Scientific Research Publishing

Journal of Financial Risk Management, 2024, 13, 333-341
https://www.scirp.org/journal/jfrm
ISSN Online: 2167-9541
ISSN Print: 2167-9533

Concept—Integrated Valuation Model

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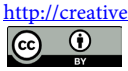
How to cite this paper: Nuijten, M. (2024). Concept—Integrated Valuation Model. *Journal of Financial Risk Management, 13,* 333-341.
https://doi.org/10.4236/jfrm.2024.132016

Received: April 23, 2024
Accepted: June 10, 2024
Published: June 13, 2024



Abstract

Many biotech companies are focusing on the development of innovative drugs for the treatment of orphan diseases or oncology drugs with orphan indication, which are considered "very expensive" by healthcare authorities. These biotech companies need support for developing the optimal pricing strategy for their drug in order to maximize the economic value from an investor's perspective. Investors also require validation of the economic value of R&D project to avoid an inappropriate investment decision. Therefore we developed an Integrated Valuation Model, which allows early phase assessment of the pricing potential of the drug for various positioning strategies and the corresponding economic value for the investor. The Integrated Valuation Model is especially developed for innovative drugs for the treatment of orphan diseases or oncology drugs with orphan indication. A late phase application is the support of justification of "high" drug price during price negotiations with national health authorities, especially when the drug price exceeds incremental cost effectiveness ratio, e.g. €80,000 per QALY and authorities require huge discounts up to 80%.

Keywords

Drug Price, Valuation, Medical Innovation, Market Access, Reimbursement

1. Introduction

Registration authorities (EMA, FDA) mainly consider the clinical value of the medical innovation, whereas national health authorities take a broader perspective by including clinical, economic criteria and potentially other criteria, like equity and social values. Value-based pricing is the most widely accepted approach in the pricing and reimbursement process in Europe, which varies from the narrow concept based on the incremental cost-effectiveness ratio (ICER)

threshold to broader approaches. An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in gain in Quality Adjusted Life Years (QALYs) (incremental effect) to provide a ratio of extra cost per extra QALY gained for the clinically more superior and more expensive therapy vs. the standard of care. In Netherlands we are willing to pay a maximum of €80,000 per QALY for oncology drugs, whereas in England, the upper limit is GBP30,000 per QALY. This maximum acceptable ICER is called the threshold, which is used in price negotiations in countries with formal requirements for submission of cost-effectiveness data. For example, in 2016 the Dutch National Health Care Institute ("Zorginstituut Nederland"—Zin, 2016) advised a discount of 55% for pertuzumab with an ICER of €150,000 per QALY in advanced breast cancer, at which price the ICER for pertuzumab reduces from €150,000 per QALY to the threshold of €80,000 per QALY, the upper threshold for oncology in Netherlands. However, these discounts may result in prices of medicines that are unacceptably low for pharmaceutical companies and investors.

Another example for an orphan drug is the reimbursement of Spinraza, the first effective drug for SMA, which was initially denied due to an excessively high 'cost per QALY' of €600,000. The Ministry of Health demanded a discount of 85%, which meant a price drop from €240,000 to just €36,000, while the minimum investor price was at least €100,000 according to our calculation (Nuijten, Fugel, & Vis, 2018).

Summarising, value-based pricing determines the maximum price from the national payer's perspective, based on health economic concepts. This price should exceed the minimum price for the investor acting in the international financial market, which is based on economic valuation theory. Value-based pricing is especially relevant for innovative drugs with premium price versus current standard of care.

2. Integrated Valuation Model

2.1. Synopsis

Recently we (Nuijten & Capri, 2022) published the Integrated Valuation Model, a "value for access to market model" (V4A2M Model®), which is an interactive dynamic tool for the economic valuation of R&D projects. This is the first paper that is integrating the payer's perspective and the investor's perspective. This model does not only generate the economic value at T = 0 based on expected clinical outcomes and probability of registration by EMA and FDA, but it also incorporates the expected probabilities of reimbursement, actual market access, and the resulting sales. The Integrated Valuation Model can identify proactively scenarios at the early onset of the clinical development program, which will maximize 1) the potential market size at time of launch, and 2) the probability of reimbursement at an acceptable drug. Hence the incremental opportunity of the dynamic Integrated Valuation Model compared with the traditional static Discounted Cash Flow (DCF) method is that this economic value reflects a more re-

alistic economic value based on registration and market access requirements.

