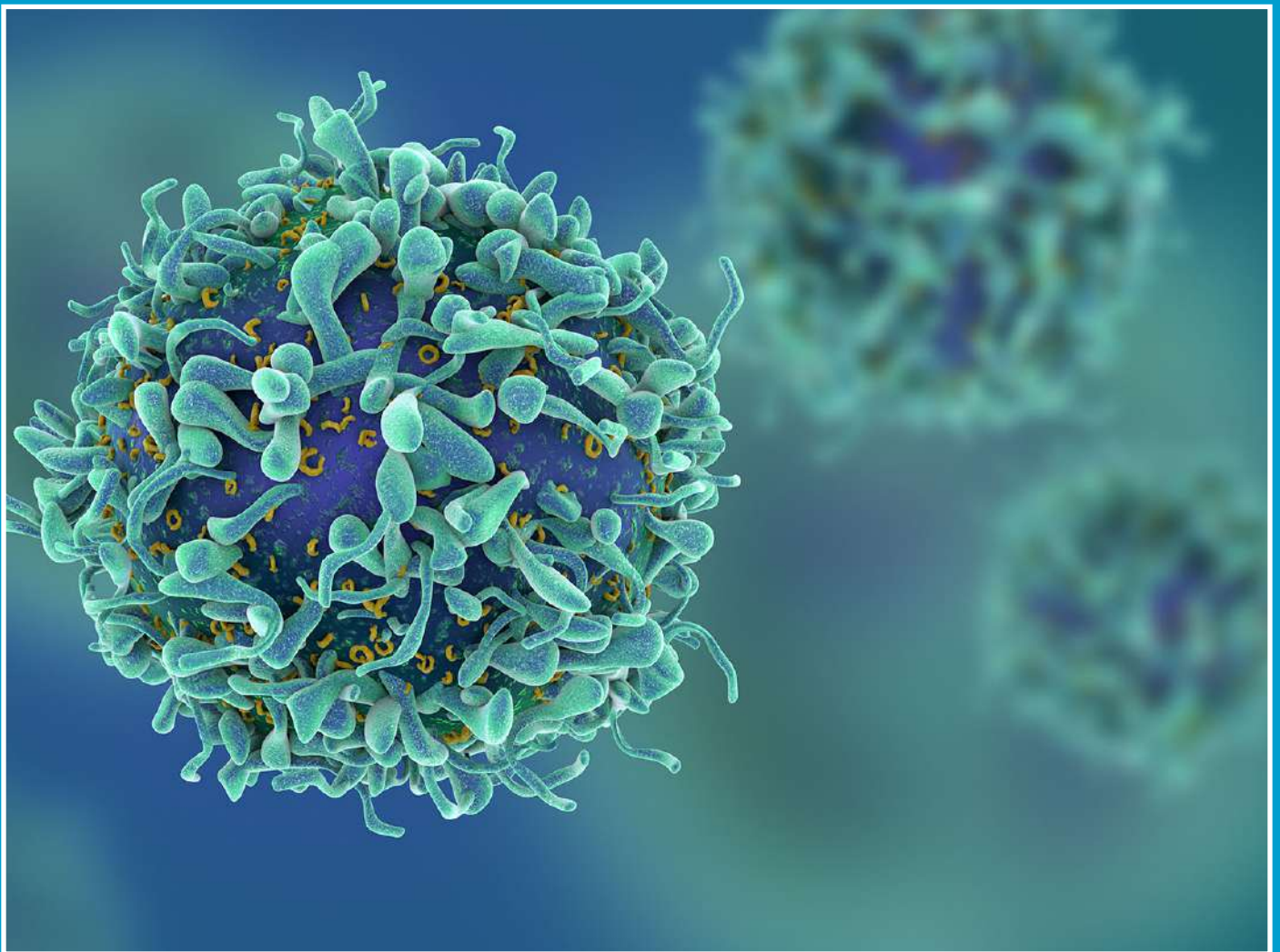


The Evidentiary Drift in Oncology: When Regulators Say Yes, and Payers Say Maybe



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Over the past decade, oncology drug development has increasingly relied on expedited and early access pathways. In the United States, these include FDA's accelerated approval and breakthrough therapy designation. In the European Union, EMA grants conditional marketing authorization and PRIME support, while in the UK, MHRA has developed its own expedited pathways, often in coordination with NICE for parallel appraisal. While the mechanisms differ, they share the same intent: to allow regulators to act quickly on compelling early evidence in high-need indications. But the same data that enables regulatory approval often does not lead to broad reimbursement or timely access.

