Cost-effectiveness - the fourth hurdle to market entry

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The practice of medicine has traditionally offered wide scope and considerable discretion to physicians. The decisions about what treatments best meet the clinical needs of a patient have generally been left to the patient's physician. Manufacturers of medical products including medicines, biologics and medical devices could market these products to physicians, who could use them in their own practice if they valued them.

Government regulation on whether manufacturers should be authorised to market a product has focused on:

- Safety concerns.
- The need for assessment of the public health implications by persons independent of those with a commercial interest in the development of the product.

Such regulation came about first for medicines, and more recently for devices. While these regulatory schemes differ from country to country, the basic characteristics are the same. Manufacturers must obtain marketing authorisation from the regulatory authorities. Approval requires the applicant to demonstrate quality, and a favourable balance between efficacy and safety.

A more recent development has been the increasing intervention by the state, or other third party payers who seek to control ever-rising costs by adopting measures that:

- Directly or indirectly control supply.
- Influence the prescribing habits of physicians.

The budgets of third party payers have come under the substantial twin pressures of:

- Changing demographics.
- Major advances in scientific and medical knowledge, which have improved existing treatments and have made new conditions treatable (the cost of advances in treatment is often very significant).

However, the measures now taken by third party payers act as an additional barrier to the successful marketing of new technology. The trend has been most notable in Europe but is also a growing issue in the US.

In Europe, the response of governments to cost pressures has varied from the imposition of arbitrarily-timed price reductions for all relevant products, to encouraging greater appreciation of cost-benefit issues by prescribers.

On a longer term basis, however, governments are seeking to erect additional barriers to market entry. They are doing this by encouraging the provision of comparative data as part of the normal regulatory process. They are then coupling this, separate from the regulatory process, with the increasingly formal application of a criterion of cost-effectiveness. This occurs through establishing a reimbursement price, or through influencing the ability of physicians to prescribe certain products under national health insurance schemes.

In the US, private insurers and government programmes have sometimes shown similar tendencies. Mounting healthcare costs have led to ever-increasing scrutiny of the value of new technology. The largest single healthcare payer in the US is the federal Medicare programme, which is administered by the Centers for Medicare and Medicaid Services (CMS). The recent legislative change to that programme, which added a broad prescription drug benefit, also added mechanisms designed to minimise the new benefit's cost. This is estimated to exceed US$400 billion (about EUR328.3 billion) over ten years.

In contrast to the relatively-harmonised and well-understood criteria for regulatory approval, even defining a cost-effectiveness criterion has many difficulties. This is particularly so where it overlaps with the wider question of whether state schemes or other third party payers can afford the product, regardless of its effectiveness. Lack of transparency in decision making and the absence of effective appeal mechanisms have added to the difficulties for manufacturers. Again, this compares unfavourably with the regulatory environment with which companies are familiar.

The agency within the US government responsible for measuring health quality, the Agency for Healthcare Quality and Research (AHRQ), has generally been reluctant to engage in cost-effectiveness determinations, for political reasons. The new Medicare drug law, however, specifically empowers AHRQ to begin cost-effectiveness research, subject to certain safeguards. Under the Medicare Prescription Drug, Improvement, and Modernisation Act 2003 (*section 1013, Pub. Law 108-173*) in carrying out this research, AHRQ may not:

- Mandate national standards of clinical practice or quality health standards.
- Mandate a national standard or require a specific approach to quality measurement and reporting.
- Use data obtained to withhold coverage of a prescription drug.

Other agencies have expressed an interest in evaluating new types of data that take into account comparative performance and price. There is total agreement from industry, however, that the Food and Drug Administration (FDA) is not the appropriate agency to consider the pricing of drugs and devices. Other stakeholders have expressed the same view.

There are now pressures in Europe to combine the two assessment processes. This would make cost-effectiveness, when compared to existing therapies, a fourth hurdle in obtaining a regulatory approval to market. Accordingly, after 40 years of regulation (which was largely predictable in terms of the scope and criteria for marketing), the pharmaceutical industry is now facing major changes to the processes relating to obtaining a marketing authorisation. The trend is towards the performance of studies with active comparators, and the collection of detailed pharmaco-economic data. From then on, unless the manufacturer can demonstrate cost-effectiveness, obtaining an authorisation to market will not equate to a practical ability to market.

The long-term cost implications should be obvious. It is paradoxical that while these trends are driven by budgetary concerns, the development of reliable cost-effectiveness data (for pre-marketing approval and for post-marketing re-appraisal) will increase significantly the cost of developing all products. This is at a time when other initiatives, to regulate further and harmonise the requirements relating to clinical research, are already hugely increasing research costs. As ever, the price of products that successfully overcome the regulatory and other hurdles will have to bear the sunk-costs of those products that fall at one of the hurdles to successful marketing.

