The Evaluation of Ultra-Innovative Drugs: A Broader Perspective

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KEY POINTS . . .

Innovative drugs, especially in orphan diseases, often exceed the ICER and are therefore not reimbursed.

Health authorities leave the responsibility for medical innovation to the market. Therefore, medical innovation relies on the market mechanisms and optimal return of investment for investors.

The Discounted Cash Flow method can be applied to justify an orphan drug price based on market mechanisms.

This is the second of two articles in this issue on the topic of evaluation and innovation. Drs. Nuijten and Vis explore the application of economic valuation methods to justify a drug price, when the ICER exceeds the threshold.

Background

The judgment of the clinical benefit of medicinal products by reimbursement authorities used to be based mainly on traditional clinical trial outcomes (efficacy and safety), but currently in most Western countries, coverage decisions are also based on cost effectiveness and budgetary impact. Reimbursement decisions can then be based on the maximum amount society is willing to pay to gain one quality-adjusted life year (QALY). For instance, in the UK the threshold for most treatments ranges between £20,000 and £30,000 per QALY [1].

The definition "ultra-innovative" is typically restricted to "first-in-class" drugs that demonstrate innovation for which society may want to facilitate investment. The term "ultra-innovative" is used instead of 'expensive,' which implicitly includes a value judgment of "too expensive." Many pharmaceutical companies (especially biotechnology companies) are commercialising ultra-innovative drugs like biologicals and orphan drugs with cost-effectiveness outcomes, which will probably exceed the upper threshold of £30,000/QALY, whereas the annual costs per patient are probably considered substantial from the perspective of the payer (e.g., the National Health Service).

Alternative Policy Approaches

We apply concepts from health economics, business valuation, and finance to create alternative perspectives on how we evaluate ultra-innovative drugs.

The ultra-innovative drugs include the orphan and non-orphan biologics. In this paper we focus on the orphan drugs for purpose of illustration, but the concepts can also be applied to non-orphan biologics. This paper focuses on countries that have requirements for cost-effectiveness outcomes in the national reimbursement submission. In this paper, we use the terms "valuation" and "evaluation," which are different concepts. **Valuation** refers to the summary of evidence into a single unit; whereas **evaluation** refers to the summary of evidence into pros and cons (Franklin's rule). Health technology assessment (HTA) bodies do evaluations, but for-profit firms do valuations (e.g., discounted cash flow).

Challenging the Use of Cost-Effectiveness Outcomes for the Assessment of Ultra-Innovative Drugs

General issues in cost-effectiveness analysis

The use of cost effectiveness as final criterion in the reimbursement process for listing of new pharmaceuticals can be questioned from a scientific and policy point of view. There is a lack of full consensus on main methodological issues and consequently we may question the appropriateness of the use of cost-effectiveness data in health care decision making. Another concern is the appropriateness of the selection and use of an incremental cost-effectiveness threshold (i.e., cost per QALY gained). It may lead to inappropriate reimbursement decisions because of inaccuracy in the applied methodologies, as well as the cost per QALY threshold. Differences between West-European countries, especially discounting of costs and outcomes (QALYs) and threshold, reflect differences in willingness to pay for health care and may lead to unequal access of new innovative pharmaceuticals.

We apply concepts from health economics, business valuation, and finance to create alternative perspectives on how we evaluate ultra-innovative drugs.

Specific issues for orphan drugs in cost-effectiveness analysis

There are also specific clinical and economic issues for orphan medical products and rare diseases that complicate the application of standard cost effectiveness evaluation of orphan medical products, principally because of the limitations to the clinical data available when products are launched and the associated uncertainty resulting in a large confidence interval of the incremental cost-effectiveness ratio (ICER), which induce authorities to make a negative coverage decisions. The US Food and Drug Administration (FDA) also approves drugs with little evidence of effectiveness, if the drug is in a therapeutic area with no alternative treatment.

The current reimbursement process is based on the standard cost-effectiveness concepts, which do not allow another methodology for health economic assessment because of the specific issues for orphan drugs. Any change of the current assessment of orphan drugs for reimbursement would require a process involving all stakeholders, which should not be related to the reimbursement of a specific orphan drug.

