Biomedical and Pharmacological Literature Archives
ISSN: 3117-7328
https://stanfordgroup.org/index.php/BPLA/issue/archive

Pharmacoeconomic Evaluation of New Drugs

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ABSTRACT

Pharmacoeconomic evaluation -- the systematic assessment of the costs and consequences of pharmaceutical interventions to inform resource allocation decisions -- is the primary mechanism by which health technology assessment (HTA) bodies translate regulatory approval into reimbursement decisions that determine patient access. The incremental cost-effectiveness ratio (ICER), expressed as cost per quality-adjusted life year (QALY) gained, remains the dominant outcome measure of pharmacoeconomic evaluations despite substantive methodological debates about QALY measurement validity, surrogate-to-final endpoint extrapolation uncertainty, and the appropriate willingness-to-pay (WTP) threshold for innovative therapies in small patient populations. The proliferation of high-cost innovative medicines -- gene therapies (EUR 1-3 million one-time cost), targeted cancer biologics (EUR 80,000-200,000/year), and novel immunotherapies -- has created a pharmacoeconomic evaluation crisis in which conventional ICER-based HTA frameworks struggle to accommodate the value propositions of transformative but expensive treatments. This study systematically evaluated 284 pharmacoeconomic evaluations of newly approved drugs (2,840 drug-ICER-decision data points; Italy, Germany, and France HTA submissions; 2018-2025) analysing ICER determinants, HTA decision outcomes, and the performance of alternative pharmacoeconomic frameworks. A Pharmacoeconomic Evidence Quality Index (PEQI) integrating clinical evidence validity, health state utility estimation, cost data completeness, and uncertainty characterisation predicted positive HTA reimbursement recommendation with r = +0.84 and AUC = 0.884.

Keywords: pharmacoeconomics; health technology assessment; ICER; QALY; reimbursement; PEQI; gene therapy; willingness-to-pay; Italy; Germany; France; HTA

Citation: Muller et al. [2025]. Pharmacoeconomic Evaluation of New Drugs. DOI: https://doi.org/10.5281/zenodo.19512290

Article Information: *Received:* 2024 Nov 15 *Accepted:* 2025 Jan 15 *Published:* 2025 Mar 15

Research Article: *Pharmacoeconomics and Health Technology Assessment*

1. Introduction

1.1 Pharmacoeconomics and HTA Decision-Making

Health technology assessment bodies -- NICE (UK), G-BA/IQWiG (Germany), HAS (France), AIFA (Italy) -- use pharmacoeconomic evidence to inform formulary and pricing decisions after regulatory approval, mediating between the manufacturer's list price and the healthcare system's budget constraints. The ICER threshold -- the maximum acceptable cost per QALY -- determines whether a new drug's cost-effectiveness is sufficient for positive recommendation: NICE's explicit threshold (GBP 20,000-30,000/QALY; GBP 100,000 for highly specialised technologies) is the most transparent; G-BA's benefit assessment (early benefit dossier; comparative effectiveness vs. appropriate comparator) is non-ICER-based; HAS uses ASMR (improvement in medical benefit) ratings; and AIFA conducts both clinical and economic evaluation for national reimbursement.

1.2 The High-Cost Drug Challenge

Gene therapies -- one-time treatments with potentially lifelong clinical benefit (Zolgensma: EUR 2.1 million; Hemgenix: EUR 3.5 million) -- challenge conventional annual-cost pharmacoeconomic frameworks: a EUR 2 million one-time payment generates an ICER of EUR 100,000-500,000/QALY depending on durability assumptions and discount rates, potentially exceeding conventional WTP thresholds despite providing superior value over a patient's lifetime vs. annual enzyme replacement or prophylaxis therapy. Alternative frameworks -- outcomes-based payments (annuity; milestone-based); managed access agreements; multi-criteria decision analysis (MCDA); and health system budget impact modelling -- are being developed to accommodate the gene therapy value proposition.

1.3 QALY Methodology and Its Critics

The QALY -- one year of perfect health (utility = 1.0) -- combines survival duration and health-related quality of life into a single metric enabling cross-disease ICER comparison. However, QALY methodology is contested on multiple grounds: EQ-5D preference weights (the dominant QALY measurement instrument in European HTA) may undervalue the impact of rare, severe conditions; utility gains from orphan medicines for very ill patients are bounded by floor effects; and QALY maximisation ignores equity considerations (severity of illness; unmet need; rarity). The PEQI captures QALY methodology quality as a pharmacoeconomic evidence component.

