LEADING ARTICLE

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The Effect of Pharmacoeconomics on Company Research and Development Decisions

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Summary

There is a strong rationale for integrating pharmacoeconomics into research and development (R&D) project selection and termination decisions. The average cost for the typical new drug introduction now exceeds $US300 million. Furthermore, a growing proportion of phase III projects are terminated because of economic factors relative to efficacy and safety concerns. While the use of pharmacoeconomic studies by payers is still evolving, the pressures on firms to show that new products are cost effective will only intensify in future periods. Accordingly, it is important for firms to begin analysing the cost effectiveness of new drug candidates early in the R&D process.

The cost effectiveness of a new therapy can be simulated prior to clinical testing using different assumptions about the efficacy, tolerability, pricing and formulation of the new therapy. These models can be refined and updated as data become available from clinical testing and other sources. A key objective is to make uncompetitive projects fail sooner while channelling development resources to projects with high expected returns. Cost-effectiveness analysis should be an integral component of the firms's strategic action plan and its return on investment analyses.

The use of pharmacoeconomics in research and development (R&D) decisions has been growing over time. Nevertheless, few companies appear to currently employ it as an integral part of their strategic decision-making approach to selecting and terminating projects. A 1993 survey found that only 40% of major pharmaceutical companies used pharmacoeconomics for R&D decisions, compared with over 90% in the case of marketing and reimbursement decisions.[1] This situation is changing, however, given the new competitive dynamics now at work in the industry.

The primary objective of this article is to consider how pharmacoeconomics can be employed in the R&D process to improve a company's productivity and return on its investment. Ideally, pharmacoeconomic analysis should begin early in the development stage. It should be refined in an iterative fashion as new data become available from clinical trials and other sources, as a major function

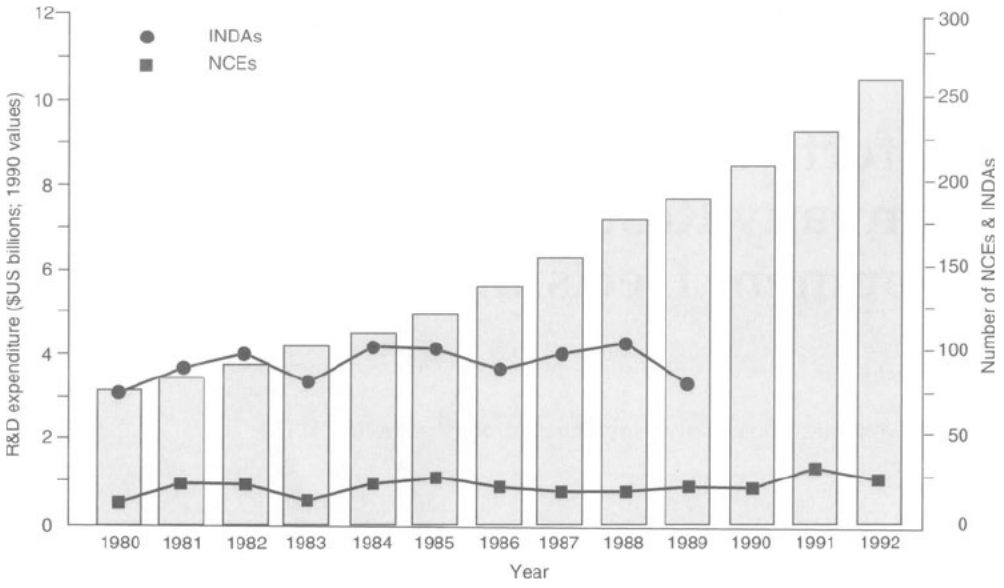

Fig. 1. Expenditures on research and development (R&D), and the numbers of new chemical entities (NCEs) and investigational new drug applications (INDAs), between 1980 and 1992.[3,4]

of pharmacoeconomics in the internal decision-making process is to identify uncompetitive projects at an earlier stage.

1. The New Competitive Dynamics

Although there is great optimism at the present time about the scientific potential for important new drug discoveries, there is also mounting evidence that R&D costs are growing rapidly in real terms. DiMasi et al.[2] found that it took an average of $US231 million (1987 values) and 12 years to discover and develop a typical drug in the mid-1980s. This figure includes the cost of candidates that fail in the R&D process, and the interest or time costs associated with the long investment period for new drugs. If this number were simply updated for general economy-wide inflation, the current cost of discovering and developing a new drug introduction would exceed $US300 million (1995 values). However, there is reason to believe that the rise in R&D costs for new drugs significantly exceeds general inflation.

Figure 1 shows the annual R&D expenditures of Pharmaceutical Research and Manufacturers of America (PhRMA) member companies between 1980 and 1992. It also shows the annual number of investigational new drug applications (INDAs) and new chemical entities (NCEs) approved by the US Food and Drug Administration (FDA). It indicates that R&D expenditures have increased several-fold since the early 1980s, while the annual numbers of INDAs and NCEs have changed only moderately.

