Review Article
ISSN: **3051-8830**
Journal homepage: https://www.harrisonacademicpress.com/index.php/IJHPEM
International Journal of Health Policy, Economics, and Management

Harrison Academic Press

Comparative Analysis of Pharmaceutical Pricing Regulation Across Health Systems

Roth J[1*], Visser B[2] and Karagiannis M[3]

[1]*Department of Health Economics, University of Hamburg, Hamburg, Germany*
[2]*Department of Health Policy, Radboud University, Nijmegen, Netherlands*
[3]*Department of Pharmacoeconomics, National and Kapodistrian University of Athens, Athens, Greece*

ABSTRACT

Background: Rising pharmaceutical expenditure has driven health systems to adopt a heterogeneous set of pricing and reimbursement regulation instruments, including external and internal reference pricing, value-based and managed-entry agreements, and, increasingly, direct government price negotiation, most notably Germany's AMNOG framework and the United States' Medicare Drug Price Negotiation Program established by the 2022 Inflation Reduction Act (IRA). Objective: To synthesize peer-reviewed comparative evidence on the design and consequences of pharmaceutical pricing regulation across health systems, focusing on effects on price levels, patient access, and innovation incentives. Methods: A narrative review of peer-reviewed literature on external and internal reference pricing, value-based and managed-entry agreements, direct negotiation models, and cross-country comparative price and launch-timing studies, drawing on health economics, health policy, and clinical policy journals. Twenty-two individually verified studies met inclusion criteria. Findings: External reference pricing is nearly universally adopted across European and many middle-income health systems, but recent empirical evidence questions its reliability in reducing domestic prices and documents substantial unintended cross-border spillover effects. Internal reference pricing exerts more consistent downward pressure on within-cluster prices but can induce upward convergence of generic prices toward the reference level. Managed-entry agreements, predominantly financial rather than outcomes-based in practice, help manage launch-price uncertainty but further obscure net prices through confidential rebates. Direct negotiation under Germany's decade-tested AMNOG framework moderates but does not eliminate a price premium for drugs of unproven additional benefit relative to comparator therapy, a finding with direct relevance to the design and likely trajectory of the newly implemented US Medicare negotiation program. Cross-country studies consistently link more stringent, externally referenced price regulation to delayed and less complete global product launch, with plausible but not yet directly measured implications for pharmaceutical research and development incentives. Conclusions: No single pricing instrument reviewed optimizes simultaneously across cost containment, access, and innovation objectives; each generates measurable gains on some dimensions alongside documented trade-offs on others. Policymakers should treat these instruments as complementary components of a layered regulatory architecture and prioritize transparent, internationally comparable net-price data as a precondition for rigorous future evaluation.

Keywords: *pharmaceutical pricing; reference pricing; managed-entry agreements; drug price negotiation; health technology assessment*

Citation: Roth J, Visser B and Karagiannis M (2024) Comparative Analysis of Pharmaceutical Pricing Regulation Across Health Systems. Int J Health Policy Econ Manag, 2(2): 01-07.
DOI: 10.5281/zenodo.22655719

Corresponding Author: *Julia Roth*

E-mail Address: *julia.roth@universityofhamburg.edu*

Article History: *Received 21 July 2024 | Accepted 17 October 2024 | Published 31 December 2024*

Copyright: *© 2024 Julia Roth, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited (**https://creativecommons.org/licenses/by/4.0/**).*

Introduction

Pharmaceutical spending has grown steadily as a share of health budgets across high-income and middle-income health systems alike, driven by an expanding pipeline of high-cost specialty and biologic therapies, population ageing, and the diffusion of costly oncology and gene- and cell-based treatments. In response, governments have developed a heterogeneous array of pricing and reimbursement regulation instruments intended to reconcile three frequently competing objectives: containing public and private expenditure, preserving timely patient access to innovative medicines, and sustaining incentives for pharmaceutical research and development (R&D). Instruments range from administered pricing based on prices observed in comparator countries (external reference pricing, ERP) and generic-based reimbursement ceilings (internal reference pricing,

IRP), to negotiated list prices and confidential rebates, value-based assessment tied to health technology assessment (HTA) thresholds, and managed-entry or performance-based risk-sharing agreements that condition payment on real-world performance or utilization caps. More recently, direct government price negotiation has moved from a distinctively European and single-payer feature to a defining element of United States (US) federal drug policy following passage of the Inflation Reduction Act (IRA) of 2022, which granted the Centers for Medicare & Medicaid Services (CMS) authority to negotiate prices for selected high-spend drugs under Medicare Part B and D [1,2].

