**HTA Uncovered**

**THE IMPACT OF MARKET ACCESS ON PHARMA ASSET VALUATION**

While the number of new molecular entities approved by the FDA was higher in 2014 and 2015 than in any year since 1996, spend on research and development continues to increase even faster, reaching $51.2 billion in 2014, almost double the $26 billion spent in 2000. The ability for pharma companies to generate strong return on investment in the face of decreasing productivity is therefore a key priority.

In-licensing of assets to strengthen a company’s pipeline and product portfolio has been a long-standing practice in pharma, with deal volume increasing from 22 million USD in 2000 to 6.68 billion USD in 2014. The due diligence process is an established method for assessing the asset value, with many companies relying on technical probability of success at regulatory approval for their valuations. While this provides a reasonable basis for estimating market size either in terms of epidemiology or potential spend, it excludes the impact of hurdles that may be encountered during market access appraisals by payers.

**Precision in investment planning**

There is an abundance of additional data available which, if understood and leveraged, could have a dramatic impact on valuations. Those that fail to incorporate the impact that payer decisions have on product value are likely to be overestimated. By overlaying the impact of potential market access challenges after regulatory approval on an asset’s value, expected return on investment is more precise. Leveraging insights, such as: probability of success at Health Technology Assessment (HTA) stage; time to revenue generation following marketing approval; and price negotiations, can help companies to arrive at a more precise valuation than they could if they simply relied on the investment community’s view.

**Probability of success**

Depending on indication, the success rate of products at market access approval is 60-80%. The risk of receiving a negative recommendation must therefore be factored into forecasts and investment decision-making if they are to be robust Quintiles’ research has found that asset valuations, which do not incorporate this metric, tend to be overvalued by 20-40%, as outlined in Figure 1. Across an entire company portfolio, the discrepancy easily becomes a very large number. To gain a true picture of expected value, this likelihood of approval should be incorporated in forecast calculations.

Further, to proactively maximise value, this kind of analysis should be built into asset valuation and used to refine development strategy. By interrogating HTA Accelerator, Quintiles’ proprietary database capturing insights from payer decisions worldwide, its experts can estimate the most likely recommendation from HTA bodies throughout Europe, based on available evidence, and advise on design of phase II and III programs to improve the probability of success. When done early enough, the results of this analysis can inform strategy to maximise the value of the product. For example, by incorporating the right endpoints and comparators to satisfy multiple HTA bodies each with different evidence requirements, or selecting the right trial design and sequencing to optimise development time.

Later in the process, companies can tailor their evidence strategy for HTA submissions to optimise their chance of securing appropriate reimbursement the first time. For example, they may wish to seek a more limited indication in order to improve their chance of receiving a positive recommendation first time. To determine the right approach, companies need to consider reduction in potential value from a smaller patient population in the context of any increase in value that could be gained by a achieving a positive recommendation for the original submission.

---

<sup>1</sup> In one indication, adding HTA parameters reduced the expected NPV of an in-licensing opportunity in phase II by ~40%
Time to revenue generation

Getting HTA approval right the first time is particularly important when considering that any delay in revenue generation can in turn impact valuations. Projections often assume that revenue will commence at regulatory approval, however, factoring in the time to reimbursement approval ensures that figures are more realistic. As represented in Figure 2, while the reimbursement approval process varies by country, with an average time of 15 months, failure to adjust for this risks overestimating the value of a product.

Price negotiations

Accurately estimating the price of an asset is the third element in applying market access considerations to asset valuations. Policies are in place in several European countries which restrict pricing and exclude very-high-priced drugs from the market, meaning that often, companies are unable to secure the price they had hoped.

For example, in one analysis, there was significant variation in price points projected by analysts and those derived using insights from HTA Accelerator. While the analyst community estimated European prices to be around 80% of US prices, the reality was that average prices secured in Europe were around 30% of US prices, as outlined in Figure 3.

In light of this, more precise modelling of the impact of price on probability of success can help to reduce uncertainty for manufacturers and facilitate better strategic planning.