- Biotech companies: The incorporation of the critical determinants for reimbursement may lead to a refinement of the economic value of the R&D project, which increases the external validity of the valuation and provides a more realistic value at time of investment and provides opportunities for proactively fine-tuning the clinical program to increase the economic value of the R&D project.
- Investor: An economic valuation, which is only based on the expected clinical outcomes, may have a high internal validity, but it may overestimate the economic value of the R&D project. Consequently, this may lead to an inappropriate investment decision by the investor. The incorporation of the critical determinants for reimbursement may lead to a fine-tuning of the economic value of the R&D project, which increases the external validity of the valuation and provides a more realistic value at time of investment and provides opportunities for proactively refinement of the clinical program to increase the economic value of the R&D project.

The Integrated Valuation Model may guide the direction of prioritizing the primary indications by showing the impact of hypothetical improvements on clinical measures (e.g. x% increase in response rate or x% decrease in side-effects) and costs by means of extensive scenario analyses. These scenario analyses may encourage the development of a drug in indication A, while the development of a drug in indication B would not be justified.

The information derived from the core model may lead to the following decisions, which will depend on the study drug phase:

- The outcomes of the models for the primary indications may support prioritizing process and portfolio investment decisions: the drug development for one indication may be cancelled, if it appears that there is no market potential for the drug.
- The information on specific subpopulations with co-morbidity or risk factors may lead to a modification of the clinical trial program, which will allow a scenario analysis of the clinical pharmacoeconomic assessment in this subpopulation.
- The following components of the design of a clinical trial may be adjusted based on clinical information derived from the core model: study period, study population, comparators, primary and secondary clinical outcomes and sample size.
- The information on standard of care (usual care) may also lead to clinical program modification by adding a treatment arm of patients using the most relevant comparator from a market access perspective.

2.2. Concept

The investment decision for a new R&D project for medical innovation at the year of patent registration (T = 0) depends on its economic value. A common approach is the use of the DCF method, which provides the net present value

(NPV) of the R&D project based on the free cash flows and cost of capital.

The cash flows from operations correspond with the future sales from the new innovative drug and the costs for R&D, production, and marketing. The R&D costs of unsuccessful clinical programs are also assigned to the R&D project. The cost of capital is the minimum rate of return necessary to convince the investor to make an investment, e.g. 9% for pharmaceutical and 12% for biotechnology companies (Nuijten & Vis, 2016; Nuijten & Van Wilder, 2021).

This Integrated Valuation Model does not only generate the economic value at T = 0 based on clinical expected clinical outcomes, but it also incorporates an analysis based on the expected chance of reimbursement, actual market access, and the resulting sales, which may lead to different values. Subsequently the model allows testing of other scenarios on clinical and economic critical determinants for reimbursement. The goal is to identify proactively scenarios at the early onset of the clinical development program, which will maximize 1) the potential market size at time of launch, and 2) the probability of reimbursement at an acceptable drug. Hence the incremental opportunity of the dynamic Integrated Valuation Model compared with the traditional static DCF method is that the initial economic value reflects a more realistic economic value based on market access requirements. In addition, it also is the trigger for reconsidering the initial clinical program (e.g. indication, comparator, outcomes, subpopulations, study design), and the associated market access and pricing strategy, which may also require an adjustment based on reimbursement constraints for positioning, and pricing based on clinical and economic criteria (cost-effectiveness and budget impact).

The Integrated Valuation Model applies the concept of Value of Information, which means that the economic value of the R&D project can be updated after each phase of clinical program e.g. after phase 1, phase 2, or phase 3 trials, based on the most recent clinical data from the trials, but also incorporating any changes in reimbursement and pricing legislation and corresponding changes in data requirements for national market access applications based on a local pricing and reimbursement scan performed in the key countries.

The Integrated Valuation Model does not only yield the economic value of the R&D project, but it provides an integrated comprehension ("Verstehen") of relationships between clinical and economic critical success factors and constraints (e.g. budget impact and cost per QALY) from the perspective of the payer, and the economic value for the investor, e.g. the minimum drug price to satisfy the investors. The Integrated Valuation Model allows sensitivity and scenario analyses to identify the key critical success factors, and critical assumptions, which may guide prioritizing the next steps in the clinical and strategic marketing planning of the compound.

3. Application

3.1. Description

The concept of the Integrated Valuation Model is summarized here, but more

details are provided in a key scientific publication in Journal Market Access Health Policy, a high-ranked peer-reviewed journal (Nuijten & Capri, 2022). The Integrated Valuation Model integrates the perspectives of the payer and investor by bridging concepts from health economics and economic valuation in order to provide a forecast of potential market size and pricing potential for a drug in early clinical development phase.