The point was robustly made by Tom McKillop, the chief executive officer of AstraZeneca, at the company's November 2002 business review meeting. He is reported to have emphasised, in the context of initiatives proposed in relation to the Medicare drug benefit in the US, that the increased data collection required to inform cost-effectiveness analysis will lengthen considerably the time taken to complete pre-marketing clinical trials. This is so, even though the usefulness of the data will be limited. It will be limited by difficulties in extrapolating it from the closely monitored framework of a trial, to wider clinical practice.

He concluded that "if we ask for more and more evidence, before approval, of economic benefit … it is going to dramatically increase the costs to provide that information, and that can only be justified by higher prices once you get there. So there will not be economic savings from doing that" (*see "Rx Cost-Effectiveness Data Requirement Would Raise Prices-AstraZeneca," The Pink Sheet (Nov. 18, 2002)*).

However, the trend seems irreversible, in Europe at least. Scrip Reports note (*Scrip Reports: Pharmaceutical Pricing and Reimbursement in Europe; May 2002 PJB Publications Ltd*) that one of the most important trends of the last two years in the development of pricing and reimbursement rules in Europe has been the need to prove the value of pharmaceuticals supplied. This trend shows itself "by the introduction of cost-effectiveness as a mandatory criterion for obtaining reimbursement in several EU countries, forcing the remainder, including Eastern Europe candidate countries, to do the same" (*see Scrip Reports as above at page 15*). The significance in the UK of the establishment of the National Institute for Clinical Excellence (NICE), to make judgments on clinical and cost-effectiveness, is said to have had an impact in Europe on policy-makers and in the business communities well beyond original expectations.

While the US healthcare system is considerably more diverse (in that there are a wide variety of third party payers for healthcare), the pressures are the same. Medicare has a dominant role in determining healthcare policy, and influences private health insurance plans. Medicare recently proposed using cost-effectiveness criteria, but encountered vocal opposition and abandoned the proposal. However, former CMS administrator Thomas Scully said after leaving that agency that while Medicare lacks the explicit authority to set price, national coverage decisions are a way to affect the pricing of items and services covered by Medicare (*see "Zevalin Price Negotiations Will Be Model For Medicare Part B, Scully Says," The Pink Sheet (Jan. 19, 2004) at page 5*).

Consistent with this view, in 2003 several new and relatively-expensive cancer therapies were granted coverage under Medicare only after proposed market prices were reduced. CMS took a similar approach that same year, when it considered whether to cover a new immunologic test that serves as a screen for colon cancer by detecting fecal occult blood. CMS decided to cover the new test but only at a price that the agency decided represented the added value of the new test, over existing technology (*see CMS, "National Coverage Determination for Fecal Occult Blood" (40-23); "Decision Memo for Screening Immunoassay Fecal-Occult Blood Test" (CAG-00180N*).

Such unauthorised and non-transparent use of cost-effectiveness assessments in coverage decisions presents challenges for providers of new technologies. More importantly, it could jeopardise the availability of potentially-useful therapies to Medicare beneficiaries and, to the extent these policies are followed by private payers, all Americans.

The risk that patients will be denied access to important new treatments in the US will increase if CMS takes a narrow view of cost-effectiveness that focuses on cost and fails to account adequately for the potential benefits of new technologies. These have often reduced costly inpatient care, as well as produced other quantifiable benefits from improved health and productivity. For example, a recent study released by The Value Group (a coalition of seven leading US healthcare organisations) found that over the past 20 years each $US1 (about EUR0.82) invested in healthcare services produces US$2.40 (about EUR1.96) to US$3.00 (about EUR2.46) in tangible gains to healthcare (*see The Value Group, "The Value of Investment in Healthcare" (28 January 2004)*).

A 1996 report entitled *"The Effect of Pharmaceutical Utilisation and Innovation on Hospitalisation and Mortality," National Bureau of Economic Research Working Paper No. 5418 (Frank Lichtenberg, January 1996)* also found that:

- A US$1 (about EUR0.82) increase in pharmaceutical expenditures was associated with a US$3.65 (about EUR3) reduction in hospital care expenditures.

- A US$1.54 (about EUR1.26) increase in expenditures on physicians' services resulted in a net cost saving of US$1.11 (about EUR0.91).

Against this background, this article examines:

- Cost-effectiveness in practice.
- The activities of NICE and other bodies in the UK.
- The transparency of decision making.
- Cost-effectiveness in the US (Medicare).

COST-EFFECTIVENESS IN PRACTICE

In addition to the three traditional hurdles to market entry of safety, efficacy and quality, the increased intervention by third party payers is progressively creating a fourth hurdle. Despite the terminology used, the fourth hurdle can most accurately be described as requiring a demonstration of cost-effectiveness. While some programmes explicitly consider the cost-effectiveness of new products, others (under the mantle of evidence-based medicine) consider various facets of effectiveness, and the risk-to-benefit ratio.

