International Journal of Technology Assessment in Health Care, **18:2** (2002), 184–191.

HEALTH TECHNOLOGY ASSESSMENT

The Pharmaceutical Industry Perspective

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Abstract

Increasingly, health technology assessment (HTA) is used to aid decisions on the reimbursement of pharmaceuticals or recommendations for their use. The pharmaceutical industry seeks to work in partnership with HTA agencies; however, this presents a number of challenges. Clinical trials will need to include appropriate measures that capture economic and patient benefits as well as relevant clinical endpoints, and the industry will want to seek international harmonization of the many guidelines for economic evaluation. The problem of demonstrating cost-effectiveness of a product before it is available for use must be addressed, possibly by conditional reimbursement to allow collection of real world evidence. It is also important that reimbursement decision makers minimize bias, play fair, and adhere to the written rules they issue. If the industry fairly demonstrates the value of a product using the best available evidence, HTA agencies should be transparent in the rationale for their recommendations.

Keywords: Health technology assessment, Pharmaceutical industry, Economic evaluations

The development of new technologies to improve health and patient well-being presents dilemmas for healthcare decision makers facing the issues of value for money and affordability. To address such issues, many countries now have agencies to assess developments in health care, resolve ethical issues around patient selection for treatment, consider cost-effectiveness of different products, and decide on the allocation of budget for new treatments. Increasingly, pharmaceutical companies are committed to both meeting the needs of patients for better medicines and taking full account of the realities of healthcare economics. The industry seeks to work in partnership with health technology assessment (HTA) agencies, healthcare providers, and governments (3). However, for the long-term benefit of patients, it is important that decision makers also consider the impact of the agencies and their recommendations on the research-based industry, which faces long lead times and huge cost when developing innovative products. This article presents the pharmaceutical industry perspective on HTA and discusses the implications for both the industry and the agencies. It is also important to highlight that this paper addresses health technology *assessment*, rather than appraisal. By assessment, we mean the scientific evaluation of a technology. We define appraisal as using the assessment to judge whether the agency can afford the technology or determine the appropriateness of funding the technology.

Table 1. Movement of HTA's Role in Drug Appraisal from Voluntary to Mandatory

	1997	2000
Mandatory	Australia, Canada (Ontario)	Australia, Canada, United Kingdom, Netherlands, Denmark, Finland, Portugal, Ireland, plus 3 US MCOs (Regence, Blue Cross/Blue Shield, Foundation Health)
Encouraged		France Belgium, Norway, New Zealand
Voluntary	UK, Spain, Italy, France, Belgium, Germany, United States	Spain, Italy, Germany, U.S. Academy of Managed Care Pharmacy
Upcoming		Japan

HTA AROUND THE WORLD

Most developed countries now have a mechanism to evaluate developments in health technology, incorporating economic evaluation. When first introduced, most countries make the health economic assessment voluntary, but over time there is a move toward a mandatory system (Table 1). In addition to their national role, some HTA agencies are also seeking an international role. In the United Kingdom, the National Institute for Clinical Excellence (NICE) is seeking to extend its role to the international arena, claiming that it can serve as a model for similar agencies in other countries (2). In 1999, when NICE made its recommendation on the use of zanamivir for influenza, an immediate and significant impact was apparent throughout the world. Managed care organizations in the United States and HTA agencies in Australia, the Netherlands, France, Scotland, Ireland, Japan, Canada, and Germany all made similar recommendations to that issued by NICE, and in other countries the registration process for zanamivir was adversely affected. Such global impact is likely to increase as NICE becomes more established. In Europe, lack of expertise and a desire to avoid duplication of effort may result in a Euro-INFO type body in the not-too-distant future.

HTA IN PRACTICE

But how well is the HTA process working? HTA has been used in pricing and reimbursement decisions in Australia since 1993. Yet some years later, there are still problems. A review of 326 submissions made to the Australian Pharmaceutical Benefits Scheme found significant problems with 218 (67%), and 31 submissions had more than one problem (1). Of the problems identified, 62% were considered to be due to uncertainty in estimates of comparative clinical efficacy, 29% were due to modeling issues (including clinical assumptions and cost estimates), 5% were due to problems with the choice of comparator, and 2% were due to serious calculation errors (Figure 1). The authors considered that 64% of the problems were avoidable. These problems were identified from the viewpoint of the HTA agency. Yet there is a different view to be seen from the perspective of the pharmaceutical industry. These submissions were compiled with the best evidence available at the time. However, reimbursement agencies prefer head-to-head comparator trials, and the pharmaceutical industry is rarely able to supply these. Therefore, it is not surprising that 62% of the perceived problems identified by the evaluators were due to uncertainty about comparative clinical efficacy. Furthermore, as models are mostly based on placebo-controlled studies and nonclinical trial evidence, it is not surprising that many perceived problems were due to modeling issues.

