

Background

According to the White House, the United States has less than five percent of the world’s population and yet funds around three quarters of global pharmaceutical profits.² This disparity creates a fundamental equity paradox: reforms targeting US affordability trigger strategic manufacturer responses that risk negatively impacting global access. On May 12, 2025, Executive Order 14297 established Most-Favoured-Nation (MFN) pricing, benchmarking US federal drug prices to the lowest or second-lowest net prices paid in developed nations, adjusted for purchasing power parity (PPP). Unlike the legally-blocked 2020 predecessor, the 2025 policy succeeded through broader scope, political leverage, and voluntary negotiations yielding 16 manufacturer agreements by February 2026.^{1,3}

MFN achieves its domestic goal - reducing US Medicare/Medicaid drug prices - while creating the inverse effect internationally: delayed launches in lower-income OECD markets, compressed R&D investment, and strategic withdrawal from smaller EU markets.^{1,4} Ex-US markets have moved from downstream recipients of global pricing strategy to active inputs into US benchmarking risk - decisions in one market now cascade into US benchmarks and rebate exposure in ways not previously anticipated.^{1,4,5}

Objectives

To evaluate MFN policy architecture and its three-model implementation cascade; to analyse transatlantic health policy trade-offs between US affordability objectives and global access implications; to model price compression effects under MFN versus traditional IRP mechanisms using Symaptics SyMAP[®]; and to identify priority policy levers capable of safeguarding equitable medicine access.

Methods

This mixed-methods policy analysis integrated 1) a structured literature search (February 2026) to highlight policy implications of MFN implementation and 2) quantitative modelling using Symaptics SyMAP[®] (February 2026).¹ The SyMAP model tested nine pricing approaches - four traditional IRP constructs (Highest List to Lowest List), three US MFN methodologies (GENEROUS, GLOBE/GUARD Method I, GLOBE/GUARD Method II), and two alternative benchmarks (Lowest Net, Average Net) – applied across the 19-country GLOBE/GUARD reference basket for five high-revenue products (Opdivo, Dupixent, Keytruda, Mounjaro, Skyrizi).¹