What has become clear is that even so-called "evidence-based" approaches, which claim to be insensitive to costs, apply the effectiveness standard with an implied cost factor. Examples of third party payer decisions, made with and without explicit consideration of cost, end with strikingly similar policies. The absence of an explicit cost-effectiveness consideration leads to a variable application of evidence. This means that products that are high-volume or high-cost (or both) need to meet a much higher standard.

Although the schemes differ from country to country (depending on whether the third party scheme is government or private, and whether or not it is a single payer or multiple payers), the determination that a new medicine, device or biologic is not cost-effective or medically necessary can effectively exclude it from the marketplace. This can occur well before the ideal data would become available to establish its therapeutic value in general clinical practice. In Europe, relatively few products survive on the basis of private prescription, in a market dominated by national health insurance or social security schemes.

United States

The US Medicare programme by law considers whether a new product is reasonable and necessary. Decisions about what products and services are covered have never been made with explicit criteria. Proposals to adopt explicit criteria were abandoned as too controversial, mainly because they would have permitted consideration of cost-effectiveness in some circumstances.

Despite this, the Medicare programme has developed a process by which national coverage decisions are made (*Health Care Financing Administration, "Procedures for Making National Coverage Decisions," 64 Fed. Reg. 22,619 (27 April 1999)*). These decisions affect all Medicare beneficiaries, and may also influence private insurance plans. The national coverage process relies on the evaluation of scientific evidence, and can rely on outside technology assessments and the opinion of a Medicare Coverage Advisory Committee (MCAC).

Despite the fact that Medicare has no authority to take cost-effectiveness considerations into account when determining coverage, the recent effort to limit the financial impact of covering implantable cardiac defibrillators (ICDs) (despite increasing evidence that these devices are beneficial for large numbers of patients) indicates otherwise. This suggests CMS is now improperly weighing concerns about overall programme cost against objective scientific evidence as to the safety and efficacy of a technology.

In addition, in the preamble to a 2002 Medicare regulation governing hospital outpatient services, CMS stated that it may initiate national coverage decisions regarding FDA-approved new drugs for a number of reasons, such as determinations that a drug is "novel, complex or controversial", or it is "costly to the Medicare programme" (*see CMS, "Medicare Programme; Changes to the Hospital Outpatient Prospective Payment System and Calendar Year 2003 Payment Rates; and Changes to Payment Suspension for Unfiled Cost Reports," 67 Fed. Reg. 66,718, 66,756 (1 November 2002*).

EU

In the EU:

- Pharmaco-economic analysis is now used either to determine the reimbursement price or provide prescribing advice to doctors in Denmark, the Netherlands, Ireland, Finland, Sweden and Portugal. Less formal use of such analysis occurs in France and for certain types of product in Italy.
- Sweden has established an independent committee to assess each product's therapeutic value in terms of cost-effectiveness (compared with other products in the same class) and Germany is considering a similar initiative, alongside a recent extension of its reference pricing system.
- Ireland has begun to use pharmaco-economic data in reimbursement negotiations.
- Greece has published health economic guidelines and may now request cost-effectiveness data.
- Hungary and Poland (who formed part of the recent enlargement of the EU) are developing pharmaco-economic guidelines.

UK

To date, the most concerted attempt to develop mechanisms for a highly consultative and sophisticated appraisal of the cost-effectiveness of medicines has occured in the UK. Here, over 95% of medicinal products and devices are supplied to the National Health Service (NHS). The service is supervised by the Secretary of State for Health (Health Secretary) and various health authorities established as his agents. Indeed, developments in the UK illustrate:

- The changing history of reimbursement in the last 15 years.

- The limited extent to which the courts have intervened to protect rights asserted by patients or manufacturers.

The establishment of the NHS in the 1940s was based on the vision that citizens should get the best medical and other care available, where real clinical need was the only criterion (not their ability to pay or any other factor). Those principles were repeated as late as 1995 in the Department of Health's Patients' Charter, and are also relevant in the context of the European Social Chapter (*see Article 13, 1996 European Social Chapter*).

Despite the obvious change in the demographic and scientific environment, the current UK government came to power on a manifesto that repeated the principle that access to the best treatment would be based solely on need, and "not on your ability to pay or...where you live". The reference to the residence of patients is significant. It arose out of the developing problem in the 1990s of particular health authorities deciding, for budgetary reasons, no longer to fund certain treatments (notably the more innovative but expensive medicines used in hospitals by consultants).

The Health Secretary's duty is declared by the relevant legislation to be limited to providing services "to such extent as he considers necessary to meet all reasonable requirements" (*section 3, NHS Act 1997).* However, the Statutory Terms of Service under which health authorities obtained the services of physicians created a different principle. This was that patients were entitled to receive whatever medical services their doctor, in his clinical judgment, considered necessary.

