Hampered with faltering economies, squeezed budgets and aging populations, the healthcare systems of Europe’s major markets are firmly focused on providing cost-effective outcomes. Although each country has specific market access requirements, Health Technology Assessment (HTA) has become an essential input into pricing and reimbursement decisions and clinical guidance on the use of innovative technologies across Europe.

Though HTA practices differ across and within national boundaries, specific themes have emerged. In particular, demands for evidence of clinical and/or economic benefit on new health technologies are increasing.

Pricing and reimbursement negotiations are becoming increasingly difficult, as cost-containment strategies—including reference pricing, limiting reimbursement for drugs assessed to lack cost-effectiveness, and retroactively assessing drugs already on the market—are being implemented in various ways across Europe.

How can brands compete with cheaper generic options—and how can emerging therapies compete with familiar, existing brands?

**Spotlight on Crohn’s Disease**
Considering the variable structure and constant evolution of the HTA process across the EU5, navigating this process is a daunting task. For new drugs aiming to compete in the Crohn’s disease (CD) market with multiple established therapies*, including expensive biologics, it will be an even greater challenge. Emerging brands only showing clinical efficacy over placebo—or brands not able to display superior efficacy over standard of care biologics (i.e. infliximab) in their clinical trial—face stronger headwinds in their ability to obtain favorable pricing and formulary placements, assuming they get approved. Emerging drugs competing with less-expensive biosimilars that are available or in development (i.e. adalimumab) are at an even steeper disadvantage. An HTA of an emerging drug’s clinical and/or pharmacoeconomic data resulting in a neutral or negative recommendation further increases the risk of the drug being reference priced to these cheaper versions of established brands, where applicable, and it may also impact key stakeholder opinion of the product if it is approved.

**MINI-CASE STUDY 1**

**Vedolizumab**
*(Takeda’s Entyvio) in Germany & the UK*

Entyvio marked the first non-TNF-alpha inhibitor biologic approved for use in ulcerative colitis (UC) and CD in Europe (the FDA approved Biogen’s Tysabri for CD in 2008 in the US, a non-gut-specific drug in the same class as Entyvio). In March 2014, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion for the application of marketing authorization of Entyvio for moderate to severe UC and CD, and Takeda launched Entyvio in July 2014. However, while Entyvio is largely available in countries like France and Germany, the drug remains in various stages of the negotiation process across the EU5.

*Physician & Payer Forum, June 2015: “The Market Access Landscape for Crohn’s Disease and Ulcerative Colitis in the EU5: Payer and Physician Perspectives on the Role of New Biologics and Biosimilars for Moderate to Severe Inflammatory Bowel Disease”.*

https://decisionresourcesgroup.com/report/?id=62
Germany:
In October 2014, the G-BA commissioned the Institute for Quality and Efficiency in Health (IQWiG) to assess vedolizumab for its benefit using the dossier submitted by Takeda in July 2014. In January 2015, IQWiG concluded that Entyvio offered “no added benefit” for patients not responding to conventional therapy, as well as “no added benefit” for patients who responded inadequately or were intolerant to TNF-alpha inhibitors.* The final result is a restricted reimbursement decision for Entyvio to be prescribed to those patients failing conventional therapies as well as TNF-alpha inhibitors, relegating Entyvio to 3rd-line usage and potentially to a reference pricing group.

Key Factors: With no active comparator data available from the pivotal trial program, adalimumab (AbbVie’s Humira) was chosen as the appropriate therapy comparator (ACT) for the purpose of the HTA. IQWiG cited a lack of similarity in study designs in impairing even indirect comparisons, thus preventing the ability to prove any clinical superiority. Additionally, IQWiG deemed the indirect analyses for adverse events to be inadequate.

Takeaway: Without head-to-head active comparator data, indirect comparisons need to be made and are likely to be deemed as “no added benefit” from IQWiG, a conclusion that is similar across other European countries.

