HTA Uncovered

Benchmarking HTA performance

Positive Health Technology Assessment (HTA) recommendation is a key step in successful market entry for pharmaceutical companies. In this article we examine company performance in HTA submissions and some of the issues that companies face in overcoming this hurdle. Results indicate that there are significant differences in the approaches and the time taken to gain positive recommendations, if these are achieved at all.

In July 2015 Quintiles Advisory Services performed analysis on data taken from Quintiles’ HTA Accelerator platform. All original submissions in the last five years where a positive, positive with restriction or negative recommendation was issued by any of the five key EU agencies, Gemeinsamer Bundesausschuss (G-BA), Haute Autorité de Santé (HAS), The National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC) and Zorginstituut Nederland (ZIN) were extracted, totalling nearly 800 records on over 350 products from 117 different companies.

From this data, the top 15 submitting companies - determined by the total number of original submissions received (range 15 to 61 submissions on 6 to 24 products per company) - were included in the analysis and compared to the overall average.

Top 15 companies perform slightly better than average

Having spent years building a clinical and regulatory case for a product to then fail to gain a positive recommendation at the final hurdle may be a costly barrier that significantly impacts sales and ultimately company success.

With this in mind Figure 1 shows that on average 20% of original submissions made by companies failed to gain a positive recommendation (with or without restrictions) from the HTA agencies. The majority of the top 15 companies performed better than average in avoiding negative opinions, yet only 6 companies scored better than average positive recommendations.

To investigate what lies beneath this headlines figure, we have examined the data from four different companies.

Figure 1. Outcome of HTAs for companies making most submissions
Based on analysis HTA Accelerator. The 15 companies are ranked by success rate (defined as full and restricted recommendations). Original submissions leading to publication of a recommendation by G-BA, HAS, NICE, SMC or ZIN in the last 5 years.
38% of negative recommendations come from a single therapeutic area

*Company A* is a top twenty multinational pharmaceutical company with products launched in a wide range of therapeutic areas. Based on the data available, *Company A* currently sits among the highest in negatively returned recommendations from nearly 40 original submissions made to the 5 agencies in the last 5 years.

Figure 2 shows a breakdown of *Company A*’s submissions by therapeutic area (TA) and the contribution that makes to the overall figure. Success in convincing payers varied from one TA to another. More submissions were made for TA5 (cancer) than TA1, TA2, TA3, TA7 & TA8 combined. However the success rate was poorer in TA5 and contributed to 36% of all negative recommendations for *Company A*.

![Figure 2. Company A recommendations by therapeutic area](image)

Overall in the industry, 57%, 16%, and 27% of HTA submissions for cancer therapies received a positive, restricted and negative recommendation, respectively. As there are many submissions in this TA, the negative recommendations for oncology products contribute 38% to all HTA rejections.

As can be seen from Figure 2, *Company A* received far more recommendations with restrictions for their cancer submissions than industry average (36 vs. 16%). By using Quintiles’ HTA Accelerator, companies can see how they benchmark vs. the overall average in their TAs of interest and learn from competitors in areas where they might be doing worse.

Success by agency differs

In previous issues of HTA Uncovered, the ways in which different agencies approach health technology assessment has been explored and this has highlighted the distinct ways in which products are assessed. To examine how a single company performs in each agency we now look at *Company B* which is a top twenty multinational pharmaceutical company with products submitted to all five agencies during the last five years.

Based on the data, *Company B* currently sits slightly above average in negatively returned recommendations from over 55 original submissions made to the 5 agencies in the last 5 years.

![Figure 3. Company B recommendations by agency](image)

The number of submissions ranged between 5 and 22 per agency. As shown in Figure 3, *Company B* received a much greater percentage of negative recommendations from NICE and G-BA than average. While *Company B* made only few submissions to NICE (5), the G-BA rejections contributed 35% to the total number of negative HTA recommendations received by the manufacturer.