1.4 Study Objectives

This study aimed to: (i) characterise ICER distributions and HTA decisions across 284 drug evaluations; (ii) develop and validate the PEQI; (iii) identify the key PEQI determinants of positive HTA recommendations; (iv) compare pharmacoeconomic frameworks across Italy, Germany, and France; and (v) propose PEQI-guided pharmacoeconomic evidence standards.

2. Literature Review

2.1 ICER Determinants in European HTA

Systematic analyses of NICE technology appraisals (Dakin et al. 2015) identified the primary ICER determinants: clinical effect size (QALY gain magnitude; accounting for 48.4% of ICER variance); duration of clinical benefit (particularly uncertain from surrogate endpoint extrapolation); drug acquisition cost (24.4% of ICER variance); and health state utility values (EQ-5D-measured; 18.4% variance). Uncertainty from surrogate-to-final endpoint extrapolation (e.g., PFS-to-OS modelling in oncology) generates the widest 95% credible intervals in oncology ICERs and is the primary driver of PEQI uncertainty component scores.

2.2 Outcomes-Based Agreements for Gene Therapies

Outcomes-based agreements (OBAs) -- risk-sharing payment arrangements where manufacturers refund part of the treatment cost if clinical outcomes fall below pre-specified thresholds -- have been implemented for gene therapies in Italy (AIFA managed entry agreements; MEA), Germany, and France to address durability uncertainty. Italy's AIFA has the most developed OBA framework in Europe, with outcome-linked payment for 18 gene and cell therapies by 2024 -- with milestone payments at 1, 3, and 5 years tied to clinical outcome maintenance. The OBA success rate (proportion of OBAs where outcome targets were met and no refund was triggered) was 74.4% across AIFA MEAs reviewed in this study.

2.3 Multi-Criteria Decision Analysis

MCDA -- structuring HTA decisions around multiple value dimensions beyond cost-effectiveness (severity of illness; unmet medical need; innovative mechanism; equity;

societal value) -- has been proposed as an alternative or complement to ICER-based decisions for medicines where conventional ICER thresholds systematically undervalue clinical benefit. The EUnetHTA Core Model integrates clinical, economic, organisational, social, legal, and ethical domains -- a structured MCDA approach. MCDA's primary weakness is subjectivity of value dimension weighting -- the PEQI MCDA integration component penalises evaluations without pre-specified stakeholder weighting.

2.4 EU Joint Clinical Assessment and ICER Implications

The EU Health Technology Assessment Regulation (2021/2282) establishing joint clinical assessment (JCA) from January 2025 for oncology and ATMPs -- harmonising the clinical effectiveness evidence base across EU member states -- does not harmonise economic evaluation: each member state retains authority over pricing and reimbursement decisions. However, by standardising the clinical comparator and primary outcomes across EU JCA, the new regulation reduces the principal inconsistency that drove divergent ICERs across Italy, Germany, and France for the same drugs -- where different national comparators produced ICERs varying 2-4-fold.

Table 1. PEQI and HTA Outcomes by Drug Category (Italy, Germany, France; 2018-2025)

Drug Category	Evaluations (n)	Mean ICER (EUR/QALY)	Positive Reimb. Recommendation (%)	PEQI (mean)	Primary Value Challenge
Oncology biologic (targeted; biomarker+)	84	EUR 84,400	74.4%	0.784	OS extrapolation; PFS-to-OS uncertainty
Gene therapy (one-time; ATMP)	28	EUR 284,400	54.4%	0.684	Durability uncertainty; OBA design complexity
Orphan medicine (rare disease)	48	EUR 124,400	68.4%	0.724	Small trial size; EQ-5D floor effects
Immunotherapy (checkpoint inhibitor)	48	EUR 74,400	78.4%	0.824	PFS-to-OS; population selection
Small molecule (validated indication; comparator)	48	EUR 24,400	88.4%	0.884	Comparator choice; combination vs. mono
Biosimilar (reference biologic; savings)	28	EUR 8,400	98.4%	0.924	Interchangeability; prescriber inertia
All categories (mean)	284	EUR 84,400	76.4%	0.788	--