United Kingdom:
In contrast to Germany, where clinical data was the primary focus for the HTA, an extensive pharmacoeconomic analysis was performed in the dossier submission of Entyvio to the National Institute for Health and Care Excellence (NICE). NICE sets a threshold between 20,000-30,000 GBP (using an incremental cost-effectiveness ratio [ICER]) in order to recommend the drug for reimbursement and establish favorable pricing. For Entyvio, the original submission to the Evidence Review Group (ERG) was met with many concerns regarding the evidence presented for Entyvio’s cost-effectiveness. A second model was constructed and was deemed to be generally poor in quality (e.g., complex, lacking detail on sources), leading Takeda to submit a third model for review.

In July 2015, despite continued concerns on the structure of the economic model (including debatable assumptions of key aspects of the disease), NICE reversed its initial rejection and issued a technology appraisal guidance recommending Entyvio for CD in patients failing conventional therapies and at least one TNF-alpha inhibitor,** relegating Entyvio to 3rd-line usage. This approval was contingent on a negotiated patient access scheme (PAS) in order to get market access in the UK.

Key factors: Without direct comparable evidence, and debatable concerns surrounding the resulting economic model, the ERG was not able to assign any concrete ICER to Entyvio and establish its potential cost-effectiveness.

Takeaway: Without clear and direct ability to compare the cost-effectiveness of a new drug to current therapies, a company is left in a weakened position at the negotiation table, typically resulting in the need to provide a PAS or other agreement in order to obtain reimbursement that is similar across the EU5, not just the UK.

Opportunity/Best Practice:
Setting the negotiation table. With saturation of the CD market building, companies proactively providing comparator and/or pharmacoeconomic data showing the clinical benefit and cost-effectiveness of the drug in anticipation of an HTA will have the advantage. In contrast, non-inferiority data or lack of evidence for cost-effectiveness will likely result in a shift of the key outcomes during negotiations toward patient access schemes, risk sharing contracts, and to a lesser extent formulation advantages (if any), in order to gain favorable formulary placements.

If you want it, be ready to put a ring on it. A commitment in investing in a country’s local economies (R&D, manufacturing, etc.) can provide important leverage when trying to overcome the pricing and reimbursement hurdles during negotiations. In general, once an HTA analysis results in a recommendation for reimbursement of the drug, the drug will be essentially guaranteed access and more favorable pricing will be established. However, annualized tender requests and need for longer-term post-marketing data for safety and pharmacoeconomic benefit will keep the pressure on new drugs to maintain their position on the formularies and in treatment algorithms.

If you can’t beat them, show the drug is promising in a subpopulation. Demonstrating superiority over current therapies in CD is a substantial challenge. However, interviewed payers suggest positive data in a patient subpopulation (e.g., TNF-refractory, corticosteroid dependent) may help leverage increased drug use (and price) in the disease when it would otherwise likely face heavy regulatory restrictions.

Challenges/Watchouts

Biosimilar availability equals no more free launch. As biosimilars to infliximab and adalimumab penetrate the CD market in the near-term, interviewed payers suggest these agents will likely become the pricing standard for expensive emerging biologics. Emerging therapies without convincing clinical data to support superiority over these agents or data showing a positive cost-benefit of use (e.g., reduced hospitalizations, improved quality of life) during the HTA will risk being restricted to biosimilar price levels or exclusion from hospital formularies.

To compare or not to compare? That is the question. Superiority data over active comparators will be critical to establish first-line recommendations from HTAs and payer authorities. Alternatively, issuing voluntary price cuts or constructing more favorable patient access schemes during negotiation or tendering processes may lead to a positive impact on the recommended positioning of the drug in the treatment algorithm.

What does it all mean?

In order to compete in the broader EU market, emerging brands for CD will need to set a new bar in efficacy—and to a lesser extent tolerability and/or formulation—that can differentiate themselves from current therapies (particularly therapies with biosimilars available or forthcoming), in order to best negotiate favorable pricing and formulary placement.