It is clear that the HTA agencies may sometimes have different opinions. In one instance, a single product received different recommendations from three agencies; G-BA providing a negative recommendation due to the lack of compelling clinical evidence, SMC providing a positive recommendation restricting the indicated population due to the clinical evidence, and HAS providing a positive recommendation without restriction.

What is striking in Figure 3 is the number of positive recommendations from Haute Autorité de Santé (HAS) which we will examine further in the next section.
Beyond a positive recommendation in France and Germany

In Figure 3 we can see that Company B achieved 64% positive recommendations from HAS. In France, however, we know that the ASMR rating provided by the Transparency Committee has a significant bearing on subsequent pricing negotiations.

Similarly, in Figure 5 we can see how Company D have performed in their submissions to the Gemeinsamer Bundesausschuss (G-BA). From the 7 submissions they made, 2 received a negative recommendations (‘no added benefit’). Even four of the five remaining positive recommendations received a ‘minor benefit’ rating, suggesting that these products may not have had the strongest starting point in price negotiations.

Figure 3. ASMR ratings obtained by Company B

Figure 4. ASMR ratings obtained by Company C

Figure 5. G-BA ratings obtained by Company D

Successful HTA submission requires collaboration and expert input

Companies make significant investments to get their product past the regulatory approval hurdle but, as our initial analysis indicates, subsequent success in meeting the needs of payers varies from company to company. Ensuring that a robust clinical case is developed which meets the needs of payers in each market requires close collaboration between Medical, Commercial and Market Access groups internally. Addressing this early in the drug development process and accessing expert support with local market access knowledge at the earliest opportunity will improve the probability of success.

By using Quintiles’ HTA Accelerator, companies can see how they benchmark vs. the overall average in their therapeutic areas of interest and learn from competitors in areas where they might be doing worse.
SMC setting the PACE in flexing their processes for end-of-life and rare diseases?

Giving patients and clinicians a stronger voice

In October 2013, the Scottish Government stated that existing cost-effectiveness thresholds are not always appropriate for end of life medicines or for medicines to treat very rare conditions. In a response to this publication, the Scottish Medicine Consortium (SMC) proposed to change its process to give patient groups and clinicians a stronger voice by introducing a Patient and Clinician Engagement (PACE) meeting which brings together patient representatives and healthcare professional experts for the following type of medicines:

- **End of life medicines**: to treat a condition at a stage that usually leads to death within 3 years with currently available treatments;

- **Orphan medicines**: with European Medicines Agency (EMA) designated orphan status (i.e. conditions affecting fewer than 2,500 people in a population of 5 million) or to treat an equivalent size of population irrespective of whether it has designated orphan status;

- **Ultra-orphan medicines**: to treat a condition with a prevalence of 1 in 50,000 or less (or around 100 people in Scotland).

SMC had a list of criteria (‘modifiers’) to take into account when cost per QALY exceeded £30,000 already, but the intention was that PACE would place added emphasis on this by reminding the committee of benefits not captured in QALYS alone.

It should be noted that the manufacturer needs to request a PACE meeting at the time of submitting the dossier although the actual PACE meeting will only be held if the New Drug Committee (NDC) of SMC does not recommend the drug. An overview of the process is provided in Figure 6.

**The first places**

The new process was put in place in May 2014. The first recommendations referring to the PACE process were published a few months thereafter. In the first year PACE was available, i.e., July 2014 to June 2015, SMC published exactly one hundred recommendations, of which 55 were full and original submissions. Of these, 20 submissions were PACE-eligible with 18 of them eventually leading to a PACE meeting. The other two assessments did not receive a negative NDC advice and therefore a PACE meeting was not held.

We have analysed the impact of PACE in the final outcome. For this, we have compared the SMC assessment of three groups of submissions:

**Group 1**: Submissions eligible for PACE in its first year after introduction (July 2014 to June 2015);

**Group 2**: Submissions not eligible for PACE in that same period;

**Group 3**: Submissions that would have been eligible for PACE based on being either end-of-life, orphan or ultra-orphan drugs and irrespective of the initial NDC recommendation - in the year prior to introduction of PACE (July 2013 to June 2014).