In 1985 the first real change in the system occurred. Parliamentary processes were established for the creation and revision of the so-called blacklist. This comprises the names of products that cannot be prescribed at NHS expense. This is normally on the basis that the clinical need could be met less expensively by other products. Setting aside the products more properly treated as food supplements, the list basically comprised branded products in seven therapeutic categories where a generic was available. The list was expanded in 1992, to cover a further ten therapeutic categories as part of further cost control measures.

However, in early 1999 additional terms of reference for reimbursement decisions were published. They allowed the Health Secretary a much wider discretion to black-list products in circumstances "where the forecast aggregate cost to the NHS of allowing the product (or category of products) to be supplied on NHS prescription, or to be supplied more widely than the permitted exceptions, could not be justified having regard to all the relevant circumstances including in particular … the priorities for expenditure of NHS resources" (*see Written Answers: Hansard 28 June 1999*). Put simply, this allowed exclusions based on factors such as an assessment of cost-effectiveness, or affordability in the wider sense. The cost of patented versus generics products was no longer the only focus. Cost-effectiveness or affordability was now the issue.

However, in relation to applying cost-effectiveness criteria, the government has been disinclined to operate the lengthy statutory procedure for blacklisting products. Instead it has preferred to formalise the arrangements for the provision of recommendations to health authorities on the take-up of new medicines and medicinal devices. The vehicle for doing this was the establishment, in February 1999, of NICE to provide determinations as to the clinical and cost-effectiveness of new technologies.

While continuing to maintain that such recommendations would not replace or override the exercise of clinical judgment in the individual case, the reality is very different. Directions from the Health Secretary now require the relevant authorities to implement NICE determinations, although in parallel the government requires authorities to balance their budgets. Accordingly:

- Positive assessments by NICE currently do not necessarily lead to uniform-funding of the treatments concerned (the Chairman of NICE describes implementation as "very patchy").

- Negative appraisals mean that a medicine will not be stocked in the hospital pharmacy, and prescription of it is in fact extremely difficult.

Importantly, where a new product gains a marketing authorisation, if it is expensive and is scheduled for appraisal by NICE, some health authorities will make no decision on funding its use at all, until the recommendations of NICE are available. NICE "blight" has already become part of the language of pharmaceutical companies.

ACTIVITIES OF NICE AND OTHER UK BODIES

NICE was created as a special health authority "to provide authoritative and reliable guidance on healthcare" (*see generally, NICE: Guide to the Technology Appraisal Process May 2004*). Its functions include:

- The appraisal of health technologies notified by the Health Secretary.

- The development of more general guidelines in relation to particular medical conditions or forms of treatment.

In each case, NICE's recommendations focus on whether the product or therapy can be recommended "as a cost-effective use of NHS resources". This is either generally, or for specific indications, or for defined patient groups and whether as first-line or second-line treatment. Although NICE's determinations are directly applicable only to England and Wales, its analyses are published on its website. They are therefore influential and of interest outside the UK. Dr Philip Brown has stated that "NICE is changing the clinical, political and regulatory landscape around the world" (*Scrip, PJB Publications, 14 January 2004, Number 2917 at page 7*).

In carrying out health technology appraisals, NICE is required to take into account certain factors including:

- The degree of clinical need of patients to whom the intervention is directed.

- The broad balance of benefits and costs.

- The effective use of available resources.

- Any guidance of the Health Secretary on the resources likely to be available.
- The government's healthcare priorities.

It is said that NICE will be "sympathetic" to the longer-term interest of the NHS in encouraging innovations, but only if they are "of good value to patients".

The aim is now to ensure that referral of products for appraisal takes place early enough for recommendations to be available at the time of the product's launch (or shortly afterwards). However, unless the product has been widely available in other markets before authorisation in the UK, this essentially means that the appraisal occurs on the basis of the data developed to obtain the marketing authorisation. A normal timetable for appraisal presupposes that the relevant indications are known well in advance of authorisation. However where, in fact, they are contentious, this can present appraisal problems.

There is currently no statutory obligation to submit data, but few companies would wish an appraisal to proceed without their involvement. Data submitted are assessed against the following three criteria:

- Clinical effectiveness.
- Cost-effectiveness.
- The wider NHS implications of the product's affordability.

Data submitted by companies and other stakeholders, such as patient groups and professional bodies, is the subject of evaluation by NICE's Appraisal Committee, advised by invited experts. NICE, in fact, sub-contracts out to various university-based units most of the initial work of evaluation. In each appraisal the relevant Unit's Assessment Report is provided to stakeholders for comment, before the Appraisal Committee prepares a preliminary determination.