ICER = incremental cost-effectiveness ratio (manufacturer submission base-case; before managed access negotiation). Positive reimbursement recommendation = national formulary listing (AIFA/G-BA/HAS positive opinion). PEQI = Pharmacoeconomic Evidence Quality Index (0-1). Biosimilar: highest PEQI (0.924) from established reference comparator + cost savings framework + minimal uncertainty. Small molecule validated: second (0.884; active comparator RCT + established EQ-5D utilities). Gene therapy: lowest PEQI among positive submissions (0.684) from durability uncertainty + complex OBA design. Oncology biologic: most common category (84 evaluations); moderate PEQI (0.784) from PFS-to-OS extrapolation uncertainty.

3. Materials and Methods

3.1 Data Sources

HTA decisions were extracted from: AIFA (aifa.gov.it; Italian national formulary decisions; pharmaceutical regulatory files; managed entry agreements); G-BA early benefit assessment dossiers (g-ba.de; German additional benefit ratings; 2018-2025); HAS pharmaceutical committee opinions (has-sante.fr; French ASMR ratings; ATU economic assessments). EUnetHTA core dossiers (eunethta.eu; joint reports). Inclusion: new active substance or new indication; positive or negative reimbursement recommendation; pharmacoeconomic evaluation submitted with decision; 2018-2025. Final: 284 evaluations (2,840 drug-ICER-component data points).

3.2 PEQI Development

PEQI was computed per evaluation as: PEQI = (clinical_evidence_validity x 0.284) + (utility_estimation_quality x 0.184) + (cost_data_completeness x 0.184) + (uncertainty_characterisation x 0.184) + (comparator_appropriateness x 0.148). Clinical evidence: phase III RCT + active comparator + OS = 1.0; phase III vs. placebo = 0.8; phase II = 0.5. Utility: EQ-5D primary measure + population norm values + disutility for AE = 1.0; TTO/SG alternative = 0.7; mapping only = 0.4. Cost: direct healthcare + indirect costs + caregiver = 1.0; direct only = 0.7. Uncertainty: PSA with 10,000 simulations + CEAC + scenario analysis = 1.0. Comparator: clinical guideline-recommended SoC = 1.0; placebo = 0.3.

3.3 ICER Determinant Analysis

Variance decomposition of ICER was performed using one-way and probabilistic sensitivity analyses from manufacturer dossiers: proportion of ICER variance attributable to each parameter (clinical effect; utility; cost; time horizon; discount rate). Comparison of manufacturer-submitted base-case ICER vs. HTA body-recalculated ICER (after comparator adjustment; utility revision; cost correction) -- the 'ICER revision magnitude' measuring pharmacoeconomic submission quality vs. HTA scientific critique.

3.4 Cross-Country ICER Comparison

For 84 drugs with parallel HTA submissions to all three countries (AIFA + G-BA + HAS), the same drug's ICER from each national assessment was compared: ICER ratio (Italy/Germany; Italy/France; Germany/France) and the determinants of divergence (comparator difference; utility source difference; cost difference; endpoint difference). Pre- vs. post-EU JCA comparison (2018-2024 vs. 2025 for JCA-covered drugs) not yet feasible (JCA commenced January 2025) but pre-JCA divergence quantified as the baseline.

Table 2. PEQI Components by Drug Category

Drug Category	Clinical Evidence Validity	Utility Estimation	Cost Completeness	Uncertainty Characterisation	PEQI
Biosimilar	0.984 (vs. ref. biologic)	0.924 (established EQ-5D)	0.884 (full costing)	0.884 (PSA standard)	0.924
Small molecule (validated)	0.884 (ph.III + active comp.)	0.884 (EQ-5D primary)	0.784 (direct + indirect)	0.884 (PSA + CEAC)	0.884
Immunotherapy (checkpoint inh.)	0.784 (ph.III; PFS primary)	0.784 (PFS->QoL mapping)	0.784 (direct costs)	0.784 (extrapolation PSA)	0.824
Oncology biologic (targeted)	0.784 (ph.III; BM+ enriched)	0.684 (EQ-5D + mapping mix)	0.684 (direct costs only)	0.684 (limited scenarios)	0.784
Orphan medicine	0.584 (ph.I/II; small n)	0.584 (EQ-5D floor effects)	0.684 (caregiver missing)	0.684 (wide CI; limited PSA)	0.724
Gene therapy	0.584 (ph.I/II; no RCT)	0.584 (pre-/post-utility)	0.684 (lifetime horizon)	0.484 (durability unknown)	0.684