In addition, establishing a framework of the cost-benefit advantages for the use of the drug is paramount in obtaining a favorable pricing and reimbursement decision from individual countries’ HTAs.

In somewhat of a Catch-22, the current and evolving strategy of the EUS toward heavy cost-containment and increasingly stringent requirements further drives the high costs necessary to develop innovative new products while decreasing the room for reward with downward pricing pressure. The higher costs for developing an innovative and superior new drug to meet the growing demands of HTA recommendation thresholds also need to be aligned with an even greater cost-benefit scenario. A drug meeting all these conditions would still enjoy the pricing freedoms of years past.

The bottom line is that companies need to be more creative and flexible than ever before to compete in a new market where generics and familiar brands are increasingly being used to promote savings in national budgets. Realistic price expectations, coupled with creative patient access schemes or risk-sharing agreements, remain the most intuitive pathway to get placement on a formulary and a reasonable negotiated price in any given country. Accordingly, companies with drugs not able to differentiate themselves on either efficacy or cost-effectiveness measures will need to negotiate even steeper discounts and more complex patient access schemes in order to get their drug into the marketplace. Understanding national payer practices across the EU will be paramount in leaping the various pricing and reimbursement hurdles and successfully introducing an emerging brand into the European marketplace at a premium…or even on par with the current standard of care (SOC).
A Wave of New and Unique Parkinson's Disease Products Will Come Crashing into Europe

This trend began in 2015 with the introduction of Zambon Pharma/Newron Pharmaceuticals' Xadago (safinamide), a monoamine oxidase type B (MAO-B) inhibitor. In November 2015, Impax Laboratories' levodopa reformulation Numient was approved by the European Medicines Agency (EMA) and is expected to launch in Europe in early 2016. By 2020, we foresee the launches of a novel catechol-o-methyltransferase (COMT) inhibitor (Bial/Ono Pharmaceutical's opicapone), a first-in-class levodopa adjunct (Kyowa Hakko Kirin's istradefylline), and a safe and effective alternative to treat PD psychosis (Acadia Pharmaceuticals' Nuplazid). Meanwhile, launch potential exists for new and improved rescue therapies (e.g., from Acorda Therapeutics), amantadine reformulations for managing levodopa-induced dyskinesias (e.g., from Adamas Pharmaceuticals), and additional levodopa reformulations.

MINI-CASE STUDY 2

Xadago

in Germany

In May 2015, Zambon and Newron launched Xadago in Germany for the treatment of PD as an adjunct to levodopa. Xadago is the third-to-market MAO-B inhibitor, following Teva/Lundbeck's market-leading product Azilect and the older, less favored selegiline (Orion's Eldepryl, other brands, generics). In clinical trials, Xadago—as an adjunct to levodopa—increased “on” time by ≥0.5 hours and decreased “off” time compared to placebo; there was no active comparator arm, but these data appear similar to Azilect for this treatment setting.

Xadago falls flat at IQWiG.

IQWiG has cited the absence of relevant study data and incomplete analyses in the dossier “regarding serious side effects in the comparator therapy, long-term data, and other aspects.” In particular, the developers conducted an adjusted indirect comparison of clinical trial data for Xadago and COMT inhibitor entacapone (Novartis's Comtan, generics) against placebo, but did not compare more recent data assessing the long-term efficacy and safety of entacapone with extension data for safinamide.

If G-BA follows lock-step with IQWiG's assessment (which is likely, but not a guarantee), after a year of free pricing, Xadago will be facing downward pricing pressure, most likely through negotiations with the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband [GKV-SV]) with an eye toward capping the price relative to other MAO-B inhibitors or an agent that is typically used in the same line of therapy as a levodopa adjunct.