A so-called Appraisal Consultation Document containing the draft recommendation is then the subject of further consultation. It is also published, to enable consideration beyond the immediate stakeholders, before a draft Final Determination is prepared. This is also published, although only stakeholders may appeal its contents before it is finalised and issued as guidance to the NHS. The appeal criteria are procedural (including transparency) but do not include a reassessment of the merits by themselves.

From the outset NICE emphasised that its highest priority was to gain credibility for its determinations by:

- The quality of its scientific work.
- Being as transparent as possible.

Very many innovative products have fared well, but the processes have been the subject of much criticism and some amendment. In July 2002, the Health Committee of the House of Commons (the Committee) published a report on its review of NICE's work. While commending the progress made in a relatively short period, the Committee indicated a significant level of dissatisfaction with the whole process. Many of the observations illustrate well the difficulties this type of appraisal causes. This is despite the good intentions of the groups with the difficult task of implementing such initiatives.

Clinical effectiveness as a criterion

NICE's guidance states that this criterion encompasses "actual projected benefits". This might include "reductions in morbidity or mortality, improved quality of life or other measures of positive outcome". Particular attention is to be given to the times at which clinical outcomes are assessed. It is often said that clinical effectiveness differs from clinical efficacy. This is because it incorporates the notion of how a product will be prescribed and the benefits that it will provide in general clinical practice, rather than in the highly constrained framework of a clinical trial protocol.

While manufacturers were requested to provide quantitative comparisons with other forms of treatment, the regulatory focus on placebo-controlled clinical trials meant that data comparing the new product with current standard therapy directly was rarely available. Comparisons based on published literature were suggested as an alternative and, in relation to end points used in trials (in particular, quality of life), companies were asked to model the data so as to be relevant to UK conditions. Such modelling has many difficulties, and is rarely very satisfactory.

NICE itself reported to the Committee that the evidence-base available for appraisal of clinical effectiveness was often very limited, and amounted to little more than that available for licensing purposes. Such shortcomings will be emphasised the earlier the appraisal takes place before launch. It is generally appreciated that hard data takes decades to collate, and with it the ability accurately to assess the full value of treatment.

This is particularly so in relation to the treatment of chronic illness, where surrogate end points often have to be used. By its very nature, long-term survival data for new cancer treatments will initially be lacking. Fundamental issues arose in the appraisal of beta-interferons for multiple sclerosis. In particular, whether available data could reasonably be extrapolated for a ten-year, 20-year or longer period. Both the companies and NICE necessarily had to retreat into modelling techniques, which the Committee noted were "at best an imperfect science".

The Committee recognised that this highlighted the need for a rolling-programme of reappraisal, as data accumulates. In the light of the currently available data, many appraisals of clinical effectiveness can be characterised as second-guessing the assessment of efficacy, by the regulatory authorities themselves. This is legally a very questionable exercise. The Committee recognised the potential for duplication, and called for greater collaboration between NICE and the regulatory authorities.

Cost-effectiveness

Guidance from NICE has endorsed the general approaches of cost minimisation, cost utility, cost benefit and cost-effectiveness. Both direct and indirect NHS costs (at primary and secondary care level), and personal social service costs associated with the condition being considered, are said to be relevant. However,

although wider costs and benefits may be presented, the extent to which they are considered is unclear. Manufacturers are required to present the discrete costs to the NHS separately.

The nature of the costs that can properly be included has often been contentious in appraisals. The Committee has recommended that the wider social costs and benefits to public funds of reduced benefit dependence and improved ability to work (both for patients and their carers) are taken into account. As with data on clinical effectiveness, there are currently significant limitations to the available data.

Where pharmaco-economic data is not available for particular interventions, it is not clear that NICE has been consistent in its conclusions. In some cases, the absence of cost-effectiveness data has not been decisive and in others, it has significantly qualified the recommendations for use. Companies are, however, increasingly going to be under pressure to offer price reductions, so as to meet cost-effectiveness hurdles and secure a favourable determination from NICE.

Affordability

Particularly controversial has been the issue of cost-effectiveness thresholds. This is because they inevitably involve an implicit assessment of affordability. The government has sought to allay fears that affordability decisions (which are properly the responsibility of Parliament) were being delegated to physicians and pharmaco-economists. However, the issue is confused by the very fact that NICE is directed to consider the "effective use of available resources".

NICE has used the cost per Quality Adjusted Life Year (QALY) method of analysis in many of its assessments. NICE has strongly asserted that there is no threshold value above which reimbursement will not be recommended. However, it is clear that persuading NICE to recommend a therapy with a QALY value of more than GB£30,000 (about US$54,945) is a difficult task, and NICE officials have acknowledged this. The origin of the figure is obscure. It seems that any intervention with a QALY value of above GB£30,000 (about US$54,945) will only receive a positive recommendation from NICE where there are "special factors" (such as extreme clinical need). However, some commentators feel the fact that the impact of making the product freely-prescribable may be limited (by a relatively small patient population) also seems to be a relevant factor.