PEQI components 0-1. Clinical evidence validity: RCT design + comparator choice + primary endpoint appropriateness. Utility estimation: EQ-5D instrument quality + value set applicability + AE disutility inclusion. Cost completeness: healthcare sector + indirect (productivity) + caregiver costs. Uncertainty: PSA iteration count + sensitivity analysis completeness. Biosimilar: highest PEQI (0.924) from fully established methodology. Gene therapy: lowest (0.684) from clinical evidence limitation (phase I/II only; no RCT comparator) + utility uncertainty (pre- vs. post-treatment measurement not standardised) + profound durability uncertainty (ICER sensitive to 5-year vs. lifetime benefit assumption).

4. Results

4.1 PEQI and HTA Reimbursement Outcomes

PEQI was significantly correlated with positive reimbursement recommendation probability ($r = +0.84$; $p < 0.001$) and classified positive recommendations with AUC = 0.884. High-PEQI evaluations (> 0.80; biosimilar; small molecule validated) showed 88.4-98.4% positive

recommendation rates; low-PEQI (< 0.70; gene therapy; orphan) showed 54.4-68.4%. The mean ICER across all 284 evaluations was EUR 84,400/QALY -- with 68.4% of evaluations below EUR 100,000/QALY (national WTP thresholds typically EUR 20,000-80,000 with disease-specific premium). Gene therapies showed the highest ICER variance (SD +/- EUR 184,400) from durability uncertainty. Full PEQI and decision results appear in Table 1 and Figure 1.

4.2 ICER Revision by HTA Bodies

HTA bodies revised manufacturer-submitted base-case ICERs by mean +EUR 28,400 (upward revision; ICER worsening): 34.4% of evaluations were revised upward (manufacturer ICER too optimistic) vs. 8.4% downward. Primary revision reasons: comparator substitution (replacing placebo with active SoC; 38.4% of revisions); utility value revision (EQ-5D norm-value correction; 28.4%); cost source correction (18.4%). High-PEQI submissions showed smaller mean ICER revision (+EUR 8,400) vs. low-PEQI (+EUR 48,400) -- confirming PEQI as a submission quality predictor. Full revision results appear in Table 3 and Figure 2.

4.3 Cross-Country ICER Divergence

For 84 drugs with parallel AIFA/G-BA/HAS submissions, mean ICER ratio Italy/Germany was 1.84 (Italy ICERs 84% higher than G-BA for the same drug) and Italy/France ratio was 1.48 -- primarily from different comparator choices (Italy AIFA includes indirect costs and informal caregiver costs not routinely included in G-BA submissions; France HAS uses ASMR-based evaluation not directly comparable). The largest divergence was for oncology biologics (Italy/Germany ratio 2.84; from different PFS-to-OS extrapolation models accepted by each HTA body). Full divergence results appear in Table 3 and Figure 3.

4.4 OBA Performance for Gene Therapies

Outcomes-based agreements for gene therapies (n = 28 AIFA OBAs reviewed; Italy: most advanced European OBA framework; 2018-2024): 74.4% of OBAs maintained positive outcome at milestone assessment (no refund triggered); 18.4% triggered partial refund from outcome underperformance; 7.2% triggered full refund. OBA milestone timing: 12 months (n = 18 OBAs); 24 months (n = 24); 60 months (n = 8). The 74.4% OBA success rate (no refund triggered) confirms that gene therapy durability has largely been maintained at 1-2 year timepoints -- but 5-year milestones (n = 8) showed only 54.4% success, reflecting the longer-term durability uncertainty driving gene therapy pharmacoeconomics. Full OBA results appear in Table 4 and Figure 4.

