available guidelines on how to distribute resources. Second, should we use these criteria to grant a higher price to major innovations? If so, what about aspirin for myocardial infarction?

Problems may occur if decisions are not considered in terms of costs and benefits. It is incorrect to believe that major therapeutic advances like Sumatriptan can be financed simply by cutting down on useless expense⁵. New technology can significantly increase efficacy (see Graph 1 displacement of c' to d'). but their introduction requires that the corresponding resources can be found. The elimination of useless expense from b' to c' covers a fraction of this expense. However, it is evident that the remainder can be obtained by eliminating more older techniques (between a' & b'). Clearly, in such a context one cannot be satisfied by studying evolving profiles under treatment from a strictly medical viewpoint. Rather, one should also integrate economic data into the same analysis. (Graphs and tables).

Graph 1 : Financing of major therapeutic advances



2.2 Interest of cost effectiveness analysis

The challenge before decision makers, regardless of political affiliation, is to improve the health of the population while controlling expenses, a task that will inevitably engender tensions. If greater resources are devoted to a particular drug, its prescription should also bring a gain in health at least as important as that which could have been obtained by allocating funds to finance other pharmaceutical products. Conversely, if a drastic policy of regulation applies to a drug, it is necessary to ensure that this reduction is not made at the cost of an unacceptable deterioration of health status.

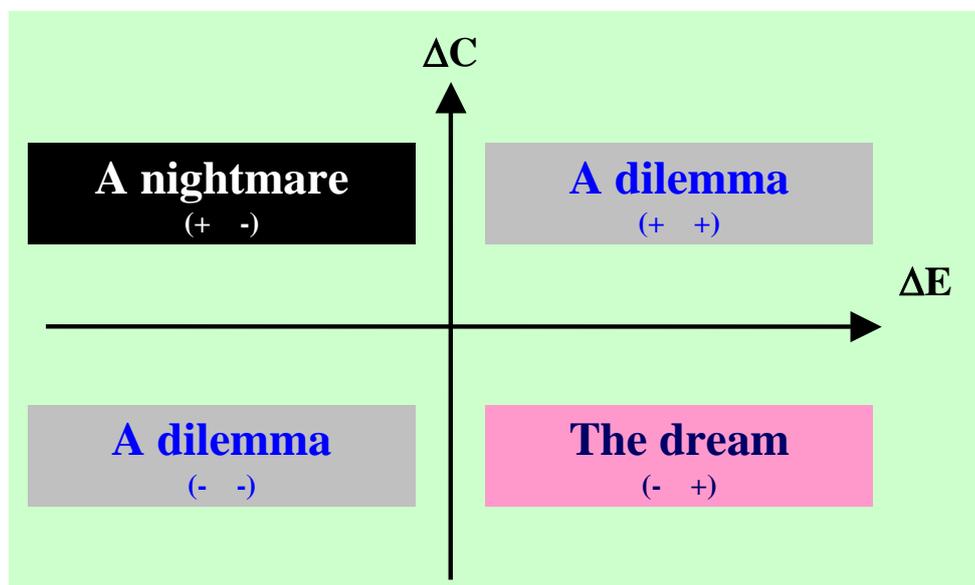
A precise formulation of the problem can be obtained from randomized trials and techniques such as decisional analysis. A decision tree and marginal cost benefit analysis are the standard tools that are used.

The first task is to record possible strategies and key parameters, epidemiologic or clinical, that can influence the result and the cost of treatment under the indication concerned. The therapeutic problem is decomposed with the help of a decision tree that includes 3 types of nodes : decision nodes, chance nodes, and terminal nodes. The branches issued from the first node correspond to the different choices of therapies (for example, the choice of an antibiotic). The branches emanating from the chance nodes represent the diverse events and their associated probabilities that can arise from actions taken (for example, failure of the first antibiotic therapy, a second outpatient treatment, or the referral to a hospital). Lastly, the terminal nodes record the results obtained and the resultant costs.

For each mode of treatment, the total expected costs and benefits are calculated. To do this, one starts at the terminal nodes where the costs of treatments and their results are jointly recorded. For each chance node one calculates the value of the branches it gives rise to, by multiplying the value of each corresponding terminal node by the probability of the branch in question and adding the results. The value of each chance node is therefore equal to the sum of the values of each one of the branches (method of calculating averages). In proceeding back to the roots of the tree, each chance node distributes in turn its value to the branch to which it is attached (back chaining procedure).

The possible strategies can be represented graphically (Graph 2), with the benefits on the horizontal axis and cost on the vertical axis. Each quadrant corresponds to a possible therapeutic strategy.

