Compiled and designed by pharmaLevers GmbH

Market Access Uncertainty

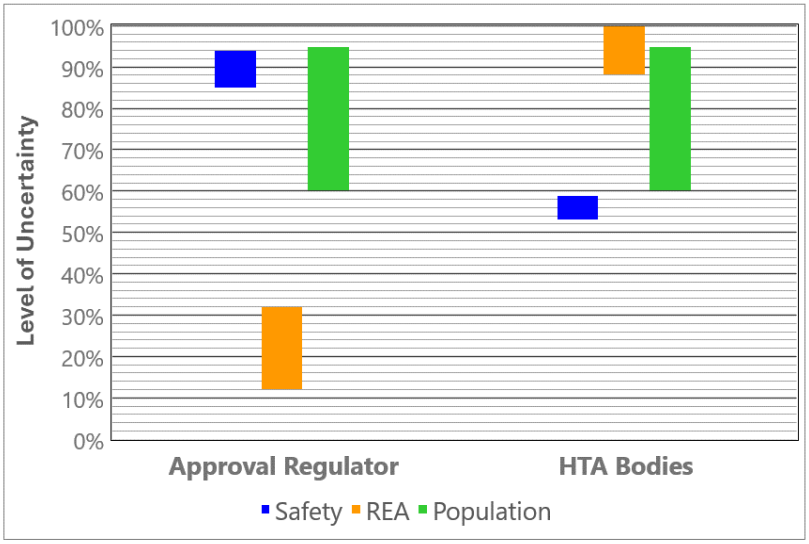
Most people feel uncomfortable in a situation of uncertainty because, unlike risk, uncertainty is subjective and not measurable [1]. They need more time for evaluations and postpone decisions in the hope of getting even more information. Many people do not make rational decisions under uncertainty[i]*. Irrational decisions are unpredictable and lead to unforeseen outcomes that impact the business.*

Decision Making under Uncertainty

There is no consensus about the definition of uncertainty, but the HTA-DIA Working Group has elaborated a key concept with twelve building blocks [2]. Uncertainties arise from clinical and economic inputs. While marketing authorization regulators weight clinical benefit and harm, HTA bodies weigh incremental clinical benefits and costs against a benchmark (Relative Efficacy / Relative Effectiveness Assessment - REA) considering willingness to pay (WTP) and e.g. medical need. Consequently, uncertainties about safety are a bigger concern for regulators (85-94%) than for HTA bodies (53-59%), while in terms of relative effectiveness they are 12-32% and 88-100% respectively. In contrast, uncertainty about the patient population is similar between regulators and HTA bodies (60-95%) - see figure 1. The average number of uncertainties are 7.4 (SD 3.8) per drug and institution [3] (US/EU). The degree of uncertainty has an impact on both the assessment of the REA and total reimbursement (RRs 1.9 and 1.6). However, the d**ifferences could only be demonstrated for high vs. low uncertainty levels**. Interestingly, a high level of uncertainty was associated with faster time between EMA approval and HTA recommendations (NICE, SMC, ZIN) than with a low level of uncertainty (HAS) [4]. The degree of unexplained uncertainty is higher for medicinal products with a **conditional marketing authorization** (CMA) and their recommendations for inclusion in the positive list are limited and very heterogeneous (29-95%). The reasons for this are uncertainties regarding clinical benefits, study design and questions of economic modelling [5].

[i] https://wirtschaftspsychologie-aktuell.de/magazin/leben/unter-unsicherheit-entscheiden-wir-nicht-rational

- *The average number of uncertainties are 7.4 (SD 3.8) per drug and institution* [3].
- *Uncertainty may or may not influence decisions but needs to be considered [5].*
- *A high level of uncertainty does not mean a longer time to HTA decision* [4].
- *Medicines with conditional marketing authorization CMA) are often not reimbursed due to uncertainties* [5].



Own representation of pharmaLevers based on the reference below:

Source: Vreman RA et al. Decision Making Under Uncertainty: Comparing Regulatory and Health Technology Assessment Reviews of Medicines in the United States and Europe. Clin Pharmacol Ther. 2020;108(2):350–7.

Figure 1: Level of Uncertainty – Regulators vs. HTA Bodies [3]

«Uncertainty may or may not influence decisions but needs always to be considered» [6]. There is no standard method for representing uncertainty [6]. «The presence and impact of uncertainties must be communicated to all relevant stakeholders during the HTA output stage» [7]. Communication methods for uncertainty include quantified representations such as efficiency limits, acceptance curves, tornado diagrams [8] and others like the ICER Value Framework [9].