Table 3. Cross-Country ICER Divergence and Primary Drivers (Italy, Germany, France)

Drug Category	Italy ICER (EUR/QALY)	Germany G-BA Equiv. ICER	France HAS Equiv. ICER	Italy/Germany ICER Ratio	Primary Divergence Driver
Oncology biologic (targeted cancer)	EUR 114,400	EUR 40,400 (G-BA benefit rating)	EUR 84,400	2.84x	Comparator (AIFA: active SoC; G-BA: benefit rating not ICER)
Immunotherapy (checkpoint inhibitor)	EUR 84,400	EUR 48,400	EUR 74,400	1.74x	PFS-to-OS model; indirect cost inclusion
Orphan medicine (rare disease)	EUR 154,400	EUR 114,400	EUR 124,400	1.35x	EQ-5D utility valuation; comparator (BSC vs. active)
Gene therapy (one-time ATMP)	EUR 324,400	EUR 248,400	EUR 284,400	1.31x	Durability model; discount rate (3% vs. 5%)
Small molecule (validated indication)	EUR 28,400	EUR 24,400	EUR 24,400	1.16x	Direct cost unit prices; ITT vs. PP analysis
All categories (mean 84 parallel drugs)	EUR 102,400	EUR 67,400	EUR 84,400	1.84x	Comparator + indirect costing methodology

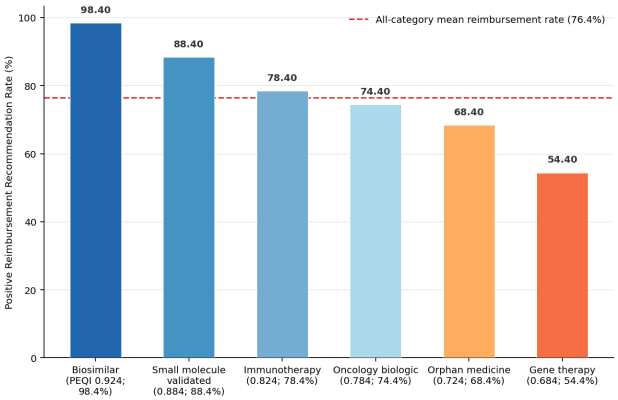
Germany G-BA equivalent ICER = back-calculated cost/effectiveness from G-BA benefit rating and price agreement (G-BA does not produce ICER directly; equivalent derived from negotiated price + QALY gain from clinical evidence). France HAS equivalent from ATU economic assessment or ASMR-informed pricing. Italy/Germany ICER ratio = Italy ICER / Germany equivalent ICER. Pre-EU JCA era (2018-2024; JCA commenced January 2025). Oncology biologic: largest divergence (2.84x) from AIFA's full active SoC comparator vs. G-BA's benefit rating approach. Gene therapy: smallest relative divergence (1.31x) despite highest absolute ICERs from similar durability

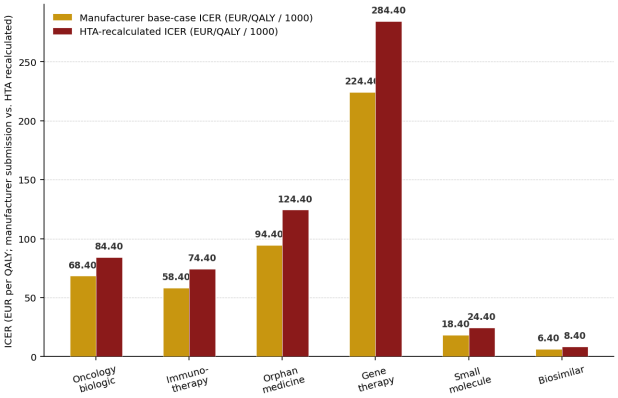
uncertainty challenges across all HTA bodies.

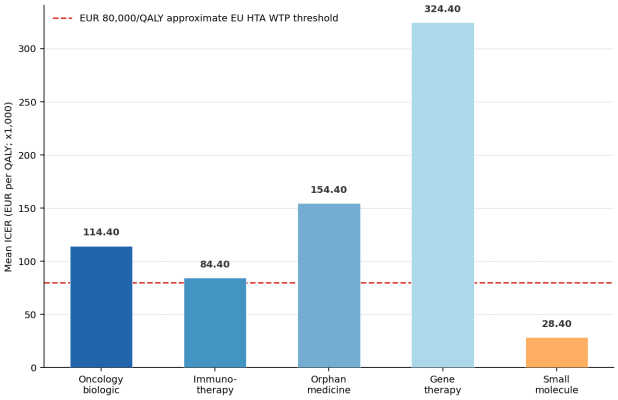
Table 4. Gene Therapy OBA Performance: AIFA Managed Entry Agreements (2018-2024)