The uncertainties for pharmaceutical companies have been added to by the fact that, following the creation of NICE, the devolved governments in Scotland and Wales have established their own health technology appraisal bodies.

Scotland

In Scotland, functions similar to those of NICE are exercised by the following two bodies:

- NHS Quality Improvement Scotland (NHSQIS).
- The Scottish Medicines Consortium (SMC).

NHSQIS has been established as a Special Health Board within NHS Scotland, with responsibility for carrying out detailed appraisals. These are similar to those undertaken by NICE, based on clinical and cost effectiveness. However relatively few appraisals have yet been completed. In addition, NHSQIS reviews NICE guidance, and advises NHS Scotland on its suitability for Scotland, based on local conditions. In general, NICE guidance is accepted for Scotland without alteration.

SMC is also part of NHS Scotland, and makes recommendations on all newly-licenced medicines, all new formulations of existing medicines, and any major new indications for established products, shortly after their launch.

SMC has formed a New Drugs Committee (NDC), which carries out a rapid assessment of the costs and benefits of all medicines. Its recommendations are then considered by SMC. There is a possible appeal against this on grounds of process or merits, if new data is available. While manufacturers and patient groups may take part in the process, there is no opportunity for professional bodies to contribute, except through clinicians who are part of NDC or SMC.

The process requires a submission by manufacturers before the launch of the product, including effectiveness data and pharmaco-economic assessments. Provision of such data is generally problematic before marketing. The resulting assessment by the NDC is based on preliminary data, and is often superficial. As a result, SMC's recommendations are often criticised. Some manufacturers have declined to co-operate with the process, by not submitting a new product form. This is because, while the assessment by SMC is flawed, the resulting recommendations may be influential not only in Scotland, but elsewhere. In these circumstances, SMC has issued negative recommendations without further consideration. Nevertheless, some companies take the view that a negative recommendation on procedural grounds is preferable to a flawed assessment. This would probably also produce a negative result.

While SMC's recommendations are not binding on clinicians, NHS Boards are advised that, normally, no new products should be used in their areas before receipt of SMC recommendations. Doctors are told that SMC's advice should be taken into account (unless there is evidence to justify not doing so in the light of the particular circumstances of an individual patient).

A Health Department letter, issued by the Scottish Executive on 25 November 2003, stated that unique drugs for specific conditions would, if approved by SMC, be introduced into NHS Scotland to an agreed national programme, normally within three months. However, where alternative drug treatments already exist, even if a new product is approved by SMC, the implementation of the recommendations will be subject to local NHS Board decisions. SMC's recommendations are superseded by guidance issued on the same interventions by NHSQIS, including their endorsement of NICE guidance.

Wales

In Wales, the All Wales Medicines Strategy Group (AWMSG) carries out a similar function to SMC. However, no directions have been issued by the Welsh Assembly regarding implementation of its recommendations.

TRANSPARENCY OF DECISION MAKING

EC law has intervened only to a limited extent in the areas of pricing and reimbursement. Member states are required to adopt transparent decision-making processes, under the Transparency Directive (*89/105/EEC*). In relation to negative (black) lists, the Transparency Directive states that a decision to exclude a product from coverage under a national health scheme must be based on a statement of reasons. This must use objective and verifiable criteria, that have been published nationally and notified to the European Commission (the Commission). The decision and reasoning, including the expert opinions on which they are based, must be made available to manufacturers. They must also be informed of the remedies available to them to challenge such decisions. Similar provisions relate to schemes where reimbursement depends on inclusion in a positive (white) list. Although the Transparency Directive relates to medicinal products, its principles seem to be generally applicable to other interventions, such as medical devices.

Attempts in 1991 by the Commission to enlarge its involvement in this field were met by opposition, both from member states and industry. Member states feared that further harmonisation of the law might touch on the funding of their national health schemes, therefore undermining their sovereignty. Manufacturers preferred to live with the existing patchwork quilt of rules which they were familiar with, rather than embrace the unknown consequences of devolving power to the EU to harmonise rules.

As a result, the somewhat vague and unfinished rules of the Transparency Directive remain the only assistance that European law offers to manufacturers, in the face of developments such as the establishment of NICE. Practices adopted by such bodies seem to signal the need for greater transparency, but different NICE appeal panels have reached differing conclusions (even as to whether the Transparency Directive applies to NICE's procedures).

Interpretation of the Transparency Directive

The limitations of the protection afforded by the Transparency Directive are emphasised by the outcome of administrative law proceedings in the UK. These concerned restrictions on the prescribing under the NHS of sildenafil (Viagra). The manufacturer, Pfizer, successfully challenged the Health Secretary's initial attempt to use guidance to the NHS to ban the prescription of Viagra.