Regulators focus on whether a therapy demonstrates an acceptable balance of efficacy and safety to justify approval in a defined patient population with limited options. HTA bodies and payers, by contrast, assess the therapy's value using the pivotal clinical data package as a base, but often requiring additional evidence on overall survival, quality of life, or economic impact to support comparative and cost-effectiveness assessments. This divergence in focus can be described as evidentiary drift: a disconnect between the thresholds required for regulatory approval and those demanded for reimbursement and access.



This dynamic is most visible in high-cost, novel modalities such as antibody-drug conjugates (ADCs), bispecific antibodies, and messenger RNA (mRNA) cancer vaccines, particularly when approval is granted based on efficacy endpoints such as response rate or progression-free survival, supported by safety data, but without mature overall survival or quality-of-life outcomes. Moreover, these approvals are frequently based on single-arm studies, while HTA bodies typically require randomized controlled trial evidence to assess comparative effectiveness. The result is faster market entry, but a widening gap between initial regulatory approval and evidence of long-term, real-world effectiveness.

What Counts as Benefit? Depends Who You Ask

In Europe, teclistamab, a bispecific antibody for relapsed multiple myeloma, was approved by the European Medicines Agency based on a 63% response rate. While EMA granted approval, the UK's National Institute for Health and Care Excellence (NICE) reached a different conclusion, initially declining reimbursement due to uncertainty in survival and quality-of-life outcomes. Only after the sponsor submitted longer-term data and revised pricing did NICE agree to a managed access arrangement.

A similar dynamic can be seen in the United States. The Institute for Clinical and Economic Review (ICER), while not a government agency, provides assessments that many payers consider in coverage deliberations. In its review of tisagenlecleucel (Kymriah) for relapsed or refractory B-cell acute lymphoblastic leukemia in children and young adults, ICER rated the evidence as “promising but inconclusive.” The review highlighted small trial populations, lack of direct comparators, and limited follow-up, leaving questions about durability and safety. While FDA had granted accelerated approval, ICER concluded the available data did not sufficiently support a confident value assessment. Such evaluations may not determine coverage directly but can shape payer discussions, especially under expedited approval pathways.

In both regions, regulators prioritized early efficacy in high-need populations, while payers required additional evidence to justify broad and sustained access.

Early Evidence Rarely Stands Alone

The examples above reflect a broader challenge in oncology drug development: early evidence sufficient for regulatory approval frequently requires additional data before payers and HTA bodies grant reimbursement. Accelerated or conditional approvals are often granted on the strength of surrogate endpoints, single-arm studies, or expedited pathways, with the expectation that confirmatory studies will establish long-term clinical benefit, but these same features frequently become red flags for payers.

Health technology assessment (HTA) bodies and insurers typically expect data that demonstrates not just activity, but long-term clinical relevance such as improvements in overall survival, quality of life, or health system efficiency. Trials based on response rate or progression-free survival often lack the durability, generalizability, or comparative value needed to support these claims.



Common limitations include:

- **Lack of comparators:** Many accelerated approvals are based on non-randomized or single-arm trials, making it difficult to contextualize benefit.
- **Short follow-up:** Key outcomes like durability of response, overall survival, and long-term toxicity often remain unmeasured at the time of approval.
- **Narrow patient populations:** Highly selected trial cohorts may not reflect the broader group eligible for treatment post-approval.

These gaps create friction downstream. HTA bodies may request additional analyses, set conditional coverage criteria, or defer full reimbursement decisions until confirmatory data matures. Meanwhile, sponsors face mounting pressure to prove that early signals translate into lasting, population-level value.

Rather than relying on regulatory approval as validation, developers need to anticipate the evidentiary expectations that follow. In essence, payers are not looking for entirely different data, but for evidence that goes beyond regulatory benefit-risk assessment to demonstrate value, including comparative effectiveness against standard of care, long-term outcomes, and cost effectiveness in real-world contexts.

The same evidentiary gaps resurface when looking across newer oncology modalities. Despite differences in scientific approach, they run into the same payer demand: proof of durable, comparative, and patient-centered benefit.

Across novel oncology modalities, strong early efficacy signals rarely satisfy payer expectations for durability, comparative effectiveness, and patient-centered outcomes. For example, antibody–drug conjugates (ADCs) often demonstrate striking response rates, yet reimbursement decisions still hinge on mature survival and quality-of-life data. The same dynamic applies more broadly: distinct mechanisms of action do not eliminate the evidentiary gap. Without long-term, comparative evidence that demonstrates value in real-world contexts, innovative therapies face constrained access despite regulatory approval.