Clinical Uncertainties are forwarded to HTA for Pricing and Reimbursement

The evidence requirements of regulators such as the EMA affect what data is shared with HTA Decision-Makers and with what uncertainty; these facts are then correlated against CEA and BIA, considering unmet medical needs and other elements [4]. This task is complicated by the fact that the evidence requirements of regulators in terms of benefits and harms are insufficient for a comparative assessment of HTA authorities [3] especially since the majority of the new studies submitted to the regulatory authority lack active comparators or are not available at all [3]. Moreover, there is limited additional evidence generated in the multi-year post-approval phase. This is especially true in oncology [3].

- *Clinical uncertainty is the («insufficient»?) base for P&R decisions by HTA bodies.*
- *Comparative data are limited or lacking, with an increasing tendency.*
- *Efforts to fill evidence gaps appear to be limited.*

Uncertainty in Pricing & Reimbursement

The clinical data for the P&R application are largely identical to the pivotal studies that have been made available for marketing authorization. This means that such data are predefined for P&R issues and the value base case of a new drug (Table 1: red boxes). Deliberative argumentation is possible for HTA, SOC, WTP and additional value elements the so-called "Value Flower" [10] (Table 1: yellow boxes). The initial price of a new drug will be adjusted by mutual agreement (Table 1: green box). Medical uncertainty has a much greater impact on pricing than economic uncertainty (Figure 2) because it influences decision-making based on both clinical benefit assessment and cost-effectiveness.

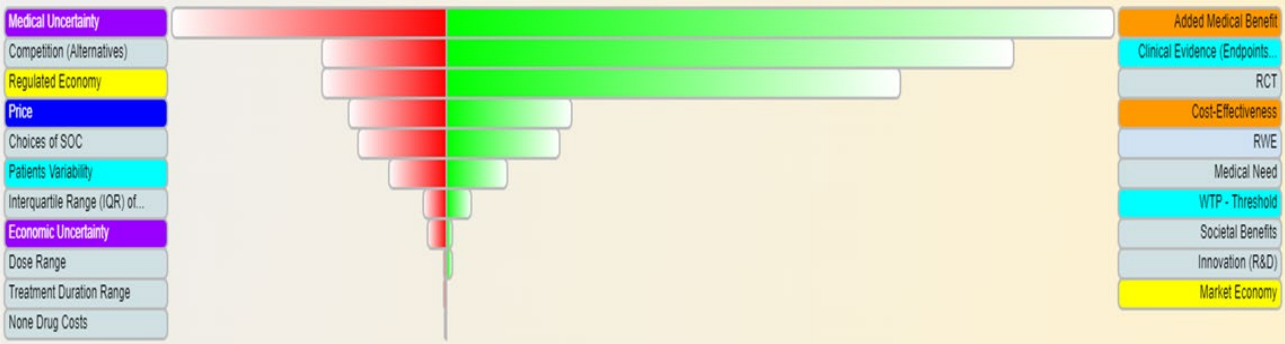
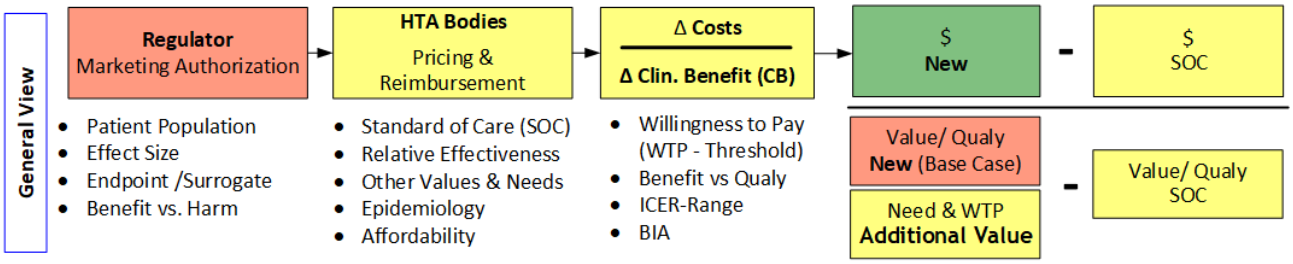


Figure 2: Comparison of influences on factor Price (short term perspective)
(Tornado diagram from an exploratory cause-and-effect relationship model for pricing under uncertainty, prepared by pharmaLevers, 2024)