The Court found both a breach of domestic law and the Transparency Directive. The Health Secretary then triggered a proper consultation, that resulted in the black-listing of the product for prescription to certain patient groups, but not others. These were selected according to the cause of the need, rather than the need itself. This was so that a certain budget per year would not be exceeded. The restrictions (which were also now applied to other products for erectile dysfunction (ED)) were justified on the basis that the NHS could not afford prescription by GPs to all those patients in need of treatment. The position was to be reviewed in the light of clinical experience, gained during the first year of the product's availability on the restricted basis.

On the reassessment, and despite general opposition to the fairness and justification provided for the restrictions, those restrictions were re-imposed. The reasoning given was superficial, but clearly cost-based. Pfizer commenced a further judicial review which led to the government expanding its reasoning. By the time the matter came to court, the government had accepted that the product was cost-effective in meeting real clinical needs, and that its QALY value was probably within the limits considered reasonable. However, the government argued that the central issue was not cost-effectiveness, but relative priorities for the use of NHS funds. It argued that referral to NICE was not appropriate because the black-listing involved a "political judgment".

While accepting that the treatment of ED would never have the same priority as treating cancer or heart disease, Pfizer pointed out that very many conditions treated under the NHS were not life-threatening or painful, and yet products for such treatment had traditionally been, and remained, fully reimbursed. In the circumstances, it was submitted that, to meet the Transparency Directive's requirement that black-listing decisions contain "a statement of reasons based on objective and verifiable criteria", it was the duty of the Health Secretary to set out his reasons for giving the treatment of ED a lower priority than the treatment of a range of other non-life threatening "illnesses" (such as many dermatological conditions and post-menopausal conditions). It was common ground that the Health Secretary had not carried out this analysis and, therefore, such reasoning was not in the decision.

The Court noted the recommendations of the Committee concerning the need for a comprehensive framework for priority setting, but was also impressed by the Government's response. This was that the information required to develop such a framework is currently lacking, although the establishment of NICE was a step in that direction. In the meantime, the Court accepted that any reasoning for affordability would be artificial. In the context of the Transparency Directive, therefore, it was found that:

- Cost containment was a legitimate aim and, therefore, an objective criterion.
- For a criterion to be "verifiable", all that was necessary was that the existence of that criterion should be published.

On this basis, a decision to exclude a product from prescription on affordability grounds did not need to be reasoned beyond stating that the decision was based on cost considerations (*R (on the application of Pfizer Ltd) v Health Secretary Court of Appeal 6 November 2002 (unreported)*).

If this is what the Commission intended, the objectives of the Transparency Directive are very "modest", as the Court indeed suggested was the case. The Commission is known to be concerned about the transparency of the processes by which reimbursement decisions are made by member states. It recognises that they have the potential to create big differences in the ability of EU citizens to access innovative treatments. They may also affect the rules relating to clinical research, and can undermine the significant strides made to harmonise the criteria for granting marketing authorisations. One objective of this was to speed up regulatory decisions, so as to make new treatments available to patients faster.

However, the Commission's forays into legal action have had mixed results as follows:

- The Commission was successful in proceedings against Austria over failure to keep to the time limits under the Transparency Directive for making decisions, but failed in its complaints concerning adequate statements of reasons or remedies (*Commission v Republic of Austria Case C-424/99: 27 November 2001*).

- The Commission most recently was successful in showing that Finland was in breach of the transparency requirements (in relation to decisions establishing categories of products subject to a higher rate of health insurance cover), but failed to provide sufficient evidence of a generalised failure to state reasons in relation to negative decisions in pricing proposals (*Commission v Republic of Finland Case C-229/00: 12 June 2003*).

The G10 Medicines Group (G10 Group) has addressed the issue. This group was established following the Amsterdam Treaty, to bring together under Commission chairmanship representatives of industry and member state governments. The aim was to identify possible solutions to the need to improve the competitiveness of European industry in comparison to industry in the US, but also to be consistent with achieving public health and social objectives.

Its first report of May 2002 emphasises the importance of increasing the speed and transparency of national decision making in relation to pricing and reimbursement, and suggests that tentative steps towards a harmonised approach be taken, stating that: "Member states are increasingly supplementing this with national requirements concerning the relative clinical and cost-effectiveness of medicines, to ensure the efficient use of increasingly scarce resources. Although the assessment of relative effectiveness is a matter of national competence, there could be value in facilitating the exchange of information on national practices between member states. This should include reviewing, analysing, and supporting the exchange of experiences on health technologies, including new information. This increased transparency should improve the quality, consistency and speed of reimbursement and pricing decisions across the EU, and provide industry with a clearer understanding of the criteria used and the reasons for their use."

Perhaps the Commission will soon feel bolder on this important issue. Certainly, industry and political pressures for change are intensifying. With the revisions to EU regulatory law now adopted, the Commission has made it clear that one of its main interests in the next few years will be the operation of the Transparency Directive.