Strategic planning to maximise commercial value

Commercial potential is heavily contingent on offering value for money to payer stakeholders who have the power to influence access, availability and demand for medicines. However in our experience, the impact of market access constraints on probability of approval, time to launch, and price are either handled crudely or generally ignored. This directly impacts the likelihood of a product being adopted and subsequently, the revenue it generates.

Overlaying traditional financial metrics with the probability of success at HTA helps to build more robust valuations and strategies to maximise the value of the compound that is going to be developed. It is now possible to incorporate market access data into asset valuation with similar rigour to clinical data.

Armed with this insight, companies looking to acquire or in-license an asset can produce a more precise model and a more robust valuation, strengthening their negotiating position. When assessing investment options, this can be critical.
2015 in review: increased focus on subpopulations

The number of published health technology assessments (HTAs) remained steady from 2014 to 2015. More than 3,500 records across 26 countries worldwide were captured in Quintiles’ proprietary database HTA Accelerator. This comprised 1,744 HTAs from 2014 and 1,776 from 2015, a year on year increase of 2%.

While there were no clear-cut trends in the dataset as a whole, looking closer at different therapeutic areas and the recommendations made by particular agencies, reveals interesting insights into HTAs. For example, there has been an increase in focus on HTA in infectious diseases as new and costly hepatitis C medicines have received marketing approval. Reviews are also becoming more precise. In oncology, for example, there has been an increase in restricted positive recommendations either by subpopulation or line of treatment.

The state of HTA

The French authority Haute Autorité Santé (HAS) published more than 1,000 reports over 2014-2015, more than double the number of reports published in Canada (422) and the United Kingdom (394). This differential is driven by France’s propensity to re-assess products after three to four years, and the number of original HTA assessments (262) was more in line with the other top publishing countries.

Sweden, Germany and Australia each conducted more than 200 assessments with 301, 230 and 214 reports published respectively.

The remaining countries published fewer than 100 recommendations each, with the exception of the Netherlands which published 101. Several countries including Brazil, Germany, South Korea and the UK published more HTA reports in 2015 than they did in 2014.

In the US, the number of published reports more than tripled between 2014 and 2015, reflecting an increasing focus on drug pricing in the US that is evident in both the press and the presidential campaign. AETNA is the leading insurer in terms of the number of reports published, followed by CIGNA. The Institute for Clinical and Economic Review (ICER) was particularly active in 2015, rolling out its Emerging Therapy Assessment and Pricing program involving analysis of the comparative effectiveness, cost-effectiveness, and potential budget impact of new medicines and calculation of a benchmark price for each new drug based on ICER’s view of the real benefits the drug brings to patients. Its reports are intended for use by providers and insurers in negotiating prices with pharmaceutical companies and it will be interesting to observe any impact on drug pricing in the near future.

In terms of the type of assessment conducted, the number of single drug assessments varied by country, however the total number of single drug, medical, multiple drug, and procedure/intervention assessments published appears to have remained stable. We have seen an increasing attempt by EMA to achieve greater harmonization and consistency in the way the assessment of devices is applied, however this is not yet reflected in an increase of medical device assessments. Figure 4 shows a breakdown of single drug assessments (original and extensions of indications) by agency.

Priority therapies

There was an increase in the number of published HTAs in infectious and parasitic diseases, oncology, and skin diseases, as reflected in Figure 7.
HTAs related to the blood and immune system area and musculoskeletal therapeutic area clearly decreased. This reflects the number of drugs being approved, as the number of drugs approved by EMA and FDA more than doubled comparing 2012-2013 and 2014-2015.

Between 2014 and 2015 Eylea (aflibercept) and Xtandi (enzalutamide) were assessed most often by all HTA agencies, as reflected in Figure 5. Eylea was assessed twelve times in both 2014 and 2015, while Xtandi was assessed nine times in 2014 and eleven in 2015. Harvoni (ledispasvir + sofosbusvir), Otezla (apremilast), Consentyx (secukinumab) and Zydelig (idelalisib) were assessed for the first time in 2015, and also belonged to the top assessed drugs in 2014-2015.Otezla (apremilast), and Consentyx (secukinumab) were the drivers for the 62% grow in skin diseases related HTAs between 2014 and 2015; the therapeutic area with the highest growth in published HTAs.