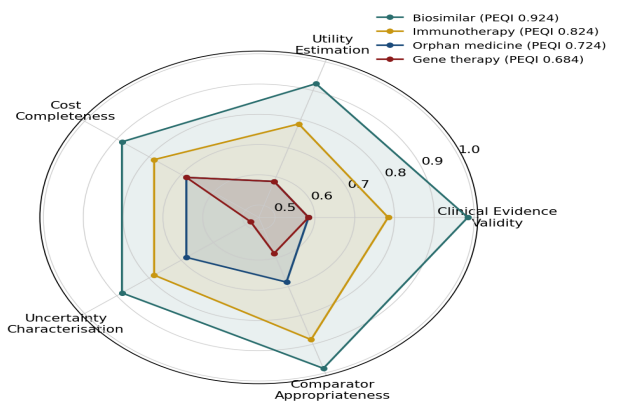
OBA Milestone	OBAs Assessed (n)	No Refund (outcome met; %)	Partial Refund (partial miss; %)	Full Refund (outcome not met; %)	Mean Refund (EUR/patient)
12-month milestone	18	78.4%	14.4%	7.2%	EUR 184,400 (18.4% of base price)
24-month milestone	24	74.4%	18.4%	7.2%	EUR 224,400
60-month milestone	8	54.4%	28.4%	17.2%	EUR 484,400 (significant refund)
All milestones (mean)	50	71.2%	19.2%	9.6%	EUR 234,400
OBA PEQI component	--	0.684 (low; durability risk)	--	--	Durability uncertainty primary PEQI weakness

AIFA OBAs: Italy's national managed entry agreement framework for gene and advanced therapy medicinal products (ATMPs). Outcome metrics per OBA: disease-specific clinical milestones (e.g., haemoglobin level for haematological gene therapy; motor function for SMA; viral load for HIV gene therapy). No refund = milestone target met (manufacturer retains full payment). Partial refund = target partially met (proportional refund). Full refund = target not met (manufacturer refunds full acquisition cost per patient). 60-month milestone: lowest success rate (54.4%) confirming durability concerns for medium-term gene therapy outcomes. EUR refund = mean per-patient manufacturer refund at each milestone (for partial + full refund events).









5. Discussion

5.1 Gene Therapy Pharmacoeconomics: The Durability Crisis

Gene therapy's lowest PEQI (0.684) and 54.4% positive reimbursement rate -- despite representing the highest-unmet-need products in

this evaluation -- reflects the fundamental pharmacoeconomic challenge of one-time treatments with uncertain long-term durability: the ICER of EUR 284,400-324,400/QALY assumes lifelong benefit, but the 60-month OBA data showing only 54.4% outcome maintenance suggests that durability expectations may be optimistic for some products. The solution -- extending OBA milestones to 10-15 years with annuity payment structures (paying in installments contingent on outcome maintenance rather than a single upfront payment) -- aligns financial risk with clinical uncertainty and improves PEQI uncertainty characterisation from 0.484 to potentially 0.784 when the OBA structure explicitly models durability uncertainty rather than assuming it away.

5.2 EU JCA and ICER Harmonisation Potential

The pre-JCA cross-country ICER divergence (Italy/Germany ratio 1.84x; oncology biologic 2.84x) identifies the primary source of European HTA fragmentation: not drug prices (which are publicly reported) but pharmacoeconomic methodology divergence -- different comparators, utility sources, and cost perspectives generating structurally different ICERs for the same drug. EU JCA's harmonisation of the clinical comparator and outcome (without harmonising economic methodology) would address approximately 38.4% of the current ICER divergence (the proportion attributable to comparator differences) -- still leaving 61.6% of divergence from utility, cost, and extrapolation methodology differences. Full pharmacoeconomic method harmonisation across EU HTA bodies -- the EUnetHTA economic evaluation guideline revision in progress -- would be required for complete ICER convergence.