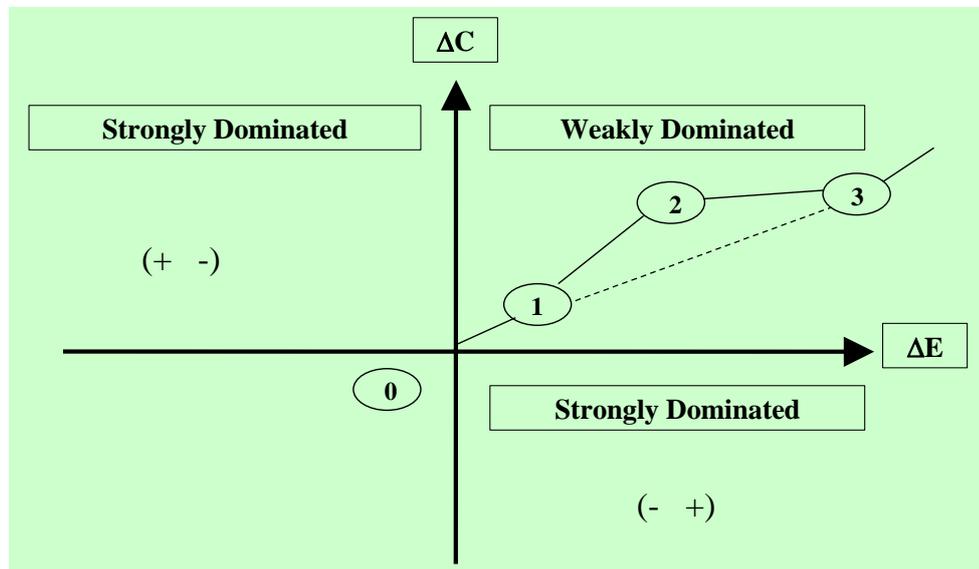
*Graph 2 : Variation of cost and effectiveness
The possible situations*



Hypothetically, these strategies are mutually exclusive. Substitution of one strategy by another corresponds in the space of choices, to the passage from one point to another, which results in a variation of cost and at the same time in a modification of effectiveness. In both cases it is a question of the differential net average values. It is differential because one only measures the gap between the two strategies; it is an average value since it is a calculation of mathematical expectation based on the probability or occurrence of events; and net value in so far as the final figure simultaneously integrates positive and negative contributions. The supplementary cost of treatment is calculated after subtracting the additional economy achieved by avoiding care. The efficacy of a treatment is judged by the sum of the negative impacts. The quotient of these two results defines the marginal cost-effectiveness ratio.

To differentiate these strategies, two efficiency criteria are used.

Graph 3 : The search for dominating therapeutic schemes



The first criterion (domination) is that a strategy should be eliminated from the choice zone as long as it is less efficacious for the same cost, or as long as it costs more for the same result (see Graph 3). This criterion permits the elimination of a certain number of non-efficacious strategies situated in the North-West (NW) zone of the graph. This leaves a large number of non-dominant strategies remaining in the NE and SW quadrants. The second strategy is more expensive and more efficacious than the first one, and the third strategy is more expensive and more efficacious than the second one. Nevertheless, the linear combination of strategies 1 and 3 results in an identical outcome while spending less money, or in better results for the same cost. According to Milton-Weinstein¹⁵, a strategy is weakly dominated if and only if the marginal cost effectiveness ratio decreases (the slope between 2 and 3 is less than the one between 1 and 2) when the total cost of treatment increases. In this case one should eliminate the strategy in question and recalculate the difference between cost and effectiveness in considering a new therapeutic choice compared to this last non-dominated strategy (in the present case strategy 1).

After considering all efficacious strategies with the help of the strong or weak dominance axioms, the national community should choose one which reflects the maximum amount it is willing to pay per additional unit of effectiveness. One option in the analysis of new drugs is to set as references, the values obtained from prior analysis on drugs already approved. The highest value of the price-efficiency ratio accepted for the adoption of the product for reimbursement measures the supplementary cost that the health insurance bodies have to handle. It indicates the maximum price for which society would be ready to acquire an additional unit of efficacy by another treatment.

Therefore, it is sufficient to compare this threshold value with the marginal cost-effectiveness ratios of the new drugs in order to know if their admission for reimbursement is legitimate or not. As long as the marginal cost-effectiveness ratio is less than this threshold value, the demand is justified. Conversely, when the ratio is greater the demand should be rejected. The objectives of contemporary medicine should not be limited to its impact on clinical outcomes, because the focus is not only on adding life to years, but also adding years to life. In measuring the subjective state of health and its course, it is necessary to introduce an indicator of the quality of life in the analysis.