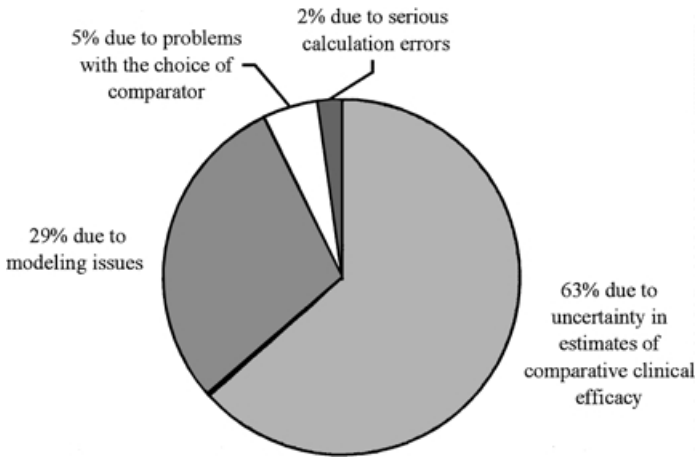

Figure 1. Problems perceived by the HTA agency in submissions to the Australian Pharmaceutical Benefits Scheme (2).

IMPLICATIONS FOR THE PHARMACEUTICAL INDUSTRY

Changes in Clinical Trials

There are indications that the pharmaceutical industry may not be providing the information required by the HTA agencies. There is a clear implication for the pharmaceutical industry—clinical trials must adapt to show value for money. Sir Michael Rawlins, chairman of NICE, has acknowledged that trials to demonstrate value for money would be more costly (4). This view was confirmed by Dr. Yamada, R&D chairman of GlaxoSmithKline, who noted that the cost of developing drugs for the marketplace has become even higher because of the need to show economic value and positive outcomes of new drugs, rather than the previous requirement only to demonstrate efficacy against disease. This presents the pharmaceutical industry with a number of challenges.

The traditional research and development departments need to involve specialists in health outcomes at an early stage in product development. A strategy for reimbursement is required when a product enters clinical development, in order to ensure that appropriate clinical trials are planned. For example, comparator trials may need to be considered earlier in clinical development. The duration of clinical trials may also need to be reconsidered—ending the study at the time appropriate for achievement of a therapeutic result may not give sufficient time to collect data relating to the economic benefit of such an outcome. Consequently, trials may need to be prolonged over the time normally taken to collect data for registration purposes.

There may also be a need to collect data relating to different endpoints—clinical measures appropriate for registration may not capture all the benefits of a treatment that are required for a full economic evaluation. Involvement of health outcomes specialists early in product development allows modeling to identify key endpoints and surrogate markers that most closely predict final outcomes of treatment. Modeling can also reveal patient populations most likely to benefit from treatment, so that sufficient numbers of such patients can be recruited into trials to provide appropriate data. To minimize delay between obtaining registration and achieving reimbursement, the phase IIIB program (designed to fulfill postregistration needs) should start soon after commencement of the phase IIIA program (targeted at registration).

Harmonization of Guidelines

In the modern world, pharmaceutical trials are costly affairs that recruit patients from many countries. The International Conference on Harmonization ensured that the major markets (Europe, the United States, and Japan) agreed on a common standard of data required for clinical registration (e.g., duration of toxicity trials). This common set of standards does not extend to economic evaluation methodologies. If the pharmaceutical industry accepts the need to increase the scope of clinical trials to collect the information required for health technology assessment, which guidelines are to be followed? There is a plethora of guidelines (Table 2). Although there are some common criteria, there are also significant differences in the details required to meet the needs of HTA agencies in different countries (Table 3). How can the large-scale trials required for evaluation of new treatments simultaneously meet all of these criteria? The way forward must be to seek harmonization of current guidelines, although it is important to standardize methodologies without stifling innovation in the evaluative techniques used.