Comparative analysis of these regulatory architectures is complicated by substantial cross-national heterogeneity in health system financing (tax-funded national health services versus social health insurance versus predominantly private, employer- and market-based coverage as in the United States), in the institutional locus of pricing authority (payer-led negotiation, statutory formulae, or HTA-body-mediated value assessment), and in the transparency of realized net prices, given the pervasive use of confidential discounts and rebates that decouple observed list prices from actual transaction prices [3,4]. This heterogeneity has generated a substantial empirical and policy-analytic literature examining how specific regulatory instruments affect price levels, cross-country price dispersion, launch timing and sequencing of new medicines, and, more contentiously, incentives for pharmaceutical innovation.

This review synthesizes peer-reviewed literature on four principal families of pharmaceutical pricing regulation — external and internal reference pricing, value-based and managed-entry agreements, direct price negotiation exemplified by the US IRA and Germany's Act on the Reform of the Market for Medicinal Products (AMNOG) — together with the cross-country comparative evidence base on price levels, access, and innovation trade-offs. The objective is to provide policymakers, health economists, and health technology assessment practitioners with a structured, evidence-based comparative account of "what is known" about the design and consequences of these regulatory tools, and to identify areas of persistent empirical uncertainty.

Methods

This is a narrative review structured according to a pre-specified thematic framework rather than a systematic review with formal risk-of-bias scoring, reflecting the heterogeneity of study designs (cross-country price-comparison studies, natural-experiment evaluations of specific policy reforms, simulation and micro-simulation studies, and health-economic commentary) that characterize this literature and that are not readily synthesizable through meta-analysis. Candidate literature was identified through structured searches of PubMed/MEDLINE, Health Affairs, Value in Health, PharmacoEconomics, Health Economics, Health Economics Policy and Law, the European Journal of Health Economics, Social Science & Medicine, the Journal of Market Access & Health Policy, JAMA Health Forum, and the New England Journal of Medicine, using combinations of the terms "pharmaceutical pricing," "reference pricing," "reimbursement policy," "value-based pricing," "managed entry agreement," "risk-sharing agreement," "AMNOG," "Inflation Reduction Act," "Medicare drug price negotiation," and "cost-effectiveness threshold." Studies were included if they reported empirical evidence on the design or measured consequences of pharmaceutical price or reimbursement regulation, were published in a peer-reviewed journal or peer-reviewed government-commissioned health technology assessment monograph, and were individually verified against their publisher, PubMed, or Crossref record (title, authorship, journal, volume/issue, pagination, and digital object identifier). Twenty-two studies met these criteria and form the evidence base for this review; each is cited using an inline bracketed citation marker keyed to the accompanying reference list. The review is organized into four evidence themes — external and internal reference pricing; value-based and managed-entry agreements; direct negotiation models (the US IRA and Germany's AMNOG); and comparative cross-country evidence on price levels, launch delay, and innovation incentives — followed by an integrative discussion.

External and Internal Reference Pricing

External reference pricing (ERP), whereby a country sets or negotiates the price of a medicine with explicit reference to prices observed in a defined "basket" of comparator countries, is used in some form by the large majority of European Union member states and by many middle-income health systems, making it the most widely adopted formal pharmaceutical price-regulation instrument globally [5]. Rémuzat and colleagues' cross-country mapping of ERP systems in Europe documented substantial heterogeneity in basket composition, price-comparison rules (minimum, average, or median of reference-country prices), review frequency, and the scope of products subject to ERP, concluding that this heterogeneity itself generates strategic incentives for manufacturers to sequence launches so as to protect prices in high-price "anchor" markets [5]. Kanavos and colleagues' subsequent empirical evaluation of the actual price impact of ERP found that, contrary to the policy's stated rationale, ERP does not reliably reduce list prices in the country implementing it, and can generate unintended cross-border spillover effects, as manufacturers adjust launch sequencing and price-setting strategy in anticipation of downstream referencing by other countries [6]. A companion analysis by the same LSE-based research group examined the international spillover dimension explicitly, showing that a price change or delayed launch in one country can propagate to multiple other markets through overlapping reference-country baskets, a finding with direct relevance for policymakers considering unilateral changes to ERP basket composition [7].