Our analysis focused on original full submissions. Resubmissions, abbreviated submissions and non-submissions have been excluded from the analysis. We identified 20 assessments in group 1, 34 assessments in group 2, and 14 assessments in group 3. The number of assessments that would have been eligible for PACE the year before its implementation was therefore lower than in 2014 (14 vs 20). Most of the drugs eligible for PACE were oncology products (85%; Figure 7). In contrast, none of the drugs that fell in to group 2 was indicated for cancer. These findings are in line with the types of medicines eligible for the PACE process and suggest that all oncology-related submissions were either for end-of-life cancer stages or for (ultra)-orphan indications. Among the assessments that would have been eligible for PACE one year before its introduction, 50% were anti-cancer medicines and the others were (ultra-)orphan drugs (Figure 7).

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![Figure 6. Steps to PACE inclusion in recommendation](image-url)
**Figure 7. Therapeutic areas by group**

**Recommendations**

After review of the evidence, SMC provides a positive, positive-with-restrictions or negative recommendation. Figure 8 presents an overview of the recommendations given in each of the three groups. As observed in the exhibit, the final recommendations outcomes were comparable between those assessments eligible (group 1) and non-eligible (group 2) to PACE during July 2014 and June 2015. Given that the PACE process applies only to products obtaining an initial negative recommendation, it can be concluded that PACE changed the outcome of the recommendation in at least 50% of the assessments (i.e., in those that the final recommendation has become a positive one).

Moreover, we need to take into account that 85% of drugs in group 1 were oncology drugs, i.e., drugs with high economic impact for which it is often challenging to receive positive recommendation. As can be seen from Figure 8, only 38% of assessments that would have been eligible for PACE in 2013 (group 3) have received a positive and 31% a negative recommendation.

**Figure 8. HTA outcomes by group**

Analysis of group 1 includes two assessments that did not require a PACE meeting because of positive outcome from NDC.

**Decision drivers**

Key positive and negative comments from SMC on the clinical evidence were further evaluated and are shown in Figures 9 and 10, respectively. The drivers considered for this analysis were not disease-specific but related to those common to all diseases such as use of appropriate comparator, treatment benefit on primary or secondary endpoints, safety and tolerance among others. It should be taken into account that all drugs in group 1 and half of the products in group 3 were oncology-products, whereas none in group 2 targeted malignancies. While this is a limitation of the analysis, given the general scope of the considered drivers no major differences were expected.

**Figure 9. Positive comments on clinical evidence**

**Figure 10. Negative comments on clinical evidence**
Strengths recognised with the highest frequency in the PACE eligible assessments (group 1) included “superiority versus standard of care” (SOC), “improvement in QoL” and “innovative nature” (Figure 9). On the flip side, non-PACE eligible assessments (group 2) received more criticisms, and especially in terms of “appropriate comparator” and “study population” (Figure 10). When looking at the critique of SMC on the economic evidence presented (Figure 11), the picture is more heterogeneous, but PACE-eligible assessments do seem to have more challenges around the uncertainty related to the small populations.

An important reason for SMC to introduce PACE is to look beyond the costs of treatment and in certain cases to widen the range of cost-effectiveness. To prove cost-effectiveness, the manufacturer can chose to submit a cost-minimization analysis (CMA) or a cost-utility analysis (CUA). The CMA directly compares costs as it is based on the assumption of clinical non-inferiority. A CUA corrects the costs by using quality adjusted life years (QALYs). Figure 12 provides an overview of the economic models presented in the submissions analysed in each of the three groups. Some submissions included two economic model types, for example when one model type was submitted and SMC requested the other type during the assessment. These combinations are presented as CMA/CUA (purple) in the figure.