Randomized Clinical Trials Versus Evidence-based Medicine

It is also important for the pharmaceutical industry to work with the agencies to manage expectations about clinical trials, explaining what can be measured in practice and the difficulties that may be encountered. Even with the desire to work in partnership and provide the information required by the HTA agencies, the real constraints of carrying out clinical trials may prevent pharmaceutical companies from fulfilling this aim. One major constraint is the limited ability of pharmaceutical companies to demonstrate true cost-effectiveness of a product before it is available for use. Perhaps the way forward is conditional reimbursement or listing based on cost-effectiveness modeling, with physicians initially able to use the new product. During the following 2 years or so of prescribing, data could be collected to see if the product was actually cost-effective in practice. This approach also recognizes the value of evidence-based medicine in reflecting real world practices, compared with the artificially controlled world of clinical trials. In randomized clinical trials, the comparator is most commonly placebo. Yet we have already seen that decision makers need the comparison with usual treatment in a naturalistic setting. Economic evaluations made after launch of a product would allow this need to be met. While the industry recognizes the political and ethical concerns that agencies may have with this approach, further dialogue should allow development of a practical solution.

Use Measures that are Relevant to Patients

The aim of any intervention in health care is to improve patient well-being. It is important, therefore, to ensure that economic evaluations are based on measures reflecting outcomes of relevance to patients. A simplistic assessment based on easy-to-measure clinical criteria, such as a change in the peak expiratory flow rate following treatment for a respiratory condition, may fail to capture the true benefit to the patient, in this case the ability to perform everyday activities. Approaches such as measurement of quality of life, patient satisfaction, and willingness to pay for alternative treatments should be given sufficient weight in any appraisal of a new intervention.

Appropriate Treatment Guidelines

There is an increasing trend toward evidence-based medicine, with the development of treatment guidelines reinforcing good clinical practice. With the increasing importance of economic evaluation in governing market access, treatment guidelines should also encompass these issues. Encouraging the use of cost-effective medicines must surely be of value

Table 2. A Plethora of Guidelines for Economic Evaluation Affect Pharmaceutical Companies

	Societal perspective	Flexibility in cost-effectiveness technique	Comparator	Incremental analysis	Role for non-randomized clinical trial data	Outcomes	Direct costs	Indirect costs	Discount cost and benefit at 5%	Sensitivity analysis
Australia	Yes	No	1	Yes	Yes	Intermediate and/or final outcomes	Yes	No	Yes	Yes
Canada	Yes	Some	2	Yes	Yes	QALYs	Yes	Yes	Yes	Yes
The Netherlands	Yes	No	1	Yes	Yes	Survival, QoL, QALYs	Yes	Friction cost	No, 4%	Yes
US PhRMA	Justify perspective	Yes	Various	Yes	Yes	Intermediate and/or final outcomes	Yes	Yes	Cost only; rate not specified	Yes
US Gold Panel	Yes	Yes	2	Yes	Yes	QALYs	Yes	Yes	No, 3%	Yes
France	Justify perspective	Yes	1	Yes	Some role	Final endpoints preferred	Yes	Yes	Cost only 2.5% or 5%	Yes
Italy	Third-party payer	Yes	>1	Yes	No	Survival, QoL	Some	No	Yes	Yes
Germany	Justify perspective	Yes	>1	Yes	Yes	Final endpoints and QoL	Yes	Yes	Yes	Yes
Spain	Yes	No	>1	Yes	No	Intermediate and/or final outcomes	Yes	Yes	No, 6%	Yes and additional analyses
Portugal	Yes	Yes	2 2	Yes	Yes	Intermediate and/or final outcomes	Yes	Yes	Yes	Yes
Denmark	Yes	Yes	Not specified	Not specified	Yes	Intermediate and/or final outcomes	Yes	Yes	Rate not specified	Yes
Belgium	Yes	Yes	Various	Yes	Yes	QALYs and QoL	Yes	Yes	Yes	Yes

Abbreviations: QALY = quality-adjusted life-year; QoL = quality of life.

Table 3. Comparison of Criteria Used for Economic Evaluation

Issue	Percent agreement
Societal perspective	≈100%
Incremental analysis	100%
Direct costs	100%
Sensitivity analysis	100%
Inclusion of indirect costs	80%
Flexibility in cost-effectiveness technique	75%
Role for nonrandomized clinical trial data	75%
Discounting cost and benefit at 5%	50%
Outcomes	40%
Comparator	30%

to society, and favorable positioning in treatment guidelines provides the pharmaceutical industry with an appropriate incentive for the development of products that deliver value for money. Pharmaceutical companies should work with opinion leaders to ensure that economic evaluations are considered when positioning medicines in treatment guidelines.