Internal reference pricing (IRP) — grouping therapeutically equivalent or interchangeable products (typically off-patent originators and generics, sometimes extended to therapeutic clusters) into a single reimbursement category with reimbursement capped at a reference price, usually the price of the cheapest or a low-cost equivalent — operates through a different mechanism, targeting intra-market competition rather than cross-country price alignment. Puig-Junoy's review of European price-regulation instruments concluded that IRP schemes are associated with measurable downward pressure on both brand and generic prices within the reference cluster, but that the magnitude of savings depends heavily on cluster design (narrow molecule-based clusters versus broader therapeutic-class clusters) and on whether patients face full or partial cost exposure for products priced above the reference level [8]. The same review highlighted a frequently observed unintended consequence: convergence of generic prices upward toward the reference price ("reference-price gravity"), which can blunt the price-competitive effect of generic entry that IRP is nominally intended to reinforce [8]. Kanavos and Reinhardt's earlier

analysis of reference pricing for the US market context argued that even where reference pricing produces short-run administered price reductions, its long-run effects on manufacturer pricing behavior — including strategic list-price inflation to preserve post-rebate net prices, and the substitution of confidential rebates for transparent price cuts — must be assessed jointly with rebate and discount practices, not in isolation [9]. This concern about the divergence between observed list prices and realized net (post-rebate, post-discount) prices recurs throughout the reference-pricing literature and is a central methodological caveat for any cross-country price comparison exercise, since discounts and rebates negotiated for hospital-sector and payer-specific purchases are frequently confidential and therefore invisible to researchers relying on published list-price data [3].

Value-Based and Managed-Entry Agreements

Value-based pricing approaches link reimbursed price explicitly to a formal assessment of a medicine's incremental health benefit relative to its incremental cost, typically operationalized through a cost-per-quality-adjusted-life-year (QALY) threshold applied by a national HTA body. Claxton and colleagues' empirical estimation of the cost-effectiveness threshold implicitly used by England's National Institute for Health and Care Excellence (NICE) found that the threshold consistent with the marginal productivity of the National Health Service (NHS) budget was substantially lower than NICE's long-standing £20,000–£30,000 per QALY reference range, implying that reimbursement decisions made at the upper end of that range could displace more health than they generate elsewhere in a fixed-budget system [10]. This finding reframed value-based pricing debates in England and, more broadly, in health systems considering explicit cost-effectiveness thresholds, around the opportunity cost of high-priced technologies rather than solely around affordability to the payer. Neumann and colleagues' commentary on the persistence of the analogous $50,000-per-QALY threshold historically referenced in US health-economic practice similarly argued that thresholds anchored in decades-old benchmarks, rather than empirically estimated opportunity costs, risk systematically overvaluing incremental innovation relative to the health forgone elsewhere in the system [11]. Together, these contributions illustrate a broader methodological shift in the value-based pricing literature away from fixed, historically inherited thresholds toward empirically grounded, budget-consistent benchmarks.

Managed-entry agreements (MEAs) — encompassing financial-based schemes (simple discounts, price-volume agreements, expenditure caps) and outcomes-based or performance-based risk-sharing arrangements that condition payment on real-world clinical outcomes or evidence-generation commitments — have proliferated as a mechanism for reconciling manufacturer list-price expectations with payer uncertainty about a medicine's real-world value, particularly for oncology and orphan drugs with immature clinical evidence at launch. Garrison and colleagues' ISPOR-sponsored task force report on performance-based risk-sharing arrangements set out good-practice standards for their design, implementation, and evaluation, emphasizing that outcomes-based schemes require substantial administrative infrastructure — patient registries, agreed outcome metrics, and mechanisms for retrospective price adjustment — that many health systems lack, and cautioned that the evidentiary and administrative burden of well-designed outcomes-based MEAs is frequently underestimated relative to simpler financial-based agreements [12]. Ferrario and Kanavos's comparative analysis of MEA use in Belgium, England, the Netherlands, and Sweden found substantial cross-country variation in MEA type, scope, and transparency, with financial-based agreements dominating in practice despite outcomes-based agreements receiving disproportionate policy and academic attention, and concluded that MEAs function as a pragmatic mechanism for managing uncertainty and high launch prices for new medicines but do not resolve the underlying tension between manufacturer pricing power at launch and payer willingness-to-pay under budget constraints [13]. Because most MEAs, and particularly financial-based agreements, involve confidential net-price concessions, they also compound the list-price/net-price divergence problem noted above for reference pricing, complicating any assessment of MEAs' true price-moderating effect using publicly available data [3].