The simplest way to introduce the concept is to imagine being able to rank order different domains as defined in the World Health Organization definition of health (physical functioning, mental and social well-being), to produce a scale ranging from perfect well-being to death. This approach generally facilitates the understanding of the uni-dimensional nature of the scale but distorts reality because it ranks only isolated problems. In other words, it does not take into account that most problems occur in association. Thus, quality of life should incorporate the multi-dimensional concept of health by taking into consideration, different scenarios or classifying different states of health.

The overall quality of life can be evaluated on a scale from 0 to 1 for each case type. The values of the coefficients are weights that can be used to adjust the quantity of life by its quality. There are five methods of determining the quality of life (QOL) coefficients of which two are direct (rating scales and visual analog scales) and 3 indirect (time trade off, standard gamble, and socially equivalent needs). The product of years (or fractions of years) spent in a given state of health and the corresponding QOL, whatever its manner of calculation, transforms the time spent in bad health into equivalent fractions of years in good health. If the same operation is repeated at the time of different stages of an illness, the number of years of life adjusted for the quality, known as QALY (quality adjusted life years) is obtained. The procedure implies a very particular specification of individual preferences^{16,17,18}. It supposes (a) the independence of longevity and quality, (b) the QOL (quality of life coefficient) is constant over time, and (c) risk neutrality. Under these conditions, the gain in usefulness for a given level of quality of life is proportional to the number of life years that remain to be lived. To decide between alternative treatments, it suffices to estimate the total cost per QALY.

In France, evaluations have been made in terms of cost additional QALY, of Erythropoietin¹⁹, on adjuvant chemotherapy²⁰, on chemonucleolysis after 7 years²¹, and for the treatment of acute myocardial infarction²². In another study, six strategies have been evaluated in terms of cost per life year gained without accounting for the quality of life, and most economic evaluations were limited to evaluating the cost of treatment per "case", per "success" or "failure", or per "hospital stay". They did not permit inter-pathology comparisons. The data published in France are summarized in Table 1.

Table 1 : Summary of marginal and averages cost-effectiveness ratios published in France

Evaluated Strategies	References and year of input of costs	Year of publication	Marg Ratio C/B in F
Net marginal cost per QALY gained*			
Erythropoietin (versus dialysis)	Fagnani (1988) ¹⁹	1990	450 000
Associated chemotherapy (versus abstention)	Livartowski (1989) ²⁰	1992	< 0
Chemionucleolysis (versus disectomy)	Launois (1990) ²¹	1992	< 0
Acute myocardial infarct < 3 hours (versus > 6 hours)	Castiel ** ²²	1990	5 810
Net marginal cost per life year gained *			
Jarvik Symbion (versus enoximon)	CRESGE (1988) ²³	1989	1 700 000
Prostate cancer screening M 60-69 yrs (versus no screening) Prevalence = 11%	Launois (1989) ²⁴	1990	196 691
Medical hypolipemiant treatment	Durand-Zaleski (1992) ²⁵	1992	28 320
SK + asp (versus Rtpa + hep) : delay < 5 hr	Launois (1988) ²⁶⁻²⁷	1990	< 0
Cross average cost per case detected**			
Screening for trisomia 21	Moatti (1987) ²⁸	1990	390 – 180 000
Systematic Wray screening for tuberculosis	Lefaire (1982) ²⁹	1987	178 – 300 000
Screening for AIDS in pregnant women	Le Gales (1987) ³⁰	1990	70 000
Systematic screening for drepanocytosis	Le Gales (1991) ³¹	1993	21 – 44 600
Screening for hemoglobinosis	Le Gales (1986) ³²	1987	10 – 15 000

* Cost difference, introduced by substituting a therapeutic option for another after subtracting the additional cost, which resulted in an economy by avoiding a larger number of treatments, divided by the increase in effectiveness that resulted.

** Quotient of cost and total effectiveness of a screening campaign compared to a reference situation in which nothing would be done (cost of treatments avoided not subtracted).

These results should be interpreted cautiously as the methodologies used were not comparable across studies. The QALYs estimated by Castiel²² used a visual analog scale. Other published studies were more homogenous in their use of the Health Measurement Questionnaire and the Rosser indicator.