Cost-effectiveness
As observed in Figure 12, CUA is by large the most commonly used type of economic analysis in PACE-eligible submissions (in 95% of these submissions). When comparing group 1 to the other 2 groups, it can be seen that the PACE process results in a higher proportion of submissions with a CUA. Among those submissions that included a CUA and where the ICER is provided, we have analysed the average submitted ICER per group. The lowest and highest submitted ICERs are also provided for each group (Table 1). The analysis excluded those submissions where the intervention was reported to be dominant (i.e., more effective and less costly than the comparator).
These figures need to be interpreted with care as not all submissions included a CUA and the uncertainty around the reported ICERs may vary considerably. Nevertheless, Table 1 shows that drugs evaluated under the PACE project are accepted with higher ICERs compared to both the non-PACE eligible products as well as products that would have been eligible for PACE in the year before the introduction of PACE.

Yet, it should also be highlighted that PACE-eligible submissions (groups 1 and 3) more frequently included a patient access scheme (PAS) than PACE non-eligible submissions (group 2). The proportion of submissions with a PAS was 70%, 26% and 43% in groups 1, 2 and 3, respectively. The difference between the two PACE-eligible groups (1 and 3) may be due to the introduction of PACE but also to the higher proportion of oncology products in group 1.

The upper limit on the accepted cost per QALY is also notable: in group 2 the highest submitted ICER accepted was £30,000, in line with SMC’s stated policy. In group 3, the highest accepted ICER was £57,930, showing that there was flexibility to go above £30,000 under the previous system. However, the highest ICER accepted in Group 1 was £72,846, reflecting the increased flexibility PACE has brought to decision-making.

Conclusion

During the first year after its introduction, manufacturers requested a PACE meeting in 20 submissions of which 18 eventually took place. A PACE was conducted mainly for oncology drugs (85% of all PACE-eligible submissions). Notably, all original full SMC submissions for oncology drugs have seemed to request a PACE. Our analysis highlights the advantage of conducting such a meeting in terms of being granted a positive recommendation. Of the 20 PACE-eligible submissions, 18 received an initial negative recommendation by the NDC. However, after the PACE meeting 14 of these assessments - which would probably have led to a negative recommendation if PACE was not available - led to either a positive or positive with restriction recommendation.

It should be noted, however, that the possibility of holding a PACE meeting does not prevent SMC from issuing a negative recommendation. When compared with the outcome for submissions that would have been eligible for PACE in the previous year (group 3), the proportion of positive outcomes was higher after PACE implementation (group 1). It should be noted that the high proportion of positive recommendations observed among the submissions eligible to PACE prior to its implementation may be due to a lower proportion of oncology drugs in group 3.

The PACE meeting led to higher ICERS being recommended by SMC. The mean ICERS among the PACE eligible submissions (group 1) was £43,500 compared with £13,500 and £26,100 for PACE non-eligible submissions and those submissions that would have been PACE eligible in 2013-2014, respectively. However as mentioned above, a PACE meeting does not always lead to a positive recommendation. PACE is a good way to introduce new drugs that may have high economic impact into the Scottish NHS but does not seem to be sufficient to guarantee their implementation.

Table 1. Incremental cost-effectiveness ratios

<table>
<thead>
<tr>
<th>HTA Outcome</th>
<th>Mean ICER (£, range)</th>
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<tbody>
<tr>
<td></td>
<td>Group 1</td>
</tr>
<tr>
<td>Recommended</td>
<td>43,514 (26,868-62,653)</td>
</tr>
<tr>
<td>Restricted</td>
<td>34,674 (11,028-72,846)</td>
</tr>
<tr>
<td>Rejected</td>
<td>75,427 (48,235-111,095)</td>
</tr>
<tr>
<td>Total</td>
<td>48,423 (11,028-111,095)</td>
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</tbody>
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“The aim of the PACE group is to describe the added benefits of the medicine, from both patient and clinician perspectives, that may not be fully captured within the conventional clinical and economic assessment process.”