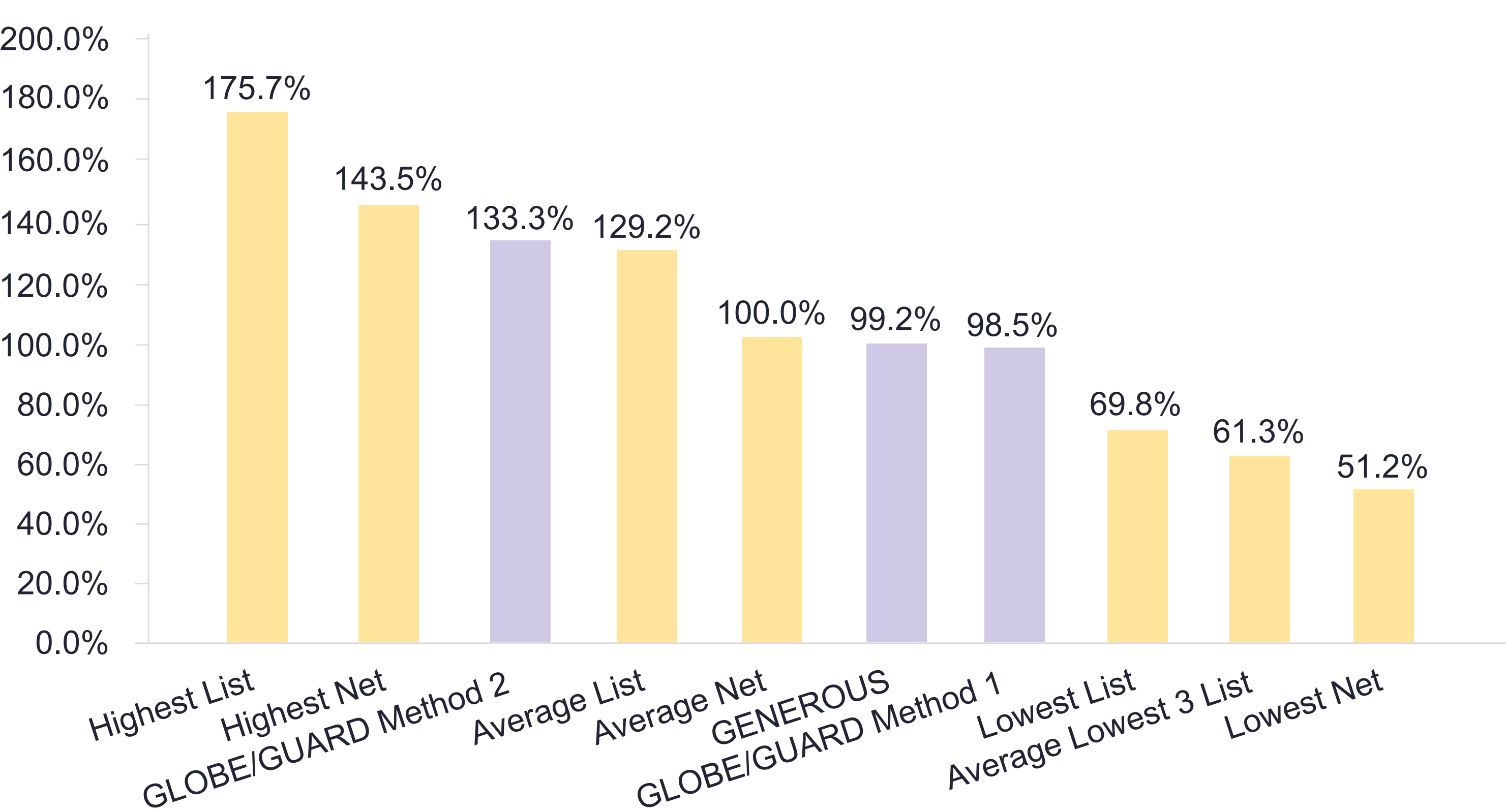
Results

Table 1: Three CMS models operationalising MFN with distinct benchmarking scopes and equity implications

Model	Status	Basket	Methodology	Multiplier	Benchmark
GENEROUS	Live: Jan 2026 ⁶	8 countries	Second-lowest country net price, PPP-adjusted ⁶	-	Voluntary; 5-year
GLOBE	Proposed; Oct 2026 ⁷	19 countries	Method I (default): lowest country price, PPP-adj. / Method II (voluntary): volume-weighted net, PPP-adj. individually. CMS uses greater of the two ^{7,8}	102% (I); 105% (II) ^{7,8}	International benchmark and PPP adjusters static for the 5-year model duration ⁷
GUARD	Proposed; Jan 2027 ⁹	19 countries	Same Method I/II as GLOBE; rebate triggered if Part D net exceeds benchmark ⁹	102% (I); 105% (II) ⁹	Annual recalculation ⁹