Table 1: Types of Uncertainties and how to tackle



Key Drivers: Clinical Benefit – SOC – Drug Price - WTP			
	Issues	**Approach**	**Further Considerations**
Medical Uncertainty	• Endpoint Projections • Quality of Evidence • Active, Placebo or no Control • Durability of Effect • Patient Variability & Subgroups • Risk-Benefit	• Towards Multi-Stakeholder Consensus • Coverage with Evidence Development (CED) as RCT, RWE, Registries • Restricted Access • Uncertainty Discount (temporary or permanent)	• Early Access at reduced Price or delayed Access at full Price? • Reversing Rebates by Evidence generation • Adjust Price to get full Access
Economic Uncertainty	• Value for Money (fair Pricing) • Other Costs or Cost Offsets • Homogeneity of Costs per Patient • Epidemiology & Budget Impact • WTP - Threshold	• Separate Price from Value issues • Patient and Population Level • Price/Volume Agreements • Cost or Budget Caps	• Define, substantiate & defend Total Value Price • Adjust Price and ICER according to WTP • Price / Volume Deals • Maximal Costs per Patient
One-time CGT Uncertainty	• Potential Cure & Savings • Level of fair Pricing • Substantial Uncertainty about long term Benefit and Durability (Evidence) • Balance CEA with Budget Impact • No reversal upfront Payment Risk	• Pricing: Uncertainty Discount • Clinical Uncertainty: Outcome- based Agreements • Economic Uncertainty: Price-Volume, Capping • Budget Impact: financial models to spread costs • Cost-Effectiveness: Shared Savings	• Dynamic Pricing Linked to CED • Fair Risk-Benefit sharing • Pricing Models mix based on Product specific Uncertainties • Monitor CGT-Market (Sales % of pharma market) to identify Affordability issues early

± predefined ± arguable ± adjustable © pharmaLevers – YCF

Uncertainties in Market Access are due to the data gaps between regulatory and HTA authorities and institutions. The yellow boxes (Table 1) are areas where the value of a new intervention leaves different interpretations open, leading to uncertainty in decision-making for pricing & reimbursement. This is also the reason for the variability of decisions. The fundamental value of a new intervention is given by regulatory clinical data and can be increased by the acceptance of additional benefit elements.

It is imperative to distinguish between medical and economic uncertainties at both the patient and population levels. Medical uncertainties lower the value and thus also the price level; they are mainly data-based, and additional evidence is needed to reduce uncertainty and thus increase the negotiated price level. On the other hand, economic uncertainties can be reduced through specific pricing models while maintaining value and price levels. For example, cost caps at the individual level or price/quantity agreements at the aggregate population level.

It is imperative to distinguish between medical and economic uncertainties at both the patient and population levels:

- *Medical uncertainties lower the value and, consequently, the price level.*
- *Economic uncertainties provide an opportunity to hold the price while adjusting.*

Uncertainty is one of the main issue for **Cell and Gene Therapy** (CGT) [11]. CGTs should be handled somewhat differently for the following reasons: significant uncertainty about benefit and durability, very small clinical database compared to historical control, no reversible high upfront costs, claim for lifetime value, no future savings from generics, often very cost-effective, resulting in a high price that requires savings to be shared with society [12]. The uncertainty with CGTs is mainly at the patient level and is usually much higher than with "conventional" drugs. Pricing models (MEAs) for CGTs tend to focus on Outcome-Based Agreements (Pay for Performance) and recent publications on this topic are recommended for reading [13], [14].

Managing Uncertainties in four Steps

In the end, uncertainties should not come as a surprise, but should appear as unavoidable residual uncertainty (Uncertainty GAP) after a planned reduction in uncertainty. Uncertainty can be avoided or reduced e.g. by early dialog with adequate trial design and evidence generation (Step 1). Residual uncertainty is a basket of one or more medical, economic, and resource uncertainties. Identifying and differentiating between them is crucial, as different pricing models can be applied with fixed or reduced prices (step 2).

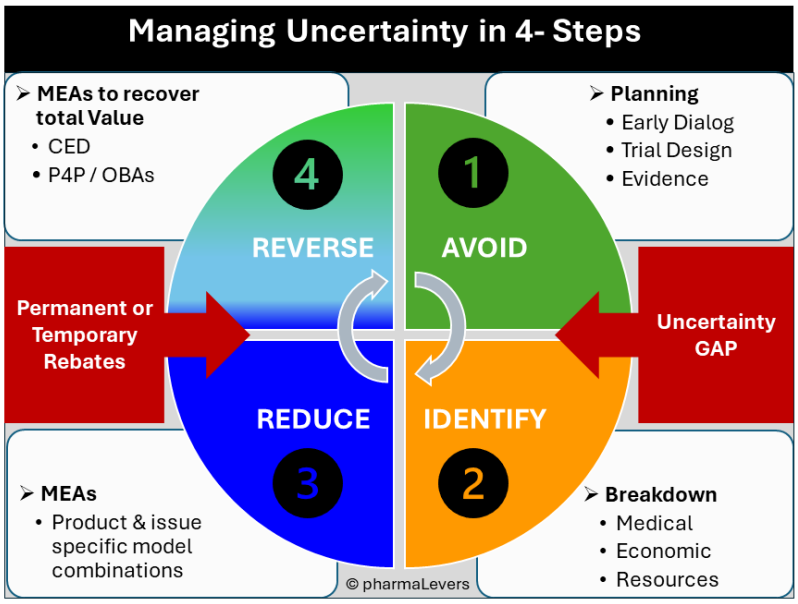


Figure 3: Managing Uncertainty in 4-Steps

Then the crucial question is whether to opt for permanent or temporary discounts and rebates[ii] on the original product price. In the majority cases, permanent uncertainty discounts are offered with different pricing models (Step 3). However, no, or only temporary discounts are possible with result-oriented outcome-based models or additional clinical data (evidence); however, these can lead to a delay in market entry and high additional costs (Step 4).

