From Evidence Gaps to Launch Delays: A Review of Health Technology Assessment Critiques and Health Economics and Outcomes Research Strategy Readiness

HTA 150

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Background & Objectives

- Health technology assessment (HTA) timelines vary across agencies and sometimes exceed agency targets and company expectations, contributing to delays in patient access[1].
- The National Institute for Health and Care Excellence (NICE) and Canada's Drug Agency (CDA-AMC) report standard appraisal timelines of 38 weeks and 20 weeks, respectively, from submission to final decision[2-3]. However, in practice, the actual time-to-decision is often longer and varies considerably.
- This study aims to review published HTA reports with delayed decisions and to identify key criticisms of the evidence base that may have contributed to the delays. The findings will support companies in preparing for future HTA submissions by informing their health economics and outcome research (HEOR) strategy and strengthening submission readiness.

Methods

- Completed and publicly available HTA reports from NICE and CDA-AMC were reviewed if they assessed pharmaceutical products for endocrine or metabolic diseases, had decisions issued between April 2022 and April 2025, and provided a final recommendation.
- HTA reports were excluded if they lacked a submission date or addressed ultra-rare indications, as review timelines for HTAs in ultra-rare indications differ from standard procedures.
- Each HTA report was categorised by the extent of delay relative to the agency's published standard submission-to-recommendation duration: No/Minor (<1.5× expected duration), Moderate (1.5–2.5×), or Severe (>2.5×).
- HTA reports with moderate or severe delays were analysed to identify key criticisms and synthesise evidence gaps across population, clinical, and economic domains.

Results

- Based on the 43 HTA reports identified, the average review time for NICE was 62 weeks, approximately 1.6 times longer than the published standard of 38 weeks. For CDA-AMC, the average was 34 weeks, which is around 1.7 times the standard review time of 20 weeks.
- After excluding HTA reports with minor delays and for ultra-rare indications, 6 NICE and 9 CDA-AMC reports were reviewed (Figure 1).
- Evidence gaps were synthesised across 8 endocrine and metabolic indications (Table 1).

Figure 1. Flow of HTA reports selection and inclusion for analysis

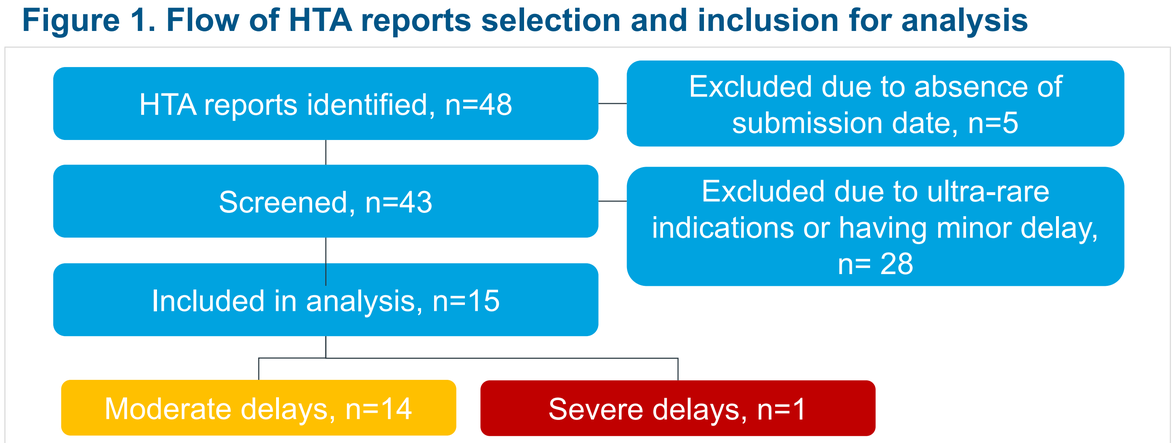

Table 1. Number of appraisals by indication

Indication	No. of reports	Indication	No. of reports
Amino acid disorders	1	Type 2 diabetes	2
Amyloidosis	1	Dyslipidemia	3
Carbohydrates-related disorders	1	Mineral disorders	2
Cystic fibrosis	3	Weight disorders	2

- The top three most common gaps within each domain are (Table 2):
  - **Population-related evidence gaps**, including *Generalisability of the trial population to the real-world population* (n=6, 40%), *Baseline imbalances between arms in trials or between trials in ITCs* (n=3, 20%), and *Under-representation of key subgroups in clinical trials* (n=1, 7%)
  - **Gaps in clinical evidence**, including *Limited relevance of trial endpoints* (n=6, 40%), *Uncertain health-related quality of life (HRQoL) outcomes including minimal important differences and measurement properties* (n=3, 20%), and *Lack of robust indirect treatment comparisons (ITCs) due to data sparseness, network structure, or violation of transitivity assumption* (n=3, 20%)
  - **Economic evidence gaps**, including *Uncertainty associated with utility values* (n=5, 33%), *Lack of data for long term extrapolation* (n=5, 33%), *and Drug acquisition (e.g., drug wastage) and compliance factors not taken into consideration* (n=2, 13%).
- Compared to NICE, CDA-AMC focused more on the methodological robustness of pivotal trials and ITCs, with criticisms related to baseline imbalances and quality of the ITCs (e.g., heterogeneity across the trials in the networks and potential violation of the transitivity assumption), highlighted exclusively by CDA-AMC.

Table 2. HTA reports gap analysis by domain

Population-related	
Evidence gaps	**% (n) of HTAs with the gap**
Generalisability of trial population	40% (6/15)
Baseline imbalances between treatment arms	20% (3/15)
Under-representation of key subgroups	7% (1/15)
Small sample size in the clinical trials	7% (1/15)
Trial population included ineligible individuals per regulatory label	7% (1/15)

Clinical evidence	
Evidence gaps	**% (n) of HTAs with the gap**
Limited endpoint relevance	40% (6/15)
Uncertainty in HRQoL outcomes	20% (3/15)
Lack of robust ITC	20% (3/15)
Lack of control arm or inappropriate comparator	20% (3/15)
Immature efficacy data (e.g., insufficient long-term trial duration) at the time of submission	13% (2/15)

Economic evidence	
Evidence gaps	**% (n) of HTAs with the gap**
Utility uncertainty	33% (5/15)
Lack of extrapolation assumptions	33% (5/15)
Underestimate drug acquisition and compliance factors	13% (2/15)
Lack of evidence for maintenance treatment	13% (2/15)

Conclusion

- A holistic HEOR strategy with a clear evidence generation roadmap plays a critical role in supporting smooth HTA process and optimal outcomes. Based on the findings of this study, we recommend the following considerations when developing a HEOR strategy:
  - Prior to pivotal trials, reviewing HTA reports of comparable analogue products and seeking expert input (e.g., scientific advice, advisory boards) on trial population, stratification factors, and endpoints can mitigate issues of generalisability. A well-structured patient-reported outcome strategy is crucial for generating robust evidence to inform economic models.
  - Conducting an early ITC feasibility assessment that considers various analytical methods, assumptions, and scenarios in the absence of direct evidence can help mitigate uncertainty and optimise the feasibility of ITCs based on pivotal trials.
  - Finally, early planning for real-world evidence generation and post-hoc subgroup and sensitivity analyses will strengthen the evidence package for HTA submissions.
- This analysis only reviewed evidence gaps in HTA reports with moderate-to-severe delays and did not include those with no or minor delays. Further research is needed to compare evidence gaps across different extents of delay and to explore whether specific evidence gaps contribute to delayed decision-making. Additionally, as this analysis only focuses on endocrine and metabolic indications, the findings may not be generalisable to other therapeutic areas.

References
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