Ideally, a branch association of pharmaceutical companies would collaborate with patient organizations (e.g., EURORDIS), the medical community, health economists, and health authorities (e.g., NICE) on the appropriate assessment of orphan drugs. This could be a comprehensive consideration of the current clinical and economic issues in the current assessment procedures, which could address the current most explored approaches:

- The adjustment of health economic concepts for orphan drugs. Cost effectiveness remains a standard assessment criterion, and we may consider a justification of a higher threshold for orphan drugs, (e.g., the inclusion of social values in the ICER). However, most classic health economists may not be willing to accept another cost-effectiveness approach, e.g. consider issues like low sample size and heterogeneity for orphan diseases, or the acceptance of a higher threshold.

- The inclusion of ICER and social values in a multi-criteria process, which captures other relevant data (i.e., rarity, disease severity, health preferences, and patient's voice evidence) (Figure 1).

Instead of further exploring the above mentioned approaches, which are within the concepts on health economics, we suggest a completely new approach by taking a broader perspective by bridging concepts from health economics and business economic valuation.

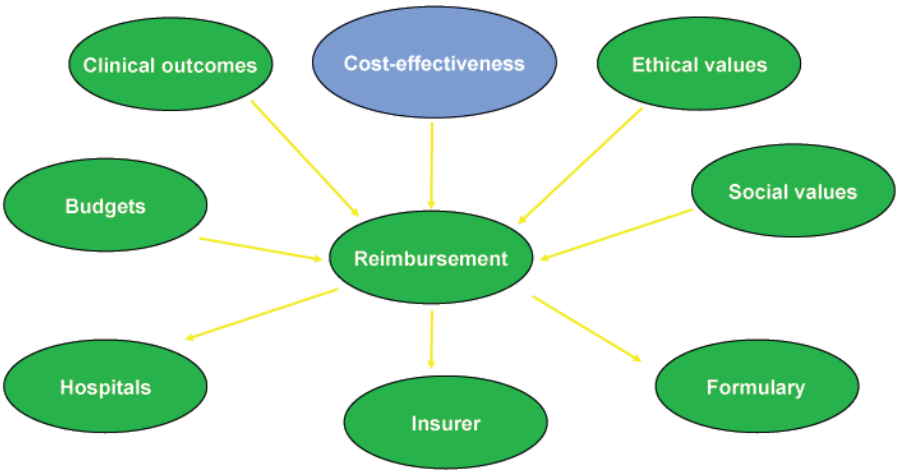
Background on Business Valuation

In a pure market economy, supply and demand are determined by individual firms and consumers. Therefore, in a pure free health market, the price of the new innovative drug would be determined by demand and supply mechanisms, and all previous considerations about the use of cost-effectiveness data or multiple-criteria decision making processes would be redundant. However, in the health care market, patients do not pay directly for treatment (moral hazard), and consequently the price of a health care service will not bring demand and supply into balance. The demand by the patient will not be limited by the price, while an increasing supply of health care services will lead to a lower price and providers even have financial incentives to increase the volume of health care services. The third party, the health insurer, who is responsible for direct payment, may have some control over price, but to a much less extent on volume. Although a health insurance company can pass on the cost of this excess expenditure through increased contributions, this is spread among all those insured.

On the other hand, the health authorities leave the responsibility for medical innovation to the market, although medical innovation has a much broader value than the economic value. Therefore, medical innovation relies on the market mechanisms in the finance market of biotechnology including the incentives of the various stakeholders, especially the capital providers (investors), who demand a required return of investment. The investor's decision-making process does not only include economic attributes, but also societal values, as an investor is a human being with multiple roles in society. In the current health care environment where innovation relies mainly on business entrepreneurship, health authorities have to accept the market mechanisms in the finance market, especially the optimal return of investment for investors in order to benefit from the societal value of medical innovation and increase the quality of life and well-being of their citizens.