Don't treat uncertainties as a surprise, but as unavoidable residual uncertainty:

- *Differentiate between medical, economic and resource uncertainty.*
- *Pricing Models: choose wisely between permanent, no, or temporary discounts.*

Limitation

This newsletter deals with uncertainty in Market Access. No claim is made to completeness and correctness; additions, corrections and comments are welcome.

[ii] The goal for rebates may be: a) price differentiation for access, compensation for uncertainty, or c) compensation for treatment failure.

References

1. Jedynak P, Bąk S. Understanding Uncertainty and Risk in Management. J Intercult Manag. 2020;12(1):12–35.
2. Hogervorst MA, Vreman R, Heikkinen I, Bagchi I, Gutierrez-Ibarluzea I, Ryll B, et al. Uncertainty management in regulatory and health technology assessment decision-making on drugs: guidance of the HTAi-DIA Working Group. Int J Technol Assess Health Care [Internet]. 2023 Jun 16;39(1): e40. Available from: https://www.cambridge.org/core/product/identifier/S0266462323000375/type/journal_article
3. Vreman RA, Naci H, Goettsch WG, Mantel-Teeuwisse AK, Schneeweiss SG, Leufkens HGM, et al. Decision Making Under Uncertainty: Comparing Regulatory and Health Technology Assessment Reviews of Medicines in the United States and Europe. Clin Pharmacol Ther. 2020;108(2):350–7.
4. Bloem LT, Vreman RA, Peeters NWL, Hoekman J, van der Elst ME, Leufkens HGM, et al. Associations between uncertainties identified by the European Medicines Agency and national decision making on reimbursement by HTA agencies. Clin Transl Sci. 2021;14(4):1566–77.
5. Mills M, Kanavos P. How do HTA agencies perceive conditional approval of medicines? Evidence from England, Scotland, France, and Canada. Health Policy (New York) [Internet]. 2022;126(11):1130–43. Available from: https://doi.org/10.1016/j.healthpol.2022.08.005
6. Parsons JE. Communicating the findings of health technology assessments: Considering uncertainty. Med Writ. 2021;30(3):56–9.
7. Trowman R, Powers A, Ollendorf DA. Considering and communicating uncertainty in health technology assessment. Int J Technol Assess Health Care. 2021;37(1).
8. Otten TM, Grimm SE, Ramaekers B, Joore MA. Comprehensive Review of Methods to Assess Uncertainty in Health Economic Evaluations. Pharmacoeconomics [Internet]. 2023;41(6):619–32. Available from: https://doi.org/10.1007/s40273-023-01242-1
9. Institute for Clinical and Economic Review. Value Assessment Framework [Internet]. Value Assessment Framework. 2023. Available from: https://icer.org/wp-content/uploads/2023/10/ICER_2023_VAF_For-Publication_101723.pdf
10. Neumann PJ, Garrison LP, Willke RJ. The History and Future of the "ISPOR Value Flower": Addressing Limitations of Conventional Cost-Effectiveness Analysis. Value Heal [Internet]. 2022 Apr;25(4):558–65. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1098301522000857
11. Frederix GWJ, Ham RM ten. Gene therapies, uncertainty, and decision-making: thinking about the last mile at the first step. Expert Rev Pharmacoeconomics Outcomes Res [Internet]. 2023;23(8):853–6. Available from: https://doi.org/10.1080/14737167.2023.2245138
12. Pearson SD, Ollendorf DA, Chapman RH. New Cost-Effectiveness Methods to Determine Value-Based Prices for Potential Cures: What Are the Options? Value Heal [Internet]. 2019;22(6):656–60. Available from: https://doi.org/10.1016/j.jval.2019.01.012
13. Phares S, Trusheim M, Emond SK, Pearson SD. Managing the Challenges of Paying for Gene Therapy : Strategies for Market Action and Policy Reform [Internet]. 2024. Available from: https://icer.org/assessment/managing-the-challenges-of-paying-for-gene-therapy-2024/
14. Horrow C, Kesselheim AS. Confronting High Costs and Clinical Uncertainty: Innovative Payment Models For Gene Therapies. Health Aff. 2023;42(11):1532–40.

Author of the newsletter:

Kurt R. Müller, PhD, MSc, BBA

Principal and Managing Director

pharmaLevers GmbH