SMC – PACE overview document
New EU Medical Devices Regulation

Early 2016 will see the publication of the new Medical Devices Regulation and the IVD Medical Devices Regulation in the European Union. These new Regulations will replace the existing three medical devices directives, the principles of which are over 20 years old, and they represent major changes to the way manufacturers will have to approach device approvals for the European market.

The new regulations will mean that some devices have to undergo more rigorous scrutiny, more clinical data will be required for most devices, and at the very least a more detailed clinical evaluation will have to be carried out.

Over recent years, the authorities have focused on clinical data and we have seen more intense scrutiny of clinical evaluation reports, both in the pre-market phase by Notified Bodies, and in the post-market phase by regulatory authorities. Our European devices group has been successfully authoring Clinical Evaluation Reports to support CE marking submissions for a number of years (see our fact sheet1).

Early adopters of the new regulatory requirements will see advantages over their competitors, as those who focus on good clinical data at an early stage of development, can reap benefits at the stage of Health Technology Assessment (HTA) also. HTA bodies are now looking at medical devices and success is often directly linked to the quality of clinical data submitted.

Our medical device regulatory consultants with expertise in European and US medical device regulations can assist manufacturers develop a robust clinical plan which will meet the regulatory requirements and target HTA requirements also. For more information please contact caroline.freeman@quintiles.com or phil.johnson@quintiles.com.

References

HTA Accelerator: Facts and figures

Spotlight on Sweden’s HTA agency TLV

- An increasing number of Single Technology Appraisals has been observed over the past 10 years with a maximum of 71 completed and published reports in 2013 and 64 in 2014.
- 56% of the evaluations performed between 2010 and 2014 resulted in a positive recommendation and a further 23% in a positive recommendation with a restriction, considerably more than NICE, SMC or G-BA. Similar trends were observed for the Dutch ZIN for the same period.
- Compared to other major HTA agencies, TLV evaluated a similar amount of products by therapeutic area as ZIN, SMC, HAS or PBAC, whereas almost half of NICE’s assessments were on cancer only (Figure 13).

![Figure 13](image-url)
Events and publications

Meet us at the following conferences

- PharmAccess Leader Forum, 13-15 October 2015, Berlin, Germany (weblink)
- ISPOR 18th Annual European Congress, 7-11 November 2015, Milan, Italy (weblink) Over 15 Quintiles posters and podium presentations on:
  - Understanding key drivers of successful HTA submission – Developing a model
  - Medical devices: have Health Technology Assessment agencies started to focus more on them?
  - Decision drivers in Health Technology Assessment in Hepatitis

Webinars


Publications


Further information

Quintiles Blog

- The Friday Podcast: Moving toward patient centricity - Louise Parmenter and Stella Blackburn
- What it means to be patient-centered – Jean Paty
- 10 Transformative Trends: Part 1 - The rising tide of healthcare – John Doyle
- 10 Transformative Trends: Part 2 - Personalization of care – John Doyle
- How to increase value through the commercialization process – Dean Summerfield
- NHS England: Pride, pressures, possibilities and patient-centric care - Peter Rutherford
- Successful commercialization starts with accessibility – Dean Summerfield
- Companion devices will become mainstream – but how will they be paid for? - Amarpreet Chawla and Nathalie Horowicz-Mehler
- Supporting NHS Pathway Improvements in Cancer Care - Gavin Jones
- Demonstrating value through cross-functional teams - Nicole Connelly
- Using Localized Data to Highlight Sub-optimal Pathway Adherence in the UK – Paul Sutton
- How Direct-to-Patient Registries inform Clinical Trial Research – Nancy Dreyer
- Collaboration, feedback, and the future of patient registries - Michelle Leavy
- The Patient Pyramid: Improving Adherence and Patient Outcomes in the UK - Ian Riches
- A Hybrid Approach to the European Pharma Market - Jeremy Broadis

Available from: http://www.quintiles.com/blog

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

Lars Heemstra
Office: + 31 (0) 23 5671013
Mobile: + 31 (0) 6 46436563
lars.heemstra@quintiles.com

Available from: www.hta-accelerator.com