Real-World Evidence: Complement, Not Replacement

As oncology developers seek to bridge the gap between early clinical signals and payer expectations, real-world evidence (RWE) is often positioned as a tool to strengthen the value proposition. When generated rigorously and aligned to unanswered questions from clinical trials, RWE can help validate benefit beyond approval. But it is not a substitute for well-conducted randomized controlled trials designed with payer-relevant comparators and outcomes in mind.

In the U.S., Medicare's Coverage with Evidence Development (CED) program offers a conditional reimbursement pathway for FDA-approved therapies. Under CED, coverage is granted while additional data is collected in real-world settings. This approach has been used for CAR-T cell therapies, reflecting the recognition that real-world data can supplement controlled trial findings and confirm benefit in broader clinical

populations. In Europe, the Netherlands' DRUP program provides a similar approach, using real-world evidence to enable earlier access to targeted oncology drugs while additional data are collected. The United Kingdom has also developed managed access arrangements that condition reimbursement on the collection of further clinical and real-world evidence, particularly for oncology therapies evaluated by NICE.

Still, payers and health technology assessment (HTA) bodies expect RWE to meet clear standards. It must be prospectively planned, methodologically sound, and targeted to outcomes that trials have not fully captured. Retrospective or loosely structured analyses typically carry limited weight in formal value assessments.

For sponsors, the strategic takeaway is clear: real-world evidence should extend clinical trial findings, not replace them.

Joint Clinical Assessment: Regulatory and HTA in Parallel

Since January 2025, Europe's Joint Clinical Assessment (JCA) has reshaped how oncology evidence is reviewed. Previously, sponsors could wait until after EMA approval to submit HTA dossiers, sometimes with more mature survival or quality-of-life data. Under JCA, HTA bodies now conduct their clinical evaluations in parallel with EMA's marketing authorization, bringing payer considerations into the process much earlier. This structural change means sponsors must align regulatory and HTA evidence strategies from the outset, rather than staging them sequentially.

JCA also comes with clear methodological guidance. It emphasizes the need for robust comparative effectiveness analysis, typically against payer-relevant standards of care, and places greater weight on endpoints such as overall survival and quality of life. For sponsors, this reinforces that evidence sufficient for regulatory benefit–risk assessment may not meet payer requirements. Building HTA-oriented comparators and outcomes into pivotal trials early is therefore essential to support both approval and access.

What Developers Must Do Differently

To bridge the gap between approval and access, developers need to align their evidence strategy to meet both regulatory and payer expectations, early in development.

Five priorities stand out:

- **Design for dual audiences and prioritize early.** Build trials that demonstrate not just efficacy signals, but also durability, quality-of-life impact, and relevance across broader patient groups. Where randomization is not feasible, consider external comparators or hybrid designs. Even modest early additions, such as preplanned subgroup analyses or patient-reported outcomes, can improve efficiency and avoid late evidence gaps.
- **Plan for generalizability from the outset.** Broaden eligibility criteria, ensure geographic and demographic diversity, and structure trials to support subgroup or histology-level insights. Confirmatory studies should be scoped early and designed with endpoints aligned to reimbursement requirements.
- **Quantify claimed value.** If the therapy is expected to improve tolerability, simplify administration, or reduce health resource use, measure those effects directly using validated tools and patient-reported outcomes.
- **Use real-world evidence strategically.** Integrate RWE generation into the development program with clear intent, targeting gaps in trial data and aligning endpoints to decision-maker needs.
- **Recognize dual thresholds.** Regulators base their decisions on benefit–risk, while payers and HTA bodies assess value in terms of comparative and cost-effectiveness. Evidence plans should anticipate this divergence and prepare to demonstrate benefit twice: once for approval, and again for access.

Strategic Evidence Requires Early Choices

Expedited regulatory pathways have expanded oncology's regulatory runway, but reimbursement ultimately comes down to evidence that demonstrates consistent, population-level value. In the United States and Europe alike, sponsors must prepare to meet payer requirements that extend beyond regulatory benefit-risk. In Europe, this alignment of regulatory and HTA timelines is reinforced by the Joint Clinical Assessment, which requires HTA bodies to evaluate clinical evidence in parallel with EMA authorization, making payer-relevant comparators and outcomes unavoidable from the start.



The critical point is timing: strategic choices made early in development determine how efficiently sponsors can generate the additional evidence payers expect. Anticipating payer needs at the outset strengthens robustness, reduces the risk of late adjustments, and increases the likelihood of turning early access into lasting access.

Key Takeaways

- Approval and access are judged by different standards; evidence must address both.
- Early efficacy is not enough; payers look for durability, real-world outcomes, and quality of life.
- In Europe, HTA reviews now run in parallel with EMA approval, requiring payer-ready data earlier.
- Small trial design choices such as comparators, PROs, and subgroup analyses can prevent costly late fixes and accelerate access.



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