The Integrated Valuation Model is especially developed for innovative drugs for the treatment of orphan diseases or oncology drugs with orphan indication, but the concept is illustrated for a new hypothetical drug (Product X) in advanced breast cancer.

The Integrated Valuation Model includes the critical disease-specific determinants for reimbursement of a new drug, with illustration to advanced breast cancer, as in the underlying paper:

- Indication and positioning: The primary population is the targeted indication for registration and reimbursement, but the model can include also specific subpopulations with co-morbidity or risk factors as backup scenario in case of failure of registration, but especially reimbursement for primary indication. Subpopulation analysis can be considered when the clinical benefit in total population is not sufficient, or the ICER and budget impact in total population is economically not acceptable. In this case study the indication for Product X is constrained to HER2-positive patients with advanced breast cancer and the model includes the following subpopulations: 1-line, 2-line, and 3-line treatment.
- Comparator: The analysis is based on a 3-way comparison of Product X versus the most recent innovative reimbursed drug in each position (**Table 1**). The advantage of the 3-way comparison is that it includes consistency: for example, if A is similar to B and B is superior to C, then A should also be superior to C.
- Efficacy and safety: The focus of the Integrated Valuation Model is primarily on clinical benefit: efficacy (PFS and OS in oncology) and safety. But it also includes secondary product characteristics such as administration and ease of use: e.g. route of administration, frequency of administration, dosing, need of monitoring, and mechanism of action. The Integrated Valuation Model allows to generate various scenarios (e.g. base case, pessimistic and optimistic) for the expected clinical product profile of Product X in the possible positions (e.g. 1-line, 2-line, 3-line) versus the expected comparators (standard of care) in each position. Pessimistic and optimistic scenario analyses are included to test the sensitivity of the outcomes of the model (economic value and drug price), to the expected product profile of Product X.

The expected clinical product profile (especially efficacy and safety profile) is critical for registration and also key for the national reimbursement processes. But the Integrated Valuation Model provides the other critical determinants for reimbursement: cost-effectiveness, and budget impact, which are the outcomes of the budget impact model, pricing matrix model, and cost-effectiveness model.

Table 1. Positioning and clinical benefits for Product X.

Position	Comparator			
	previous innovative drug	previous standard treatment		
1-line	pertuzumab + trastuzumab + docetaxel	trastuzumab + taxaan (docetaxel or paclitaxel)		
2-line	lapatinib + capecitabine	capecitabine		
3-line	eribulin	treatment of physician's choice' (TPC)		
Input for clinical benefit Product X	**Change versus new innovative drug**			
	Base case		**Scenario**	
			Optimistic	**Pessimistic**
PFS (months)	30%	% change - increase	40%	20%
OS (months)	20%	% change - increase	30%	10%
AEs (%)	10%	% change - decrease	5%	15%

TPC: capecitabine, vinorelbine, gemcitabine, taxanes, anthracyclines and other chemotherapy.

These models are interacted and linked with a discounted cash flow model in order to reflect also the economic value from the investor's perspective (Figure 1).

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3.2. Base Case Analysis

The minimum price for the investor for Product X is inversely related to the potential number of eligible patients, which is respectively €14.7, €184.5, and €942.7 per one daily unit for 1-line, 2-line, and3-line position (Table 2). The base case analysis is based on a discrete approach with rejection of reimbursement, if the ICER of Product X exceeds the threshold of €80,000 per QALY. Another scenario analysis excludes the ICER from these decision criteria, which is relevant for considering countries, like Germany or Italy, where ICER is not