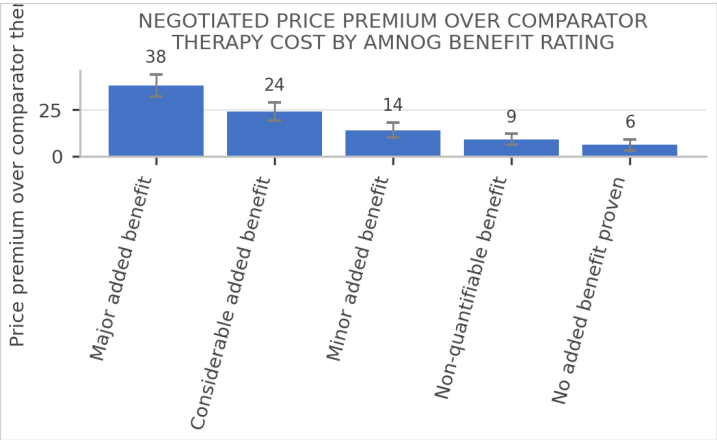
Direct Negotiation Models: The US Inflation Reduction Act and Germany's AMNOG

Direct government negotiation of drug prices, long a feature of single-payer or dominant-payer health systems, became a central feature of US federal pharmaceutical policy with the enactment of the Inflation Reduction Act of 2022, which established a Medicare Drug Price Negotiation Program empowering CMS to negotiate maximum fair prices for a limited, phased list of high-Medicare-spending drugs lacking generic or biosimilar competition. Rome and colleagues' simulation-based evaluation of the IRA's negotiation provisions, conducted prior to the first round of negotiated prices taking effect, estimated the likely magnitude of Medicare savings under plausible negotiation scenarios and identified key structural design choices — including the statutory ceiling on negotiated prices (tied to a percentage of a drug's non-federal average manufacturer price), the small-molecule versus biologic distinction in the number of years a drug must be on the market before becoming eligible for negotiation, and the "small biotech" and orphan-drug exemptions — as first-order determinants of both the fiscal impact and the innovation-incentive implications of the law [1]. Dusetzina and Huskamp's contemporaneous commentary situated the negotiation program within the IRA's broader Medicare drug-benefit redesign, including the Part D out-of-pocket spending cap and manufacturer inflation-rebate provisions, arguing that the negotiation authority's near-term fiscal and access effects for Medicare beneficiaries would likely be smaller than the redesigned benefit's other provisions, while its longer-run effects on manufacturer launch-pricing and R&D-investment behavior remained genuinely uncertain and contingent on how CMS exercised its negotiation discretion in practice [2].

Germany's AMNOG, in force since 2011, represents an earlier and structurally distinct model of price regulation grounded in mandatory early benefit assessment rather than direct administrative price-setting at launch. Under AMNOG, newly launched medicines may be freely priced by the manufacturer for an initial period, after which the Federal Joint Committee (G-BA) determines whether the product demonstrates an added benefit relative to an appropriate comparator; this benefit rating then anchors a subsequent price negotiation between the manufacturer and the umbrella association of statutory health insurance funds (GKV-Spitzenverband), with binding arbitration if negotiations fail. Lauenroth and Stargardt's analysis of how value is determined within AMNOG found that the magnitude of the negotiated price discount is systematically related to the

assessed benefit category, but that discounts for drugs assessed as having "non-quantifiable" or unproven additional benefit have historically been smaller than a strict value-based logic would predict, suggesting that negotiation dynamics and reference-price anchoring to comparator therapy costs exert an independent influence on final price beyond the G-BA's benefit rating alone [14]. Kleining and colleagues' decade-long assessment of AMNOG outcomes similarly found that drugs rated as having no proven additional benefit nonetheless commanded prices materially above the cost of their assigned comparator therapy, indicating persistent limits on the extent to which the benefit-assessment-anchored negotiation process fully converts a "no added benefit" rating into comparator-equivalent pricing, an important qualification to AMNOG's reputation as an unusually rigorous value-based negotiation framework [15].