DiMasi and colleagues at the Center for the Study of Drug Development are currently undertaking an update of their prior analyses of R&D costs.[2] Although the issue of R&D costs is best analysed with a representative sample of NCEs, the aggregate data series in figure 1 strongly suggest that R&D investment costs per new drug introduction have continued to increase significantly in real terms over the past decade.

What are the reasons for the rapid increase in R&D costs over time? Among the factors cited in the literature are increased research on drugs for

difficult-to-treat chronic diseases, higher discovery costs, and much higher out-of-pocket costs in the development phase.

With respect to this last factor, various studies indicate that approved NCEs now involve an increasing number of phase III trials, as well as an increasing number of patients per trial.[5,6] This is an important reason to begin pharmacoeconomic studies early, so that the economic prospects of a new drug candidate can be evaluated before undertaking costly phase III trials.

Another reason for beginning pharmacoeconomic studies early is that returns on new drugs are highly variable. The distribution of returns across various cohorts of new drug introductions are highly skewed across NCEs.[7,8] For example, figure 2 shows the present values of net revenue, grouped according to decile, for 1980 to 1984 US NCE introductions. The top decile has an estimated present value of net revenues that is more than 5 times the average capitalised R&D cost. Hence, these products recoup a disproportionate share of the returns on R&D. Furthermore, only the top 3 deciles have present values of net revenue that exceed average R&D costs. The products below the third decile do not typically cover the average discovery costs or the costs of the large numbers of products that fail in the development process.

This analysis indicates the importance of innovative drugs to a company's returns on R&D and its ongoing viability in the pharmaceutical industry. In particular, companies must enhance the likelihood of producing drugs with the economic characteristics of those in the top deciles if they are to earn positive, long term returns on their total portfolio of projects. Furthermore, most companies are dependent on a small number of very high volume products for the majority of their sales and profits. A large number of these blockbuster products have patents that are due to expire in the next few years,[9] with rapid sales losses now being commonplace when generic products enter the market; a recent analysis indicates that major products can be expected to lose more than 50% of their sales within the first few months of generic entry.[10]

The implications of figure 2 can also be considered from the perspective of public and private payers. Historically, the drugs in the top decile

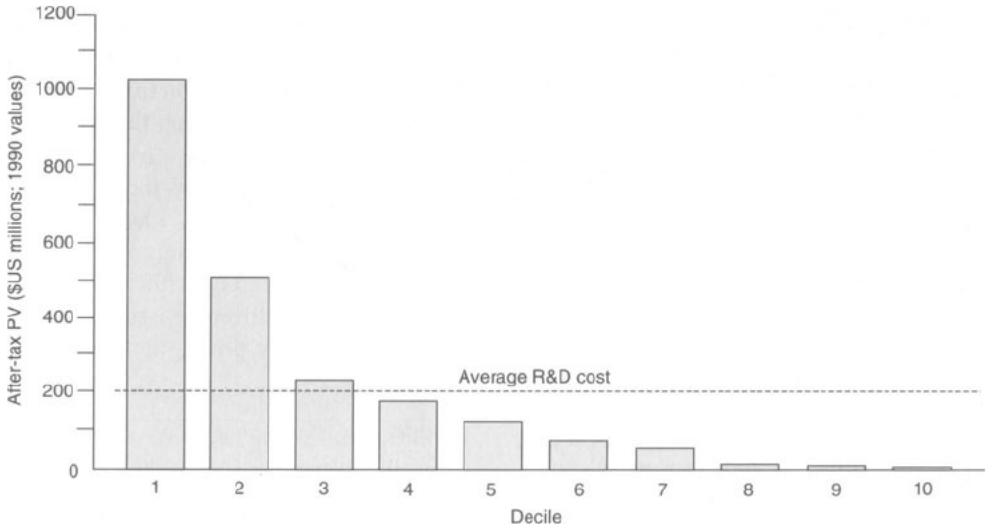

Fig. 2. Present values (PVs) of after-tax net revenue, grouped according to decile, for new chemical entities introduced in the US between 1980 and 1984.[7] *Abbreviation:* R&D = research and development.

have been the first or second products launched in their particular therapeutic class. They are typically launched at premium prices, and are the products that generally result in the rapid growth of pharmaceutical budgets of payers. With the increased cost consciousness exhibited by payers in the 1990s, there is an increasing burden on companies to show that innovative new products really do provide significant value for money to users.[11] Products that cannot demonstrate this through superior therapeutic properties will need to offer significant price discounts, relative to current entities, to be cost effective.

A recent analysis of drugs launched in the US in 1992 and 1993 shows that this competitive process is well under way.[6] The vast majority of new drugs were launched at significant discounts relative to the market leader in their therapeutic class. In the markets of countries in which drug products are subject to price regulations and reimbursement controls, there is also a growing need for companies to justify price premiums for innovative products on the basis of cost effectiveness and other pharmacoeconomic analyses.[11-13]

In this more competitive environment, it is incumbent on companies to undertake early strategic analysis of their R&D portfolios, with pharmacoeconomic analysis being one of its main tools. R&D resources should be directed towards products that can provide users with high value for money. Early indicators, using pharmacoeconomic analysis, may identify products that cannot earn an acceptable rate of return and these should be candidates for early termination.