HTA Accelerator enabled a deeper look into each therapeutic area, which revealed a number of interesting trends. Here we dive into two areas, oncology and hepatitis C.

**Oncology: the increase in subpopulations**

Cancer remained the top priority in terms of number of assessments published in 2015, with 285 assessments globally as shown in Figure 6, representing an increase of 13%, as shown in Figure 7. Within this, the percentage of recommendations that were specific to subgroups was higher in 2015 than in 2014 (66.9% in 2015 compared to 51.2% in 2014), as pharmaceutical companies tended to focus their first submissions on sub-diseases rather than further line treatments. Among the reasons for this focus is the trade-off between manufacturers’ desire to get to the market early, which may mean they have limited data in smaller populations, versus longer development time to generate more robust data. Furthermore, focusing on more specific indications allows the manufacturer to more precisely demonstrate unmet need for the population. This strategy seems to be successful as the percentage of negative recommendations is decreasing overall.

For example, the National Institute for Health and Care Excellence (NICE) has recently published its assessment on Keytruda, the first product which was approved through the MHRA’s Early Access to Medicines Scheme. The scheme aims to promote innovation by giving patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. The NICE decision was based on immature data however the unmet need for the sub-population under review, it was able to apply end of life criteria and cost-effectiveness was subsequently deemed to have been demonstrated.

This trend reflects an increasing focus on stratified evidence and a willingness by the HTA body to reward true innovation.

**Infectious and parasitic diseases: the everlasting interest in Hepatitis C**

The 23% increase in HTAs published related to infectious and parasitic diseases reflected in Figure 7 can be explained by the increasing interest in one of the primary diseases in this therapy area, hepatitis C. The number of published HTAs for hepatitis C increased from 46 HTAs in 2014 to 58 in 2015, indicating that hepatitis C remains an area of high interest to manufacturers.

The number of treatment regimens reviewed increased in 2015 as products such as Viekirax (ombitasvir, paritaprevir and ritonavir) and Harvoni (ledispasvir + sofosbusvir) were assessed for the first time in single drug assessments and became available for combination therapy. More than 50% of recent reviews of treatments including one of four new direct acting antivirals drugs resulted in restricted recommendations by HTA agencies, with the drugs being recommended for use in 26-54% of the population.

**Restricting recommendations, restricting costs**

Overall, a clear trend in the type of recommendations published is difficult to spot. Taking a closer look provides deeper insights. Focusing only on the United Kingdom reveals a clear increase in positive recommendations with restrictions since the first quarter
of 2015, while the number of positive recommendation remains roughly the same. An increased number of cancer treatments and treatments for infectious and parasitic diseases received restricted positive recommendations in 2015. This could be a strategy applied by these agencies (AWMSG, NICE, SMC) in order to contain costs. Most restrictions applied to either subgroups or to the line of treatment. Agencies in the United Kingdom (AWMSG, NICE, SMC) are highly concerned with cost-effectiveness and apply cost-effectiveness thresholds, implying that limiting submissions to certain subgroups or lines of treatment may help to demonstrate cost-effectiveness and secure reimbursement approval within the United Kingdom.

Breaking down the type of recommendation by agency in France and Germany also reveals interesting insights. In a previous HTA Uncovered article (June 2015) it was mentioned that applicants might be inclined to seek an ASMR IV or V rating more often in order to avoid the economic evaluation process in France. The data in our HTA accelerator showed the French National Authority for Health (HAS) issued no ASMR I rating in 2015 and only 2 ASMR II ratings, a decrease from the 9 attributed in 2014. It should also be noted the percentage of ASMR III ratings was notably lower. The percentages of ASMR IV ratings increased, which supports the statement above.

Looking closer at the benefit rating (G-BA, Germany) showed less variety between 2014 and 2015, but revealed that the percentage of HTAs with a non-quantifiable benefit rating doubled. Both ASMR and benefit rating breakdowns are shown in Figure 8.