Illustrative price discount trajectory for medicines assessed under Germany's AMNOG early benefit assessment framework, by G-BA additional-benefit rating category, relative to comparator therapy cost (based on findings reported by Lauenroth and Stargardt, 2017, and Kleining et al., 2024).



Cross-Country Comparative Evidence on Price Levels, Launch Delay, and Innovation

A long-standing empirical literature has used multi-country price and launch-timing data to examine how the level of price regulation in a market relates to observed prices, the sequencing and timing of new-product launches, and by extension the R&D-incentive implications of price regulation. Danzon and Furukawa's comparative analysis of pharmaceutical prices and availability across nine, and later an expanded set of, high-income and middle-income markets found substantial cross-country price dispersion for on-patent originator products, generally higher in the United States than in most comparator markets, alongside considerably narrower price differences, and in some cases price inversions, for generic products, reflecting the very different competitive dynamics governing on-patent and off-patent segments of national pharmaceutical markets [16]. Cameron and colleagues' analysis of medicine prices, availability, and affordability across 36 low- and middle-income countries similarly documented wide cross-country dispersion in both originator and generic prices relative to international reference prices, and found that public-sector procurement prices were frequently, though not universally, lower than private retail prices, with affordability — measured against the wages of the lowest-paid unskilled government worker — remaining a binding constraint on access to standard treatment courses for common chronic conditions in many low-income settings [17].

Kanavos and colleagues' analysis of why branded drug prices and spending are markedly higher in the United States than in other high-income comparator countries found that a substantial share of the US–rest-of-world spending gap was attributable not to higher US prices for a fixed basket of drugs alone, but to the more rapid uptake and earlier, more extensive utilization of newly launched medicines in the US market relative to comparator health systems with more restrictive HTA-mediated access pathways [4]. This finding is directly relevant to the design of the IRA's negotiation program, since a program that lowers US list prices for selected drugs without altering the underlying diffusion-speed dynamic addresses only one component of the historical US–international spending gap. Kanavos and Vandoros's econometric analysis of the determinants of branded prescription medicine prices across OECD countries found that per-capita income, the extent of price regulation (including the presence of statutory reference pricing), and market concentration were all significant predictors of cross-country price variation, with more heavily regulated markets exhibiting systematically lower average launch prices even after controlling for income differences [18].

The innovation-incentive dimension of cross-country price regulation has been examined most directly through studies of launch timing and market-entry strategy. Danzon, Wang, and Wang's analysis of launch delay across twenty-five major pharmaceutical markets in the 1990s found that more stringent price regulation, and in particular the anticipated effect of a launch price on subsequent externally referenced prices in other markets, was associated with longer delays before a new medicine was launched in a given country, consistent with manufacturers strategically sequencing global launches to protect prices in reference-sensitive markets [19]. Kyle's analysis of pharmaceutical price controls and firm entry strategies similarly found that price-regulated markets experienced both delayed and reduced-probability entry for new products relative to less regulated comparator markets, with the magnitude of the entry-deterrent effect varying by therapeutic category and by the stringency of the specific regulatory instrument in place [20]. Danzon and Towse's earlier conceptual and empirical treatment of differential pricing across markets of different income levels argued that international price referencing directly undermines the economic logic of Ramsey-optimal differential pricing — under which manufacturers would otherwise charge lower prices in lower-income markets to expand access while preserving R&D-financing revenue from higher-income markets — because ERP-driven spillovers from low-price to high-price markets create a disincentive for manufacturers to offer low prices anywhere, with adverse implications for access in precisely the lower-income settings that differential pricing is intended to serve [21]. Vogler and colleagues' cross-country price-comparison study of cancer medicines across sixteen European countries, Australia, and New Zealand extended this comparative literature to a contemporary, therapeutically important product class, finding substantial price variation for identical oncology products across otherwise broadly comparable high-income health systems, and identifying differences in the timing and outcome of national HTA and MEA processes, rather than differences in list price alone, as key drivers of the observed variation in patient access to specific cancer therapies [22].