2. Pharmacoeconomics and the Drug-Development Process

2.1 Early-Stage Development Planning

The R&D process for pharmaceuticals involves sequential decision-making under uncertain conditions. At each stage, the company can incur incremental costs to obtain additional information and then decide whether it wishes to continue to the next stage.[14,15]

There are a set of natural decision points or milestones in this process. These involve the decision to establish a discovery programme in a particular disease area, to form a project team for preclinical development of a promising compound, the first human testing of the compound, the first efficacy testing in patients, the decision to undertake large-scale clinical testing, regulatory submission and marketing launch. As a compound moves through each stage of development, the resource commitments also grow significantly. This relates primarily to the increased number of patients and trials at each stage.[1]

Companies should begin internal modelling analysis on the cost effectiveness of a product well in advance of the go/no-go decision on phase III trials. Before committing major resources to a development project, a company should know the potential value of a new therapy. It is also important to understand, at an early stage, who the key decision-makers are in selecting treatment regimens and how they are likely to weigh gains in clinical, economic or quality-of-life outcomes.

The first step in this planning process is to undertake an impact analysis of the illness using current treatment options. The main objective of this analysis is to find out what factors account for most of the disease impact, and also to obtain a benchmark on the cost effectiveness of current therapies.[16,17] Using information from the impact analysis, a simulation model can then be constructed, which analyses the desired effects of the new drug candidate on the burden of the illness, using the target clinical profile. This model can be used to estimate both patient progression through the health states and the cost effectiveness of various options involving different assumptions about the efficacy, tolerability, pricing and formulation of the new therapy.

1 First human testing (phase I) is performed on a small number of individuals to obtain safety information on dosage ranges. A few hundred individuals are required in first clinical trials that assess efficacy (phase II). This leads to the key go/no-go decision point on whether to undertake (expensive) phase III testing on several thousand patients to show 'substantial evidence' of tolerability and efficacy to regulatory authorities.

In the early stages of the R&D process, it is very important for the company to learn as much as possible about the sensitivity of the product's cost effectiveness to changes in various parameters. This analysis must be done with reference to existing treatment options, and is incremental in nature (i.e. how much would the proposed product alter cost effectiveness compared with the usual standard of care and other products?).[18] If it is found, for example, that the cost effectiveness of the product under consideration is highly sensitive to the costs of treating adverse effects, this will be an important input to the target profile of the drug. In addition, this kind of information will be useful in planning data-collection efforts to ensure that the correct inputs are obtained in the clinical trial process and from other data sources. The simulation model may also be useful in determining the indications toward which the drug should be targeted, if the analysis shows that the product could be especially cost effective for particular subpopulations.

As an illustrative example, it is useful to consider the steps that are necessary to construct a simulation model for a company considering a new antineoplastic therapy.[2] The first step is to model the progression of patients through different health states, according to existing antineoplastic therapy regimens. Each state is associated with different costs and patients' levels of well-being. Data inputs for the clinical parameters include the rates of progression, mortality and adverse effects.[19] Costs analysed in the model include those associated with drug administration, treatment of adverse effects, and treatment and monitoring of the underlying disease symptoms. Data pertaining to clinical parameters and resource use can be obtained, at this stage, from the published literature, expert opinions and, possibly, patient questionnaires. The model provides outputs in terms of measures such as cost per increased year of survival (possibly quality-adjusted), and can be used to simulate the cost effectiveness of a new treatment regimen with alternative profiles of clinical outcomes and economic values, and then to compare this with existing treatments.

Sharples et al.[20] developed a model of this kind in the area of transplantation, which investigated the primary clinical events after cardiac transplantation and linked them with survival and costs. Employing a Markov modelling approach, they used observed survival rates, and estimated resource use and costs for patients in this environment. The model was estimated using data from a UK hospital that performs cardiac transplants. The authors[20] showed how this model can be used to analyse the cost effectiveness of a proposed new immunosuppressive therapy. This was accomplished by tracing its projected effects on the transition probabilities between disease states and the associated resource use and costs. This is another example of how a pharmacoeconomic simulation model can be utilised by companies in the R&D planning process to assess candidate drug treatments.

This internal modelling analysis is not only useful in assessing the potential of self-originated drug candidates, but also those arising from licensing and partnership opportunities. The number of new products that originate outside the traditional pathways of the major company R&D organisations has grown dramatically in recent years, with the emergence of the biotechnology industry and related developments.[21] Agreements between companies are now structured with various milestones and key decision points.[22] Pharmacoeconomic analysis can be useful both for the negotiation of terms, and to facilitate the sale and the licensing out of compounds that the companies choose not to pursue.

2.2 Strategic Planning and Go/No-Go Decisions

The simulation model formulated in the earlier stages of development can be refined as clinical data become available, and used in conjunction with economic modelling to formulate a strategic action plan. In particular, the company can use it

2 This pedagogical example is based on a discussion with Dr Josephine Mauskopf of Glaxo Wellcome, Inc., Research Triangle Park, North Carolina, US, which recently launched a product for non–small-cell lung cancer.

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