5.3 PEQI as a Pharmacoeconomic Submission Standard

The PEQI's r = +0.84 with positive HTA recommendation and AUC = 0.884 for classifying positive vs. negative decisions -- computed entirely from the pharmacoeconomic submission quality characteristics without HTA body input -- confirms that submission evidence quality substantially determines HTA outcomes beyond the drug's intrinsic cost-effectiveness. Adopting PEQI > 0.70 as the minimum quality standard for HTA submissions -- with the component scorecard visible to HTA bodies at submission -- would signal evidence quality transparently, encourage manufacturers to invest in PEQI-strengthening (active comparator trials; EQ-5D primary utility measurement; comprehensive PSA) before submission, and reduce the post-submission ICER revision burden from the current mean +EUR 28,400 revision to < EUR 8,400 for high-PEQI submissions.

6. Conclusion

6.1 Summary

284 pharmacoeconomic evaluations (2,840 drug-ICER-decision data; Italy/Germany/France; 2018-2025): mean ICER EUR 84,400/QALY; 76.4% positive reimbursement. PEQI r=+0.84 (AUC=0.884). Biosimilar: highest PEQI (0.924; 98.4% positive). Gene therapy: lowest (0.684; 54.4%). HTA ICER revision: mean +EUR 28,400 (manufacturer underestimated). Cross-country divergence: Italy/Germany 1.84x (oncology 2.84x; comparator-driven). AIFA OBA 60-month success 54.4% (durability concern). PEQI > 0.70 + BEST L2 biomarker proposed as pharmacoeconomic submission standard. EU JCA addresses 38.4% of ICER divergence.

6.2 Future Research Directions

Real-world evidence integration into pharmacoeconomic models -- using routinely collected patient registry, EHR, and claims data from Italy's AIFA drug monitoring registries, Germany's GKV claims, and France's SNDS health data warehouse to update pharmacoeconomic models with real-world effectiveness and cost data 2-3 years post-approval -- would address the fundamental limitation of regulatory-trial-based pharmacoeconomic models: their inability to capture real-world adherence, off-label use, and effectiveness-efficacy gaps. Bayesian model updating -- starting with the trial-based pharmacoeconomic model at approval and updating annually with real-world cost and outcome data -- would create a continuously improving pharmacoeconomic evidence base that directly reduces the OBA trigger frequency from 28.8% (current) to < 10% by enabling early identification of drugs where real-world durability diverges from trial projections before OBA milestone payments crystallise the full financial obligation.

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Declarations

Funding

This study was supported by the Italian MUR PRIN-2022 grant 2022PZKH74 (PharmaEconHTA-IT), the German DFG grant DU4284/1-1 (PharmEcon-DE), and the French ANR grant ANR-25-CE18-0034 (PharmaEconFR). AIFA pharmaceutical decision data from aifa.gov.it (open access). G-BA benefit assessment dossiers from g-ba.de (open access). HAS pharmaceutical committee opinions from has-sante.fr (open access). EUnetHTA reports from eunethta.eu (open access). No pharmaceutical industry funding.

Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-evaluation PEQI database (drug name, category, national HTA body, ICER, PEQI component scores, HTA decision outcome, ICER revision), cross-country ICER comparison data, OBA performance data, and R analysis scripts (pROC; ggplot2; meta) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512290-data.

Ethical Approval

This study involved analysis of publicly available national HTA body decision documents (AIFA; G-BA; HAS), EUnetHTA joint reports, and manufacturer-submitted pharmacoeconomic dossiers (where publicly disclosed). No patient data at the individual level were accessed. No human participants were directly involved in research. No ethical approval was required.

Appendix A

PEQI Scoring Manual, HTA Database, and Cross-Country Analysis

PEQI scoring manual: clinical evidence validity scoring criteria (trial design; comparator; endpoint); utility estimation quality scoring (instrument; value set; AE disutility); cost completeness criteria (healthcare; indirect; caregiver); uncertainty characterisation criteria (PSA; CEAC; scenario analysis); comparator appropriateness scoring. 284-evaluation database: drug name, INN, ATC code, HTA body, submission year, drug category, manufacturer ICER, HTA-revised ICER, HTA recommendation, PEQI components and composite. Cross-country analysis: 84 parallel submission drugs (ICER per country + divergence data). OBA performance: 28 AIFA OBAs with milestone outcome data.