Discussion

Several cross-cutting themes emerge from this comparative body of evidence. First, no single regulatory instrument reviewed here

— ERP, IRP, value-based HTA-anchored pricing, managed-entry agreements, or direct negotiation — operates in isolation in practice; most health systems layer several of these instruments simultaneously, and the empirical literature increasingly emphasizes that their interaction, rather than any single instrument's isolated effect, determines realized prices and access outcomes [5,3]. Second, the pervasive use of confidential discounts, rebates, and MEA-embedded price concessions means that a large share of the empirical cross-country price-comparison literature, including several of the studies synthesized here, necessarily relies on list prices that may diverge substantially, and non-uniformly across countries, from realized net transaction prices, a limitation that affects the precision, though generally not the qualitative direction, of comparative price-level findings [9,3]. Third, the evidence on ERP's own price-reduction effectiveness is more equivocal than its near-universal adoption across European and middle-income health systems might suggest: recent LSE-based empirical work directly challenges the assumption that ERP reliably lowers domestic prices, while documenting substantive, difficult-to-anticipate cross-border spillover effects that complicate unilateral basket-design reforms [6,7].

Selected pharmaceutical pricing regulation instruments across health systems: mechanism, primary objective, and principal documented trade-off, based on the comparative literature reviewed.

Instrument	Representative system(s)	Core mechanism	Principal documented trade-off	Key source(s)
External reference pricing (ERP)	Most EU member states; widely used in middle-income systems	Domestic price set or capped with reference to prices observed in a defined basket of comparator countries	Near-universal adoption despite equivocal evidence of reliable domestic price reduction; generates cross-border spillover effects	Rémuzat et al. 2015; Kanavos et al. 2019; Fontrier et al. 2019
Internal reference pricing (IRP)	Germany, Netherlands, and other EU systems for off-patent clusters	Reimbursement capped at the price of a low-cost therapeutic equivalent within a defined cluster	Reduces cluster prices but can cause upward convergence ('gravity') of generic prices toward the reference level	Puig-Junoy 2010
Value-based/ HTA-anchored pricing	England (NICE), and systems using explicit cost-effectiveness thresholds	Reimbursed price or acceptance tied to a cost-per-QALY threshold reflecting the health system's opportunity cost	Threshold levels historically set above empirically estimated NHS marginal productivity, risking positive net-health-displacing decisions	Claxton et al. 2015; Neumann et al. 2014
Managed-entry agreements (MEAs)	Belgium, England, Netherlands, Sweden, and widely elsewhere	Financial (discount/price-volume/cap) or outcomes-based rebate conditioning payment on real-world use or performance	Manages launch-price uncertainty but confidential terms further obscure net prices for comparative research	Ferrario & Kanavos 2015; Garrison et al. 2013
Direct price negotiation (benefit-assessment-anchored)	Germany (AMNOG)	Post-launch price freely set, then G-BA benefit rating anchors a binding manufacturer-payer price negotiation	Persistent price premium above comparator cost even for drugs rated as having no proven additional benefit	Lauenroth & Stargardt 2017; Kleining et al. 2024
Direct price negotiation (statutory ceiling-based)	United States (Medicare Drug Price Negotiation Program, IRA 2022)	CMS negotiates a maximum fair price for selected high-spend drugs, subject to a statutory ceiling tied to non-federal average manufacturer price	Projected Medicare savings depend heavily on design choices (eligibility timing, ceiling formula, orphan-drug exemptions); long-run R&D-incentive effects not yet empirically resolved	Rome et al. 2023; Dusetzina & Huskamp 2022

