While orphan drugs offer novel treatments for patients who previously had no options, the high price points they often command have resulted in restricted access by many European Health Technology Assessment (HTA) systems and intense discussions about how to determine their value.

Against this backdrop, manufacturers are eager to understand how to value their innovation and collect sufficient evidence to support a price that appropriately reflects the improvement in clinical outcomes versus the standard of care. The analysis below indicates that patient prevalence is highly correlated with orphan drug pricing in Europe, highlighting the importance of budget impact to payer decision-making.

With European pricing so complex and interrelated between countries, early understanding of the target orphan disease epidemiology and the product value proposition and price potential are all critical to optimize launch sequence decisions.
OVERVIEW OF PRICING METHODOLOGY FOR ORPHAN DRUGS

Each country in Europe has unique post-approval pathways and methods for evaluating whether and how much to reimburse for new therapies. Today, most European countries rely on national HTA (Health Technology Assessment) processes to assign clinical and/or economic value to new drugs. However, target patient populations for orphan drugs are by definition small, standards of care may not be established, and endpoints may not yet be validated, thus posing challenges in collecting and evaluating relevant data to meet HTA needs.

While each country has its own system to assess the value of new therapies, most countries tend to consider added clinical benefit and budget impact, with some also placing high weight on cost-effectiveness. [See Figure 1].

While determinants of the final price and the pricing process itself is far from transparent, the final decision on price and access for novel orphan drugs in the above countries is determined through a combination of the HTA value assessment process, manufacturer proposed-pricing, reference pricing, and implicit and explicit price negotiations. The negotiation can be based on several factors:

Figure 1: HTA Categories of Value Assessment

<table>
<thead>
<tr>
<th>Added Clinical Benefit</th>
<th>Budget Impact</th>
<th>Cost - Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Answers the question: “Is the new intervention more effective than the standard of care?”</td>
<td>• Answers the question: “Can a health plan or government afford the new intervention?”</td>
<td>• Answers the question: “Is the new intervention value for money?”</td>
</tr>
<tr>
<td>• Improvement vs. the standard of care in relevant outcomes, not just surrogate endpoints</td>
<td>• Estimates the financial consequences of adoption of a new healthcare intervention within a specific healthcare setting or system context, given resource constraints</td>
<td>• Measured by Incremental Cost Effectiveness Ratio (ICER) vs. standard of care – Incremental cost for producing one additional unit of output, such as a QALY (Quality Adjusted Life Year)</td>
</tr>
</tbody>
</table>

| France | ✓ | ✓ | ✓ |
| Germany | ✓ | ✓ | ✓ |
| England | ✓ | ✓ | ✓ |
| Belgium | ✓ | ✓ | ✓ |
| Netherlands | ✓ | ✓ | ✓ |
| Denmark | ✓ | ✓ | ✓ |
| Austria | ✓ | ✓ | ✓ |

Legend  ✓ Consider  ✓ Strongly Consider
• HTA rating or score by subgroup (to capture the added clinical, economic and/or patient value of the therapy compared to the standard of care)

• Cost of the current therapy vs the proposed price of the new therapy, and target population size (to capture the potential budget impact of the new drug on the country’s national or regional healthcare expenditures)

• External reference prices (to ensure that list prices for the same drug in other countries are considered)

• Internal reference class prices (to benchmark against prices of similar drugs in the same country)

Additional manufacturer discounts (formal or informal) and/or managed entry agreements may then be negotiated as part of the conditions of national access.

ANALYSIS OF FACTORS INFLUENCING ULTIMATE PRICE

While HTA rating is often directly related to the decision of whether to reimburse, and quite important in the pricing negotiation, published studies and Health Advances’ internal analyses on potential correlations between HTA added benefit ratings and final prices have tended to be inconclusive, indicating the presence of many other factors.

To investigate these factors, we analyzed the prices of 13 non-oncological orphan drugs launched since 2011 in seven European countries, using epidemiologic data, public list prices and HTA reports.

As part of the analysis, we explored whether differential HTA ratings in Germany versus France influenced price differences, but found no significant effect. While German orphan drug list prices are generally higher than French prices, the degree of price difference was not statistically significantly higher for drugs which received a better rating in Germany versus France, compared to drugs which received an equal rating in both countries.

Thus, in order to identify other price predictors, we next investigated the correlation between price and disease prevalence. We found that treatments for the rarest of diseases are likely to have the highest published list price in all analyzed countries, and as prevalence increases, price decreases. The strength of the correlation ranged from moderate for France, Germany,
the Netherlands, Denmark and Austria, too strong for England and very strong for Belgium (See Figure 2.) These findings highlight the importance of budget impact considerations in payer decision-making.

DIFFERENTIAL PRICING BY COUNTRY

We also found that orphan drug list prices tended to be highest in Denmark and Germany, and lowest in France and Belgium (see Figure 3). Our analysis does not consider different VAT levels, confidential rebates and various innovative managed entry agreements [e.g. price-volume agreements] which can lead to different net prices realized by manufacturers.

SUMMARY AND KEY STRATEGIC IMPLICATIONS

Our analyses suggest that treatments for orphan diseases with the lowest prevalence are likely to have the highest price across European countries, but that orphan drug prices still differ considerably across the countries examined.

As scrutiny over pricing and value assessment increases, these data point to several success factors for realizing market access success in Europe for a novel orphan therapy:

1. Since prevalence and budget impact are key considerations in price decisions, investing in and presenting convincing documentation of the target population size and the potential budget impact to a payer system is crucial to support a pricing strategy.
   a. These budget impact analyses can be quite sophisticated and include estimates of both overall patient population size, as well as predictions for the flow of patients that would ultimately be eligible for and receive a new therapy.
   b. It is important to understand what comparator the therapy may be referenced to and the comparator’s current price as these will influence pricing flexibility.
2. The HTA result, while not directly correlated to price, will influence reimbursement and the ability to negotiate price. Thus, HTA and market access considerations (such as the comparator) should be considered early in the clinical development plan. Early and informal advice from the national HTA bodies to inform development plans should be sought when possible.

3. Since prices differ between countries, commercial launches should be prioritized carefully and early in order to maximize reimbursement success, preserve resources for later launches, and mitigate the potential negative impact of international reference pricing.

CONTRIBUTING AUTHORS

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ABOUT HEALTH ADVANCES LLC

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