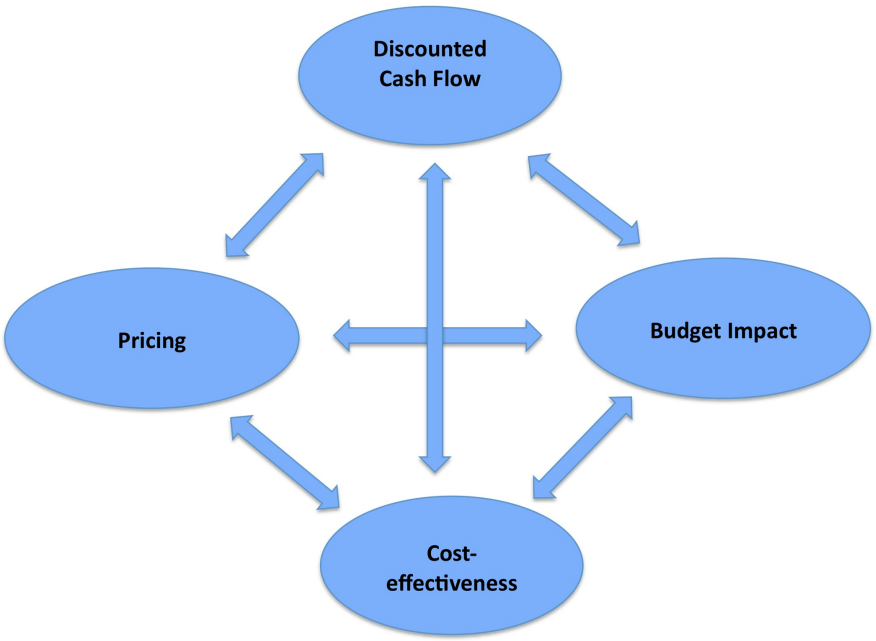

Figure 1. Interaction between pricing, health economics, budget impact and discounted cash flows (Nuijten & Capri, 2022).

Table 2. Base case results of based on defined improvement of clinical benefit for Product X.

Minimum price (BE-price)	1-line	2-line	3-line
Investor	€14.7	€184.5	€942.7
ICER discrete threshold*	€269.7	€271.1	€283.3
ICER excluded	€373.7	€746.9	€511.3
Reimbursement			
ICER discrete	yes	yes	no
ICER excluded	yes	yes	no

included in the reimbursement decision, and mainly BIA is relevant economic criterion. Research shows that the ICER reduces the pricing potential of new innovative drugs (Vreman et al., 2020).

3.3. Scenario Analyses

Findings from scenario analyses:

- These scenarios show that improvement in efficacy (PFS and OS), have much more impact on the outcomes than reduction of AEs. The optimistic scenario does not substantially change the conclusion from the base case analysis that Product X only has market potential in 1-line and 2-line position.
- Scenario analyses for 2-line and 3-line position, which include extension of label to respectively 1-line and 2-line position 5 years after market launch,

substantially reduce the BE price for the investor because extension of the potential number of patients allows the distribution of the R&D costs over more patients.

- The "time to market" is a critical factor, which has impact on the NPV. Diagnostic testing can enhance the efficiency of executing clinical trials and smaller and cheaper clinical studies may be adequate, which still will provide sufficient statistical power. Earlier market access will transfer cash inflows, e.g. actual drug sales, to earlier stages in the drug product life cycle and it will prolong the period of patent protection, which leads to higher economic value (NPV).
- The model also includes the option that the strategic scan and feasibility analyses allow improvements in clinical design of forthcoming clinical trials, which reduces R&D costs and lead to lower failures. A scenario analysis shows that increase of efficiency in trial program pays off in substantial lower BE price, up to 10%, for the investor.

3.4. Additional Findings

- The model generates information, which can guide the design of the clinical trial program including follow-up, definition of study population, most relevant comparator treatment(s), sample size, and clinical and economic outcomes and endpoints. For example, the expected optimal positioning of Product X in the future treatment practice may determine the defined study population in the clinical studies, as well as minimal number of patients for relevant subpopulations for an assessment of possibly restricted use.
- In a scenario analysis we include an innovation premium for Product X, if the clinical benefit exceeds the minimum required threshold to be considered superior to existing standard of care, e.g. 3 months OS. This innovation premium consists of 1) a potential substitution effect by Product X, which results in cost savings elsewhere in the healthcare system, and 2) the monetary value corresponding with a gain in QALYs. For example, if the incremental cost-effectiveness threshold is €50,000 per QALY, a gain in two QALYs corresponds with monetary gain of €100,000.

3.5. Further Research

Especially for innovative drugs, the level of uncertainty is higher than for traditional new generation drugs for cash flows and cost of capital. The uncertainty in cash flows relate to sales, manufacturing and R&D costs, and probabilities of failure of phases in clinical trial program leading to higher spread in values for these parameters. This higher spread has no impact on the deterministic NPV as it is based on average values, and therefore this type of uncertainty requires an extra quantification for the investors. Hence there is need for approaches how to handle uncertainty in economic valuation of medical innovation in orphan diseases.

4. Conclusion

In summary, the key strength of the Integrated Valuation Model is that it includes simultaneously constraints from the perspective of both payers and biotech companies in the proposed early phase forecast: health authorities are not willing to pay a drug price exceeding the cost per QALY and/or cannot pay the drug price because of limited budgets, but biotech companies require a minimum drug price to satisfy their investors.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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