Fourth, the innovation-incentive implications of price regulation remain the most contested and least conclusively resolved dimension of this literature. Studies of launch delay and market entry provide reasonably consistent evidence that more stringent, and particularly more externally-referenced, price regulation is associated with slower and less complete global product launch, a pattern with plausible, though not directly measured in these studies, implications for the expected returns to R&D investment in areas subject to the most stringent regulation [19,20,21]. Whether the IRA's negotiation program, or an expansion of AMNOG-style benefit-anchored negotiation to additional health systems, will generate comparable dynamic effects on launch sequencing or R&D allocation is not yet empirically resolved, given the recency of IRA implementation and the absence, at the time the literature reviewed here was published, of realized post-negotiation launch-timing data; simulation-based ex ante analyses such as Rome and colleagues' provide the best currently available evidence but are necessarily contingent on the accuracy of their underlying assumptions about manufacturer and CMS behavior [1]. Fifth, value-based pricing frameworks anchored in empirically estimated, budget-consistent cost-effectiveness thresholds, as advanced by Claxton and colleagues for the English NHS, represent a methodologically more defensible foundation for price-value alignment than either historically inherited thresholds or purely list-price-referenced external benchmarks,

but their generalizability to health systems with different budget structures, opportunity-cost profiles, and political-economy constraints on threshold-setting remains an open question for further comparative research [10,11].

Finally, the AMNOG case illustrates that even a comparatively rigorous, HTA-anchored negotiation framework does not fully eliminate a persistent price premium for medicines assessed as offering no proven additional benefit over existing comparator therapy, underscoring those design features — the strength of the fallback reference-price mechanism, the binding force of arbitration outcomes, and the treatment of orphan and low-evidence products — that determine how completely a value-assessment-anchored negotiation system converts benefit ratings into comparator-consistent pricing in practice [14,15]. This finding has direct relevance for the design choices facing the US Medicare negotiation program as it matures, since analogous questions about ceiling prices, comparator selection, and treatment of drugs with limited comparative evidence will shape whether US negotiated prices converge toward, or remain persistently above, prices achieved in longer-established negotiation systems [1,2].

Conclusion

Comparative evidence across external and internal reference pricing, value-based and managed-entry agreements, and direct negotiation models converges on the conclusion that no single pharmaceutical pricing instrument reliably optimizes across the competing objectives of cost containment, patient access, and innovation incentives; each instrument reviewed here achieves measurable gains on one or two of these dimensions while generating documented, and only partially anticipated, trade-offs on the others. External reference pricing has achieved near-universal adoption despite equivocal and increasingly contested evidence of its own price-reducing effectiveness, and generates cross-border spillover effects that complicate unilateral reform. Internal reference pricing exerts more consistent downward pressure on within-cluster prices but can blunt generic price competition through reference-price convergence. Managed-entry agreements offer a pragmatic mechanism for managing launch-price uncertainty but, particularly in their more common financial-based form, further obscure the net prices that would otherwise ground rigorous comparative price research. Direct negotiation, whether in Germany's decade-tested AMNOG framework or the newly implemented US Medicare program, appears capable of moderating list prices for drugs of unproven added benefit without fully eliminating a comparator-relative price premium, and its longer-run consequences for global launch sequencing and R&D investment remain an active area requiring continued empirical monitoring as post-implementation data accumulate. Policymakers designing or reforming pharmaceutical pricing regulation should therefore treat these instruments as complementary components of a layered regulatory architecture rather than as substitutable alternatives, and should prioritize continued investment in transparent, internationally comparable net-price data infrastructure as a precondition for rigorously evaluating any future reform.