Internal Collaboration

Close collaboration is required between departments within the company. There needs to be agreement on the wording in data sheets to meet the needs of agencies responsible for registration and those responsible for reimbursement. For example, a low dose of a product may be the most likely to be used in clinical practice, even if the data sheet acknowledges the possibility of a higher dose in certain circumstances. If agencies assessing the economic value of the product use the higher dose in evaluations, the result may give an unnecessarily pessimistic view of cost-effectiveness. Likewise, registration documentation encourages the listing of all observed or potential adverse events, even if they are extremely rare. These adverse events may incur monitoring costs that reimbursement decision makers will consider when assessing the product's cost-effectiveness. For departments dealing with the financial markets, the announcement of a potential blockbuster may be good for the share price but may cause undue concern among decision makers responsible for healthcare budgets. In all cases, a balanced picture is required that presents all relevant information without distortion to meet the particular needs of any one agency or interested party.

IMPLICATIONS FOR HTA AGENCIES

Minimize Bias

There is always the potential for bias in any study, most commonly favoring the outcome preferred by the organization paying for the research. Currently, decision makers may be wary of cost-effectiveness data or economic modeling presented by the pharmaceutical industry in support of new products. They may believe that the information presented is unrealistic when it shows the product in a good light. Yet there may be lack of awareness among decision makers of the number of similar products investigated during the development process that are discarded due to failure to reach standards of clinical outcomes likely to justify claims of cost-effectiveness. Thus, the industry will have already decided against investment in products that may not reach the exacting standards expected by HTA agencies, choosing only to present those that may have a justifiable claim to giving value for money in the improvement of health. Consequently, while it is entirely appropriate that HTA agencies critically evaluate all information presented, bias against information from the pharmaceutical industry should not be condoned.

HTA agencies readily accuse the pharmaceutical industry of bias and presenting an overly positive view of a treatment. However, there is little recognition that bias may occur in appraisals or studies carried out on behalf of agencies resulting in an overly negative view of the treatment. Such bias may occur because these agencies are operating an implicit agenda to ration use of the public purse on improvements in health care. Such agencies should aim to minimize bias in all studies and reviews, in order to arrive at fair judgments and maintain the respect of all parties involved in the provision of cost-effective health care. It is important to minimize bias by using a clear and transparent framework of acceptable measures and outcomes—in much the same way as the outcomes of clinical studies are accepted, provided that the trial is conducted using a rigorous design and analyzed using approved statistical methods.

Play Fair and Adhere to the Written Rules

Where guidelines exist for economic evaluation of a product, HTA agencies should adhere to the written rules. It is unreasonable to expect the pharmaceutical industry to jump through hoops to demonstrate cost-effectiveness or budget impact, under the guise of a fair appraisal, if the decision against the product has, in effect, been taken irrespective of the information presented. Industry concerns about fairness could be allayed with increased transparency of the judgments given by HTA agencies. It would, however, be important to the industry to maintain confidentiality of such judgments.

Politics and Policies

The involvement of politics may hamper the fair appraisal of products by HTA agencies. Politicians may leak confidential initial findings from the agencies for their own purposes, before any issues raised therein can be addressed by the company concerned. Taking into account the widespread influence of the agencies, this is clearly unsatisfactory. There should also be some consistency between public health and public finances. If the public health policy states the importance of improving the management of a specific disease, public finances should be made available for treatments able to demonstrate value for money and acceptable budget impact.

Partnership with Industry

The common aims of the pharmaceutical industry and HTA agencies should be recognized. The industry seeks to provide medicines of value, meeting the needs of patients for better medicines at a price that healthcare systems can sustain. Likewise, those responsible for public health and the allocation of public finances seek to improve the health status of patients within a budget that the country can afford. It is not in the interest of the industry to cripple the healthcare budget and national economy any more than it is in the interest of governments and reimbursement agencies to limit improvement in health of their citizens. Consequently, the needs of both parties should be recognized in the development and application of guidelines for economic evaluation of healthcare interventions. This is already the case in some countries to varying degrees, notably Canada, Australia, the United Kingdom, and France.

CONCLUSION

The research-based pharmaceutical industry accepts the need to take full account of the realities of healthcare economics, encompassing the issues of value for money and affordability of treatments. The industry is willing to adapt to meet the requirements of the agencies involved in assessment of health technologies. However, it should be recognized that the processes involved in the development of new products are time-consuming and

costly, and providing appropriate information for economic evaluation will only increase the pressures on sales to sustain further research and development. Therefore, if the industry fairly demonstrates the value of a product, HTA agencies should respond fairly with appropriate recommendations.

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