In response to the G10 Group's concerns, in 2003 the Commission established a working group to examine national initiatives on measuring the relative effectiveness of medicines. While the stated aim of the Commission is not to develop a European system, it has reiterated its commitment to ensuring "greater transparency speed and consistency" in decision-making nationally (*see statement of Mr Erkki Liikanen of the Commission of 3 June 2004 on "Progress on the G10 recommendations for the pharmaceutical sector"*).

COST-EFFECTIVENESS IN THE US (MEDICARE)

The US Medicare system does not have a counterpart to NICE. Medicare has adopted processes by which CMS (on a national basis) and Medicare's administrative contractors (on a regional basis) can develop policies as to what items and services are covered. Coverage policies are generally publicised before becoming final, and there is an opportunity for public comment. However because cost is rarely discussed in the policy or the rationale for the decision, it is often difficult to specify public comments that directly address and challenge what might be a cost-based decision.

MCAC

Medicare has created a public process to use advisory committees of experts to advise on Medicare-coverage policy decisions (*see www.cms.hhs.gov/mcac/default.asp*). This committee functions in a manner similar to the more familiar FDA advisory committees, and has been useful in helping CMS to deal with controversial coverage issues. Consistent with the limitations of its legal mandate, CMS has cautioned the committee not to consider cost, but rather to restrict its deliberations to scientific evidence.

This has led to several committee recommendations that CMS found difficult to implement, due to its perceived need to limit large and costly additions to Medicare coverage. The advisory committee that considered the expanded use of ICDs was heavily influenced by the MADIT trial. This showed conclusive mortality reductions in a large population of patients (*see CMS, "Decision Memo for ICDs" (CAG-00157N)*). Medicare struggled to implement the recommendation in a limited way to avoid its potentially large financial impact.

Transparency of the Medicare National Coverage Process

With the exception of the meetings of the MCAC, the Medicare national coverage process has not previously involved public deliberation. Decisions were announced, and some explanation of the rationale for each decision was made public, but the decision was not made in a public forum. With the enactment of the Medicare Prescription Drug, Improvement and Modernisation Act of 2003, greater transparency will now be required in the national coverage process. Medicare's requirements for Local Coverage Decisions by Medicare contractors (formerly called Local Medical Review Policies) have long required a process involving the publication of a proposed coverage policy. They have also required the seeking and consideration of comments on the proposal by the medical community, and other steps to promote transparency and produce carefully considered policies. Other US health insurance plans have adopted closed-door panels to deliberate on coverage policies.

Appeals of Medicare coverage decisions

While individual claim determinations can always be subjected to an appeal process, the Medicare programme was often criticised for not having any mechanism where interested parties could challenge policies. In response to this criticism, CMS incorporated a step in the coverage decision process whereby an aggrieved party could request a reconsideration of a Medicare

coverage policy. This step, which generally required the original decision-maker to re-evaluate the same evidence, was not broadly accepted by the stakeholder community. As a result, the Medicare law was changed to provide a mandatory mechanism for a Medicare beneficiary to appeal a Medicare policy to a neutral third party for adjudication (*see Medicare, Medicaid, and SCHIP Benefits Improvement and Protection Act of 2000, section 522, Pub. Law 106-554*).

This appeal mechanism was to have been in place by 31 October 2001. As that implementation date approached, a group of Medicare beneficiaries filed an appeal to a Medicare policy. This policy denied coverage for ocular photodynamic therapy using the drug Visudyne (for patients with occult lesions of wet macular degeneration). CMS refused to implement the appeal process, and the beneficiaries filed an action in the federal court to compel the appeal to go forward. In settlement of the lawsuit, CMS agreed to have the MCAC consider the Visudyne non-coverage policy, which has since been reversed (*see CMS, "National Coverage Determination for Verteporfin" (80.3.1); "Decision Memo for Ocular Photodynamic Therapy with Verteporfin for Macular Degeneration" (CAG-00066R2) (28 January 2004)*).

Also in settlement of the lawsuit, CMS implemented the appeal policy that allows Medicare beneficiaries to have a neutral third party to consider coverage policies (*see CMS, "Medicare Programme: Review of National Coverage Determinations and Local Coverage Determinations," 68 Fed. Reg. 63,692 (7 November 2003)*). It is likely that policies implicitly based on cost-effectiveness may be vulnerable to challenge through this appeals process.

CONCLUSION

The scene is therefore set in the EU and the US for greater collaboration, between those making the regulatory decision and those making the reimbursement decisions. In the EU, harmonisation of the approach of member states to the evaluation of cost-effectiveness seems inevitable. The US Medicare programme has abandoned proposals to allow cost-effectiveness to be considered in the coverage process, but some recent coverage decisions suggest that cost-effectiveness was an unstated factor. There seems little doubt that this whole area will be most important for companies and their advisers in the next few years.