Health authorities often challenge the high price of orphan drugs; while pharmaceutical companies argue that innovation requires significant investments. The public decision makers increasingly may seem to require insight in the underlying financial data on cost structure including cost of research and development (R&D) goods and costs of marketing. This would lead to additional disputes over how to allocate R&D failures to successful drugs obtaining EMEA or FDA approval. There is no need to have consensus regarding >

Figure 1: Value of innovation includes more than cost effectiveness.



the possible discrepancies in the costing methodology, because the hypothesis of economic valuation is that the value is not similar to price, revenues, and costs, and these terms should not be confused. Instead, the economic value of a company is based on the expected free cash flows.

If we assume that the new drug is the only product of a company, we can calculate the economic value of this company. This valuation is based on the Discounted Cash Flow method, which is based on the free cash flows and the required cost of capital. **Free cash flow** is often defined as the cash flow from operations (or net cash flows from operating activities) minus the cash necessary for capital expenditures. Cash flow from operations represents the sales from the pharmaceuticals, and cash necessary for capital expenditures represent the costs for R&D and marketing. The Discounted Cash Flow method can be used by pharmaceutical companies for justification of the drug price towards critical health authorities. In the next section we describe this approach in more detail.

The introduction of innovation is a unique one-time event, whereas retrospective statistical data on treatment patterns relate to the health care setting in the past. The actual use of an innovation refers to the future (e.g., how will the innovation be adopted by the medical community in a changing health care environment with other new emerging innovations and changing reimbursement and financing systems). Therefore, any existing statistical data should be considered with caution for making a sales forecast and requires validation, especially how the existing data can be applicable for an appropriate forecast.

The cost of capital refers to the opportunity cost of making a specific investment. It is the rate of return that could have been earned by putting the same money into a different investment with equal risk. Thus, the cost of capital is the rate of return required to persuade the investor to make a given investment. The cost of capital is determined in the market when investors provide their capital to a company temporarily and request a return of investment based on their perceived risk, which is the quantifiable uncertainty. When given the choice between two investments of equal risk, investors will generally choose the one providing the higher return [2]. The cost of capital depends on the mode of financing used—it refers to the cost of equity if the business is financed solely through equity with an adjustment to the cost of debt if it is financed partially through debt. Many companies use a combination of debt and equity to finance their businesses, and for such companies, their overall cost of capital is derived from a weighted average of all capital sources, widely known as the weighted average cost of capital (WACC). Since the cost of capital represents a hurdle rate that a company must overcome before it can generate value, it is extensively used in the capital budgeting process to determine whether the company should proceed with a project.

The justification of the orphan drug price can be based on the Discounted Cash Flow method. As the future financial performance of a pharmaceutical company is directly related to the free cash flow of a new drug, an appropriate assessment of the potential sales forecast of a portfolio of forthcoming new drugs is an important element of the financial value of a pharmaceutical company. Today, such an assessment should definitely include the estimated effects of the new emerging requirements of reimbursement authorities and payers and the effects of pharma policy changes. After the assessment of the free cash flows, the Discounted Cash Flow method can be applied to determine the threshold for the cost of capital and compared with the required cost of capital in the pharmaceutical industry in order to justify the appropriateness of the drug price.

The Discounted Cash Flow method can be used to validate the price of the new drug from a narrow investor's perspective, which does not include all other monetary and non-monetary values for society (i.e., patients, physicians, payers, providers, and employers). An analysis from a broader society perspective can include these other monetary benefits in the free cash flows, which may justify a higher drug price for the ultra-innovative drug from a society perspective. In this analysis, the revenues from the sales of the new drug are expenditures from the society perspective, whereas the other monetary and non-monetary benefits can be considered revenues.

Conclusion

Health care innovation has added tremendous value to patients, the economy, and society at large in terms of improvements in health care. In addition, innovative health solutions are able to drive real financial gains to society that outlast patent life. However, many ultra-innovative drugs will probably exceed the upper ICER threshold, which will lead to negative reimbursement decisions in countries where cost effectiveness is the main criterion in the reimbursement process.

In this paper, we propose an alternative policy approach for the evaluation of ultra-innovative drugs from a broader perspective by bridging concepts from health economics and business economic valuation. This approach may justify a drug price, especially when ICER exceeds the threshold. If innovation is funded continuously, future generations will reap even greater rewards, which also includes direct investment of the sales of the new drug in development for other indications or indirect investment of the sales in the development of another clinical entity.

References

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