The most hererogenous are used in the calculation of costs. In the outpatient (ambulatory) sector, the authors spply the specifically noted professional procedures. On the hospital level, the following 6 methods have been used:

1. The value in terms of function of the price of daily rendered which has been determined by Social Security³³
2. The value in terms of the price ov average daily charges determined in relation to the type of establishment: AP-HP (Public Assistance-Public Hospital), CHR (Regional Hospital), CHG (General Hospital) (LEGOS method)³⁴
3. The PMSI method (Project of medicalization of information systems), either PMSI AP-HP³⁵, or PMSI “Survey on the cost of medical activities”³⁶

4. The value in terms of an “arranged” daily price: I.e. the price of the cost of an hospital stay excluding prescriptions for drugs and for examinations but including the price of a specific examination and treatment individualized per patient (CEDIT-CRESGE method)³⁷⁻³⁸
5. The valorization of direct cost : this includes the medical cost of the number of days of hospitalization, the price of services carried out in other hospital departments (laboratory, radiology), the standard price of high cost services (HCL method)³⁹⁻⁴⁰
6. Approach, a Production Process (UE357 method, PRN)⁴¹⁻⁴²

Approaches 4, 5, 6 are justified only in the comparison of alternatives within the same setting, which is not our goal. Approach 3 is based on the publication of results obtained in 44 voluntary establishments in 1993. Approach 2, which depends on former studies of the CERC, is manifestly obsolete. The use of the daily service fees paid by Social Security (method 1) enables one to calculate a measure that is standard for all kinds of care regardless of where it is rendered.

In the United States of America, similar “league tables” have been published. Although the costs of examinations and hospitalizations in the USA are different from those observed in France, we present the contents in the following table (adapted from Goel) so as to have a rough comparison (Table 2).

Table 2 : Marginal cost-effectiveness ratios published in the U.S.A.

Evaluated Strategies	References and year of input of costs	Marg C/QALY Ratio US\$ year of input	Marg C/QALY Ratio US\$ year in 1992*	Marg C/QALY Ratio** FF 1992
Contrast product, low osmolarity, low risk of undesirable effects	Goel (1986) ⁴³	220 000	368 476	2 413 518
Dialysis in a hospital	Churchill (1980) ⁴⁴	40 200	102 030	668 296
Peritoneal dialysis	Churchill (1980)	35 100	89 086	583 513
Treatment of minor high blood pressure (man 40 yrs Bl. Pr diastol 90-94)	Stason, Weinstein (1976) ⁴⁵ updated 84 ⁴⁶	45 000	80 098	524 644
Intensive care of premature babies 500-999 gr	Boyle (1978) ⁴⁷	19 600	60 290	394 899
Moderate high blood pressure care (M 40 yr, diastol pressure 95-104)	Stason, Weinstein (1976) ⁴⁸	9 880	32 951	215 829
Contrast product, low osmolarity, high risk of undesirable effects	Goel (1986) ⁴³	23 000	38 522	252 319
Severe high blood pressure care (M 40 yr, diast. Pr > 105)	Stason, Weinstein (1976) ⁴⁵	4 850	16 175	105 946
Intensive care infants 1000-1499 gr	Boyle (1978) ⁴⁷	2 800	8 613	56 415
Coronary artery by-pass	Weinstein (1981) ⁴⁸	3 600	8 299	54 358

* Actualized for the 1992 value on the basis of the consumer price index of american city medical care. Source : consumer price indexes for all urban consumers and for urban wage earners and clerical workers US city average US bureau of labor statistics : monthly labour review

** After neutralizing the differences linked to the american and french price system by the Parity Index of buying power of the GPD. 1 US\$ = 6,55 FF. Source : OCDE (communication JP Poullier)

CONCLUSIONS

Since the studies of Drummond, the aforementioned methodology is well specified. The problem is one of gathering data of good quality and interpreting results from empirical studies within a limited time frame. A second problem generalizing the results to the population at large.

At the level of gathering data, either between the approval (AMM) and marketing or after marketing to re-evaluate prices, the use of randomized trials conducted in natural, realistic conditions is the best and the most acceptable method to capture the therapeutic impact likely under normal conditions. Moreover, the indications of the trials should be precise. It is clear that a new drug cannot be defined as good or bad in general, and that it is necessary to specify in which cases it works well and in which cases it performs less well. These will facilitate the management of contracts with the Administration within the frame of the specified indication, and enable the industry to avoid delays by the AMM, or have drug applications limited to restricted indications due to fear of abuse. The real role of the reimbursement-setting authority (Transparence Commission) preceding the marketing of the new drug should be to stratify medical services by establishing a prescription preference system on the basis of ratios of cost-effectiveness of a given drug in its diverse indications. It is the field of these priorities that would be the object of negotiations for limitations or extensions between the industry and the Transparence Commission.

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