The Role of Safety and Tolerability in HTA Value Assessment: Evidence Requirements and Impact Across Key European Markets

HTA14

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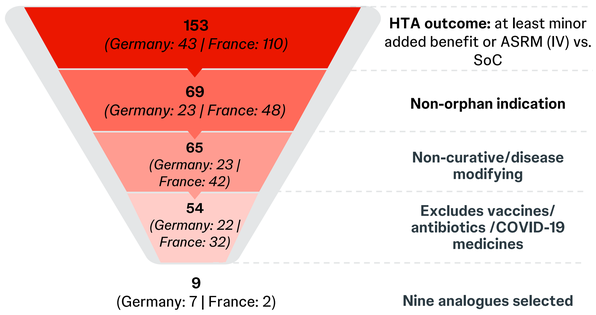
Background

- HTA decisions are predominantly driven by comparative efficacy, while safety and tolerability (hereafter referred to as safety, including adverse events and discontinuations due to AEs) are typically treated as essential prerequisites rather than independent drivers of value. Favorable safety profiles are required to support access but rarely confer added benefit on their own.
- In situations where efficacy differentiation is unclear, safety outcomes are becoming more salient in clinical and payer discussions. However, HTA bodies differ substantially in how safety evidence is assessed, weighted, and translated into value judgments, creating uncertainty around conditions under which safety improvements can influence HTA outcomes.
- Clarifying the role of safety within HTA frameworks is therefore critical to informing evidence generation and value substantiation.

Methods

- A structured review of HTA frameworks was conducted across seven markets (Germany, France, Italy, Spain, UK, Japan, Brazil) to assess the role of safety in value determination, including accepted endpoints, evidence thresholds, and pricing implications; findings were subsequently validated with market experts.
- A targeted HTA analogue analysis was performed focusing on Germany and France (see Figure 1). A total of 153 HTA reports (2019 onward) were screened to identify medicines that achieved at least a minor added benefit (Germany) or ASMR IV (France) from assessments by the G-BA and HAS, the HTA authorities in Germany and France, respectively. Inclusion criteria covered non-orphan, non-curative indications where safety was described as a positive attribute.
- Nine products were selected for in-depth assessment. For each analogue, pivotal trial design, safety endpoints, statistical significance, comparator appropriateness, and HTA conclusions were systematically reviewed to identify drivers of HTA outcomes and the contribution of safety evidence.

Figure 1. Approach for HTA analogue identification



Results

Role of Safety Across HTA Frameworks

Across the HTA systems reviewed, the contribution of safety to HTA outcomes varies by market, as summarized in Table 1. In most settings, safety is integrated within broader assessment domains (e.g. clinical benefit or cost-effectiveness), but rarely acts as a standalone driver of value.

- Germany represents a distinct case, where safety is explicitly recognized as a value dimension and may contribute to added-benefit determinations, particularly when efficacy is comparable.
- In other markets, safety typically influences decisions indirectly and through informing overall acceptability, contextualizing unmet need, or contributing to economic assessments.

Consistent with these findings, evidence requirements to demonstrate robust and attributable safety benefits remain stringent, and inappropriate comparator selection potentially negating advantages demonstrated through safety.

Accepted Safety Endpoints

Across HTA bodies, commonly accepted endpoints include:

- Adverse events (AEs)
- Severe adverse events (SAEs)
- Treatment discontinuations due to AEs (tolerability outcome)

Analogues & HTA Assessment Differences Between G-BA and HAS

Nine analogues, across oncology and cardio-renal-metabolic indications, were identified as having achieved a favorable HTA outcome (at least a minor added benefit in Germany or ASMR IV in France) and with safety explicitly cited as contributing partially or fully to the final HTA rating.

- Oncology: ibrutinib (G-BA 2020; CLL), acalabrutinib (G-BA 2021; CLL), olaparib (G-BA 2020; breast cancer), zanubrutinib (G-BA 2023; CLL), talazoparib (G-BA 2020; breast cancer), sacituzumab govitecan (G-BA 2022; mTNBC)
- Cardio-renal-metabolic: dapagliflozin (G-BA 2022: CKD), insulin degludec/liraglutide (HAS 2021; T2D), dulaglutide (HAS 2021; T2D)

Notably, three analogues - ibrutinib, acalabrutinib, and olaparib - achieved minor added benefit in Germany driven by statistically significant safety improvements (i.e. reductions in serious/severe adverse events) or tolerability improvements (i.e. treatment discontinuations), as the primary differentiator. While based on largely comparable clinical evidence, differences between G-BA and HAS outcomes reflected distinct methodological frameworks for assessing and formally incorporating safety, rather than divergent underlying data (see Table 2).