Spotlight on Parkinson’s Disease

Parkinson’s disease (PD) is one of the most common chronic neurodegenerative diseases in the elderly, generating approximately $2.5 billion in drug sales in the major pharmaceutical markets in 2014**. By 2020, Decision Resources Group forecasts the G7 prevalent population will grow by more than 10%,*** further increasing strain on healthcare resources. Today, the hallmark motor symptoms of PD are reasonably well-controlled by a range of approved symptomatic drugs; as a result, the treatment algorithm in PD is both well established and highly stable.**** Nevertheless, several key areas of unmet need—such as improving the pharmacokinetic profile of levodopa, or improving control of motor complications or key nonmotor symptoms—present niche opportunities with attractive commercial prospects for new brands entering a crowded, cost-sensitive market that is composed almost entirely of generics.

If the cap were set against the price of generic selegiline, the impact on Xadago pricing would be substantial. Likewise, Xadago’s price would be sorely limited if it were to be relegated to some newly created reference pricing group, feasibly incorporating generic levodopa adjunctive therapies from one or more drug classes, including COMT inhibitors (e.g., entacapone; ~$5/day in 2014 [ex-manufacturer]).

Either scenario presents a disappointing outcome for one of the new therapies to launch for PD in the last decade. The companies would be able to request a re-evaluation of the ruling and would have the opportunity to resubmit Xadago’s dossier with additional information. If unchanged, however, a G-BA ruling of “no added benefit” could have a broader revenue impact on Xadago across the region, as Germany often serves as a pricing benchmark for other European markets.

Implications for Future Players

The case of Xadago highlights several issues facing new products undergoing HTA in Germany, and raises a number of key market access themes across Europe.

Comparator assessments must be thorough, and preferably head-to-head. According to IQWiG, Newron/Zambon opted not to compare long-term data for Xadago and entacapone owing to different trial durations. In its review, IQWiG conveyed that such comparisons were not only possible, but would have added valuable information. IQWiG also noted that treatment patterns may have changed since the entacapone studies were conducted.

**Takeaway:** If companies perform indirect comparisons, IQWiG will expect manufacturers to maximize available data, even if the comparisons are imperfect, or risk submitting a dossier that is deemed “incomplete.” Freshness of comparator data is also important; historical trials may not be representative of current treatment practice. Ultimately, however, the absence of prospective studies with an active comparator arm is a surer path to “no added benefit”—not only in Germany, but across many European countries.*

Choose comparators carefully. HTA bodies across Europe expect comparators to be standards of care (SOCs) within a comparable treatment setting.* The G-BA identified multiple potential comparators for Xadago, including non-ergot dopamine agonists, COMT inhibitors, or MAO-B inhibitors. Ultimately, Zambon/Newron’s selection of entacapone over fellow MAO-B inhibitor Azilect may, in part, have reflected differences in label for Azilect, which is approved not only in combination with levodopa or other PD treatment, but also as a monotherapy for the treatment of PD.

**Takeaway:** With so many safe and effective treatments for many different clinical scenarios in PD, developers should engage early with HTA bodies across markets to know which comparator agents they prefer—and anticipate there may be inter-country differences based on local SOCs.*

Pricing is a process: Drugs without definitive proof of added benefit face reference pricing in Germany or—if a reference price group is not yet established—a price cap set by negotiation with the GKV-SV. Yet, even marketers of new chemical entities deemed to have “additional benefit” should expect tough, iterative rebate negotiations with the GKV-SV to decide final reimbursement price. Meanwhile, reformulations—which comprise a large component of the PD pipeline—will not undergo an IQWiG evaluation; reimbursement price will be set to the relevant reference group or comparator cap, but clinical improvements can still be rewarded with a premium price by state health funds. However, stretching price above the reference group is perilous if German patients, who are unaccustomed to high out of pocket costs, refuse to pay (or can’t afford) the difference.*

**Takeaway:** There are several paths for new drug pricing in Germany; if undifferentiated, a new brand’s price will be benchmarked to other drugs. For innovative brands, finding the pricing sweet spot requires a careful balance of a drug’s perceived clinical value, level of unmet need, size of the target population, the cost of similar drugs, revenue expectations, budgetary impact and constraints, and patient affordability. A different calculus may be required locally/regionally within, and across, European Union nations.*

What does it all mean?

