An Integrated Approach to HTA Assessments in the EU: Hype or Hope?

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Introduction

The European Union (EU) is introducing a mandatory Joint Clinical Assessment (JCA) that will produce a single non-binding outcome for oncology drugs and advanced therapeutic medicinal products in 2025 and orphan drugs in 2028[1] JCAs aim to standardise Health Technology Assessments (HTA) to increase EU-wide access to drugs and medical devices and reduce national HTA workloads[2]

Currently, there is inter-country heterogeneity in drug appraisals, which has frustrated previous attempts at HTA harmonization[2] This research aims to understand barriers to adopting conclusions from cross-national JCAs by comparing HTA outcomes between the two largest EU pharmaceutical markets, France and Germany. The pricing and reimbursement process in these countries is based around comparative clinical effectiveness, and is split into a clinical assessment followed by price negotiations.

Materials & Methods

All oncology and orphan drugs approved by the European Medicines Agency (EMA) between 2020-2021 were extracted. These drugs were filtered to only include those for which HTA outcomes from both Haute Autorité de Santé (HAS) and Gemeinsamer Bundesausschuss (G-BA) have been published.

Both HAS and G-BA produce a rating of the clinical benefit of assessed products on similar five-point scales (Table 1).[3]

Although the clinical benefit rating scales used by HAS and G-BA have a similar structure, they are not identical and some categories are not directly comparable to one another (e.g., G-BA's 'non-quantifiable added benefit' does not match any category outlined by HAS).

Ratings for individual drugs were compared and classified as 'equivalent' (same level rating), having 'minor differences' (one rating apart), or having ‘major differences’ (two+ ratings apart). Given the imperfect match between both scales, 'major differences' were determined to be a stronger indicator of clear differences in clinical appraisals.

Table 1: 'Added benefit' Rating Scales Used by HAS and G-BA When Performing HTAs

HAS	G-BA
Major (ASMR I)	Major added benefit
Significant (ASMR II)	Significant added benefit
Moderate (ASMR III)	Minor added benefit
Minor (ASMR IV)	Non-quantifiable added benefit
No added benefit (ASMR V)	No added benefit

Results

Of the 33 identified drugs, 22 (67%) had outcomes which were deemed equivalent between HAS/G-BA (Figure 1). Where differences (either minor or major) occurred, G-BA outcomes tended to be more favourable. Eight (24%) outcomes showed 'minor' differences, of which 63% were driven by the guaranteed 'non-quantifiable' added benefit granted to orphan drugs in Germany (Table 2).

Figure 1: Proportions of HTA outcomes for oncology and orphan drugs deemed equivalent or with differences (minor and major) between HAS and G-BA in 2020-2021

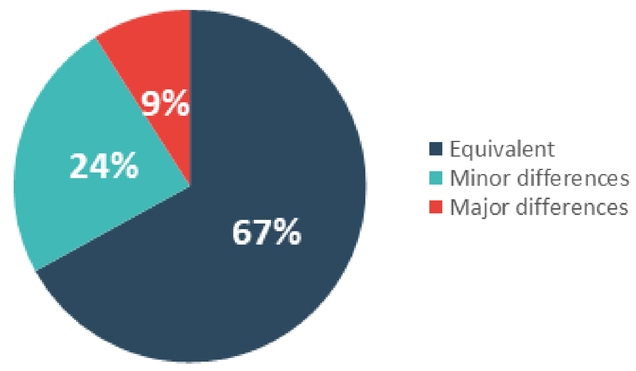

Table 2: 63% of 'minor' differences in drugs' HTA outcomes were driven by the 'non-quantifiable added benefit' for orphan drugs by G-BA (Non-quantifiable)

Drug	HAS rating	G-BA rating
Luspatercept	ASMR V	Non-quantifiable
Avapritinib	ASMR V	Non-quantifiable
Belantamab	ASMR V	Non-quantifiable
Obeticholic acid	ASMR V	Non-quantifiable
Pemigatinib	ASMR V	Non-quantifiable
Isatuximab	ASMR IV	No added benefit
Crizanlizumab-tmca	ASMR IV	Minor added benefit
Trikafta	ASMR II	Major added benefit

Only three (9%) outcomes (fenfluramine, gilteritinib and cannabidiol) showed major differences – all three were given an 'ASMR IV' in France and a ‘significant added benefit’ in Germany – caused by conflicting views on factors including comparative data, safety, and long-term outcomes.[4,5]

Case Study: Fenfluramine

One of the drugs that received a major difference in HTA outcome between France and Germany was fenfluramine, an orphan drug approved for the treatment of Dravet syndrome.

Despite the different outcomes, HAS and G-BA were aligned on the assessment of many aspects, including the relevance of the primary efficacy data, the lack of clear quality of life (QoL) benefit, and questions around the study duration and number of patients.

However, the key reason for assessment differences was safety:

- In clinical trials, there was a higher incidence of abnormal echocardiographic events in the fenfluramine group compared to placebo (16.4% vs 6%)
- Whilst the G-BA did not consider this as an important difference, HAS viewed these results in the context of fenfluramine previously having had marketing authorization as a treatment for obesity revoked for cardiac adverse events[4,5]
- This difference was likely a key driver of the divergence in benefit rating between the two markets

Conclusion

Whilst most assessed products achieved similar outcomes in France and Germany, significant divergences exist due to the different methodologies used in each country. Considering that France and Germany are two relatively similar EU markets, even larger differences in assessments are likely to be seen when considering other countries.

Unless there is significant alignment between EU Member States on how products will be appraised, finding consensus for future health technologies undergoing JCA will be challenging.

As the JCA is only planned to replace the national clinical assessment, Member States will still be responsible for pricing determinations. The impact of JCAs on national pricing decisions is unclear, and it is possible that outputs could be largely disregarded by countries.

Although the introduction of the JCA is seen by some as an opportunity to improve access and harmonize HTA across the EU, much work is still required for it to achieve its goal.

References

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