Most frequently cited AE categories from the analogues:

- Oncology: neutropenia, infections, cardiac disorders, infusion reactions
- Cardio-renal-metabolic: gastrointestinal disorders, nausea, diarrhea

No non-conventional safety endpoints were identified.

Table 1. Role of safety in HTA decision-making and access outcomes across markets

Market	Safety's role in HTA outcomes	Expected safety evidence requirement	Pricing and access implications
	Integrated within clinical benefit; **confirms acceptability rather than drives ASMR**	**High-quality RCT evidence is required**; absence of robust direct comparison or immature safety data limits positive outcomes	ASMR mainly driven by efficacy; safety alone rarely justifies price premium
	**Recognized as a distinct value domain for assessment**; in case of comparable efficacy, potential to drive added benefit	Robust, **statistically significant comparative evidence vs ACT (usually from H2H RCTs)** is usually required	**Price premium is possible when safety advantages lead to additional added benefit**
	**Considered within cost-effectiveness rather than standalone**	Safety is expected to be quantified relative to the **appropriate comparator**, ideally coming **from H2H trials** or **meta-analyses**	No formal price premium from safety; fewer AEs may improve QALYs
	**Assessed within overall clinical value** and budget impact, but **rarely a differentiator**	Comparative safety from **RCTs** is highly preferred; **high-quality RWE can strengthen** the case	Safety may influence **access/prescribing at the hospital level** if it leads to clear clinical/economic benefits
	**Secondary factor; influences decisions when linked to patient outcomes**	Robust evidence against **relevant comparators** is required, usually starting with the **SoC currently available** in Italy	Price premium is driven primarily by efficacy; safety alone is rarely sufficient
	**Considered within cost-effectiveness and post-launch adjustments**	**A high-quality, prospectively defined endpoint** over SoC is required; post-hoc or retrospective analyses are not accepted	No formal price premium from safety; fewer AEs may improve ICER
	**Fundamental prerequisite rather than differentiator** in positive HTA outcome	Clinical efficacy/effectiveness & safety from the best available evidence (**RCTs + systematic reviews**)	No formal price premium from safety

Table 2. Comparison of safety evaluation approaches in G-BA and HAS assessments

	G-BA	HAS
Scope of assessment	Assesses outcomes across four domains: • **Mortality** (overall survival) • **Morbidity** (trial efficacy endpoints) • **Health-related QoL** (scales/instruments included in the clinical trials) • **Safety** (SAEs, severe AEs, specific AEs, tolerability outcome of discontinuations)	Assesses outcomes across three domains: • **Efficacy** (trial endpoints) • **Health-related QoL** (scales/instruments included in the clinical trials) • **Safety** (SAEs, severe AEs, specific AEs, tolerability outcome of discontinuations)
Assessment of statistical significance	**Statistically significant differences between treatment arms are formally determined for each domain**	**Safety outcomes are reported descriptively**, without formal assignment of advantages or disadvantages based on statistical significance
Impact on final HTA conclusion	Findings from each assessment domain are explicitly integrated into the final benefit conclusion and overall rating	• The contribution of safety is considered holistically in the final conclusion, rather than at the endpoint level • Efficacy endpoints remain the primary determinants of ASMR ratings

Conclusions

- Safety outcomes are essential but rarely drive positive ratings on their own in HTA assessments. Across markets, positive safety profiles are necessary to support access but typically act as supportive criteria, while efficacy remains the primary driver of value.
- The role that safety plays in HTA assessment frameworks varies by agency. The G-BA more readily recognizes statistically significant safety advantages as added benefit (particularly in oncology), whereas HAS primarily uses safety to confirm acceptability.
- Only robust comparative evidence enables safety to influence HTA outcomes. Head-to-head randomized trials versus appropriate comparators, with pre-specified and statistically significant safety endpoints, are critical. Inappropriate comparator choice can negate otherwise favorable safety evidence.

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TN was an employee of IQVIA at the time this study was conducted; currently employed by Regeneron.

RXZ and EO are employees of IQVIA.

Value Assessment

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Abbreviations: ACT: Appropriate Comparator Therapy; AE: Adverse Event; ASMR: Amélioration du Service Médical Rendu; CKD: Chronic Kidney Disease; CLL: Chronic Lymphocytic Leukemia; G-BA: Gemeinsamer Bundesausschuss; H2H: Head-to-Head; HAS: Haute Autorité de Santé; HTA: Health Technology Assessment; ICER: Incremental Cost-Effectiveness Ratio; mTNBC: Metastatic Triple-Negative Breast Cancer; QALYs: Quality-Adjusted Life Years; QoL: Quality of Life; RCT: Randomized Controlled Trial; RWE: Real-World Evidence; SAEs: Serious Adverse Events; SoC: Standard of Care; T2D: Type 2 Diabetes; UK: United Kingdom

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