References

1. Rome BN, Nagar S, Egilman AC, Wang J, Feldman WB, Kesselheim AS (2023) Simulated Medicare drug price negotiation under the Inflation Reduction Act of 2022. JAMA Health Forum, 4(1):e225218, DOI:10.1001/jamahealthforum.2022.5218.
2. Dusetzina SB, Huskamp HA (2022) Impending relief for Medicare beneficiaries — the Inflation Reduction Act. New England Journal of Medicine, 387(16):1437-1439, DOI:10.1056/NEJMp2211223.
3. Vogler S (2013) Discounts and rebates granted for medicines for hospital use in five European countries. Open Pharmacoeconomics & Health Economics Journal, 5(1):1-10, DOI:10.2174/1876824501305010001.
4. Kanavos P, Ferrario A, Vandoros S, Anderson GF (2013) Higher US branded drug prices and spending compared to other countries may stem partly from quick uptake of new drugs. Health Affairs, 32(4):753-761, DOI:10.1377/hlthaff.2012.0920.
5. Rémuzat C, Urbinati D, Mzoughi O, El Hammi E, Belgaied W, Toumi M (2015) Overview of external reference pricing systems in Europe. Journal of Market Access & Health Policy, 3(1):27675, DOI:10.3402/jmahp.v3.27675.
6. Kanavos P, Fontrier AM, Gill J, Efthymiadou O (2019) Does external reference pricing deliver what it promises? Evidence on its impact at national level. European Journal of Health Economics, 21(1):129-151, DOI:10.1007/s10198-019-01116-4.
7. Fontrier AM, Gill J, Kanavos P (2019) International impact of external reference pricing: should national policy-makers care? European Journal of Health Economics, 20(8):1147-1164, DOI:10.1007/s10198-019-01083-w.
8. Puig-Junoy J (2010) Impact of European pharmaceutical price regulation on generic price competition: a review. PharmacoEconomics, 28(8):649-663, DOI:10.2165/11535360-000000000-00000.
9. Kanavos P, Reinhardt U (2003) Reference pricing for drugs: is it compatible with U.S. health care? Health Affairs, 22(3):16-30, DOI:10.1377/hlthaff.22.3.16.
10. Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, Devlin N, Smith PC, Sculpher M (2015) Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. Health Technology Assessment, 19(14):1-503, DOI:10.3310/hta19140.
11. Neumann PJ, Cohen JT, Weinstein MC (2014) Updating cost-effectiveness — the curious resilience of the $50,000-per-QALY threshold. New England Journal of Medicine, 371(9):796-797, DOI:10.1056/NEJMp1405158.
12. Garrison LP, Towse A, Briggs A, de Pouvourville G, Grueger J, Mohr PE, Severens JL, Siviero P, Sleeper M (2013) Performance-based risk-sharing arrangements—good practices for design, implementation, and evaluation: report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force. Value in Health, 16(5):703-719, DOI:10.1016/j.jval.2013.04.011.
13. Ferrario A, Kanavos P (2015) Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. Social Science & Medicine, 124:39-47, DOI:10.1016/j.socscimed.2014.11.003.
14. Lauenroth VD, Stargardt T (2017) Pharmaceutical pricing in Germany: how is value determined within the scope of AMNOG? Value in Health, 20(7):927-935,

DOI:10.1016/j.jval.2017.04.006.

15. Kleining K, Laufenberg J, Thrun P, Ehlert D, Wasem J, Bartol A (2024) Ten years of German benefit assessment: price analysis for drugs with unproven additional benefit. Health Economics, Policy and Law, 19(2):216-233, DOI:10.1017/S1744133123000117.

16. Danzon PM, Furukawa MF (2008) International prices and availability of pharmaceuticals in 2005. Health Affairs, 27(1):221-233, DOI:10.1377/hlthaff.27.1.221.

17. Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R (2009) Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. Lancet, 373(9659):240-249, DOI:10.1016/S0140-6736(08)61762-6.

18. Kanavos P, Vandoros S (2011) Determinants of branded prescription medicine prices in OECD countries. Health Economics, Policy and Law, 6(3):337-367, DOI:10.1017/S1744133111000090.

19. Danzon PM, Wang YR, Wang L (2005) The impact of price regulation on the launch delay of new drugs—evidence from twenty-five major markets in the 1990s. Health Economics, 14(3):269-292, DOI:10.1002/hec.931.

20. Kyle MK (2007) Pharmaceutical price controls and entry strategies. Review of Economics and Statistics, 89(1):88-99, DOI:10.1162/rest.89.1.88.

21. Danzon PM, Towse A (2003) Differential pricing for pharmaceuticals: reconciling access, R&D and patents. International Journal of Health Care Finance and Economics, 3(3):183-205, DOI:10.1023/A:1025384819575.

22. Vogler S, Vitry A, Babar ZUD (2016) Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study. Lancet Oncology, 17(1):39-47, DOI:10.1016/S1470-2045(15)00449-0.