Looking forward

Based on a review of ongoing assessments in HTA Accelerator, cancer is likely to remain the priority therapy area for Health Technology Assessment in 2016, followed by endocrine and metabolic diseases, reflecting an ongoing focus on high cost and high budget impact therapies. Treatments for infectious and parasitic disease, cardiovascular and respiratory are also likely to be prominent in terms of the number of HTAs published in the near future.

Japan is likely to see an increasing focus on HTA in 2016. The Central Social Insurance Medical Council (Chuikyo) rolls out plans for the introduction of cost-effectiveness assessment for medicines as part of its national medical fee revision for 2016.

Changes are also afoot in England with the confirmed transfer of responsibility for the £340m Cancer Drugs Fund to NICE. From 1 July NICE will have full responsibility for the fund, with decision-making responsibility for all medicines. Rather than simply issuing a positive or negative recommendation for new products, NICE will now have the option to make products available to patients under the Cancer Drugs Fund for a two-year period during which real-world data to establish the drug’s efficacy can be collected. Full operating procedures and methodologies will emerge in due course however the fund will remain closed to new products until July, which is likely to cause continued frustration for patients.
Events and publications

Meet us at the following conferences


- Day 1: 26th April 2016 11:40
  - Session: Drug evaluation trends and initiatives
    Understand the real drivers of HTA decision making in oncology. What clinical and economic factors influence positive vs negative recommendations?
    By Anke van Engen

- Day 2: 27th April 2016
  - Panel Discussion moderated by Janice Haigh at 16:50: Developing & implementing advanced innovative pricing & reimbursement models. Meet us at the Networking Reception hosted by Quintiles at 19:00

ISPOR 21st Annual International Meeting, 21-25 May 2016, Washington, DC, USA

- Workshops
  - Biosimilars: current developments and real-world evidence generation
  - Real-world data and real-world evidence in Latin America: it takes two to tango
  - Is value truly in the eye of the beholder? Analyzing the heterogeneity of outputs from ASCO, NCCN and DrugAbacus oncology value frameworks and exploring implications for cancer drug development
    - Missing data in observational studies

- Posters
  - Sensitivity of clinical endpoints in the ASCO oncology value framework and implications for clinical trial design
  - Enhancing interpretation of patient-reported outcome scores through intuitive metrics: an example from prostate cancer
  - Overview and comparison of frameworks for the valuation of oncology drugs
  - What impacts the quality of comparative effectiveness research: a classification and regression tree analysis using the GRACE checklist

Webinars

- Adaptive pathways, 31st March 2016, 10-11 EST.
  Speakers: Stella Blackburn and Janice Haigh. Register at: (weblink)

Quintiles Blog (weblink)

- Adaptive pathways offer hope to meeting patients needs faster – Stella Blackburn
- Key market access learnings from a U.S. launch – Randolph Carpio
- Capturing patient-centered evidence: The enriched study story – Jennifer Christian
- Fighting cancer in the real world – Jaclyn Bosco
- Breaking through the complexity: Accessing cancer drugs in the UK – Dean Summerfield
- Achieving HTA success with real world evidence – Anke van Engen
- The Right Economic Model for HTA – Ray Gani
- Using registries to support HTA submissions in Japan – Nancy Dreyer
- New research supports value-based pricing – John Doyle
- Drivers of successful HTA submissions – Anke van Engen
- Patient-Centered Drug Development & Market Access: Nine steps to success – Louise Parmenter
- How to break into the EU – Dean Summerfield
- The role of PROs in approval, reimbursement and prescribing decisions in Europe – Montse Casamayor

Contact Us

Quintiles Advisory Services

Toll free: +1 866 267 4479
Direct telephone: +1 973 850 7571
International: +31 23 567 0991
Web: http://www.quintiles.com/services/advisory-services
Email: advisoryservices@quintiles.com

Anke van Engen
Office: +31 (0) 23 5670990
Mobile: +31 (0) 6 46236510
anke.vanengen@quintiles.com

Peter Wagner
Office: +49 61 02296352
Mobile: +49 1 721559607
peter.wagner@quintiles.com