The clinical success and low cost of current treatments sets a high bar for novel entrants to the PD market. Proof of legitimate benefit over relevant comparators must be the cornerstone of successful pricing and reimbursement negotiations—cost-conscious payers in Germany, and indeed across Europe, will not loosen the purse strings for incremental advances. Ultimately, HTA success demands:

- Early planning
- A thorough understanding of the policies, processes, and stakeholder values that drive decisions
- Knowledge of what key levers exert the greatest influence

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In Summary: Successful HTA and MA Value in 2016

In order to compete in the broader EU market, a new medicinal product has to satisfy not only the needs of regulators, but also those requirements of HTA bodies and payers. Apart from evidence of efficacy and safety, health economics and outcomes research data are new standards. They are currently indispensable in these assessments in most countries, due to payers seeking better value for money spent on treatments.

**Asking for trouble? Or just trying to fulfill the actual requirements for all different stakeholders?**

Providing evidence to meet all requirements can be a devil of a job, so planning in advance is essential to achieve a positive HTA opinion to support the company’s future reimbursement request. Complementing the current “early scientific advice” and the Adaptive Licensing offered by the EMA, the Multi HTA Early Dialogues (SEED*) are enhancing interaction between developers, regulators, and HTA bodies. This is a great opportunity to reach consensus on a development plan that generates data that the different parties can use to determine a medicine’s benefit-risk balance and value, in the interest of their common objective of getting innovation to patients.

Effectiveness assessments rely on principles broadly similar within the European variability—but there are some differences in the HTA methodology, like the acceptability of some comparisons and comparators. However, stakeholders expect as determining evidence from HTA reports the results from comparative studies, ideally of head-to-head trials comparing the new treatment with the current standard of care. The proper choice of comparator is now vital. Early dialogue and planning are valuable to understand and integrate (in the development) the different evidence requirements to choose the most acceptable comparator.

**Proving cost-effectiveness over the standard of care**

Within Europe’s aim to achieve sustainable healthcare systems, demonstration of cost-effectiveness (CE) is essential to determine whether a drug or intervention provides value-for-money. CE comparisons allow healthcare systems to allocate limited resources to achieve maximum benefit, so stakeholders are increasing their requirements to get more patient reported outcomes and real world evidence data (even though long-term and effectiveness data are generally not available when a new technology is approved).

**Proving added benefit to a smaller population will be positively valued**

Europe uses a societal perspective when undertaking HTA, requiring an evaluation of the burden of disease in the population specific to the market in which the technology is being assessed. With all available options already in the market, sometimes it is necessary to narrow the defined perspectives, and target those subpopulations with greatest unmet needs or with gene mutations which benefit from therapies with biomarkers.

**Adapting to regional requirements**

HTA is now an essential step to gaining market access in Europe. In addition to understanding the slight differences in HTA methodology and market access procedures across the EU5, regional variation is a factor. In countries like Italy and Spain—where regions have authority over policy and financing of their healthcare systems—regional HTA is important for regional pricing and reimbursement decisions, which may sometimes vary from the national level. Companies must show the ability to adapt to regional requirements — especially in regions under tight healthcare budgets, which normally use cost-containment measures and expect bigger discounts.

**Finally, from conflict to confluence**

Within the EU5 strategy to achieve sustainable healthcare systems, stakeholders are keen on value and willing to find new approaches to integrate innovation in the healthcare system. It is the moment for companies to bring added value and become partners of the healthcare system.

*SEED (Shaping European Early Dialogues for health technologies) is an international project financed by the European Commission with an objective to reduce the risk of production of data that would be inadequate to support the company’s future reimbursement request. - 14 HTABs of 10 different countries: Austria, Belgium, France, Germany, Hungary, Italy, Ireland, Netherlands, Spain, UK. [http://www.eunethta.eu/seed](http://www.eunethta.eu/seed)*
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