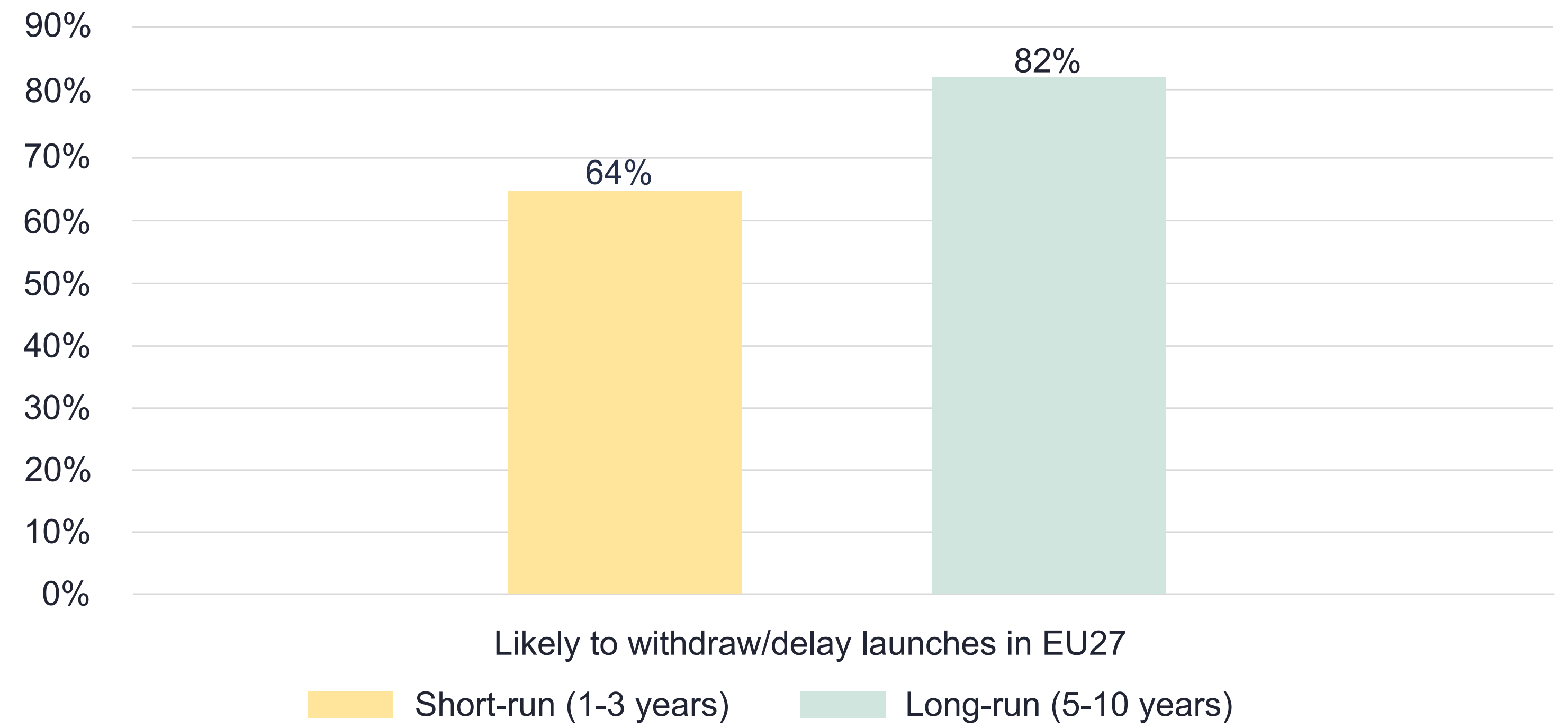
19-Country basket: Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Ireland, Israel, Italy, Japan, Netherlands, Norway, South Korea, Spain, Sweden, Switzerland, UK. Final rules for GLOBE and GUARD models expected Summer 2026.^{7,9}

Figure 1: Comparison of Average Standardised IRP Methods (% of achievable price vs. benchmark) – Symaptics SyMAP[®]



Modelling demonstrates that MFN benchmarks sit in the mid-to-high range of IRP methodologies, well above the most aggressive constructs.¹ Under Method I defaults, benchmarks are near-parity with OECD average net prices (98.5–99.2%); under Method II voluntary submissions - where manufacturers submit volume-weighted net prices PPP-adjusted individually - benchmarks can reach 133.3% of average.¹ CMS applies GDP per capita PPP adjusters to country-level prices under both methods, ranging from 1.000 (floor applied where country GDP exceeds the US: Ireland, Norway, Switzerland) to 1.638 (Japan).^{7,9} High-income, high-volume reference basket markets therefore represent elevated MFN risk concentrations - pricing and launch sequencing decisions in these markets are likely to attract the closest manufacturer scrutiny given their disproportionate potential to influence US rebate exposure under both Method I and Method II.^{1,7,9}

Figure 2. Distribution of launch responses to MFN pricing in both the short and long run - EUCOPE survey results⁴



Manufacturer survey data (Figure 2) confirm the anticipated structural impact on both access and innovation.⁴ In the short run (1–3 years), 64% of manufacturers anticipate withdrawing or delaying launches in selected EU27 countries; in the long run (5–10 years), this rises to 82%.⁴ Critically, 57% anticipate a decrease in R&D expenditure, while 0% expect an increase – indicating that revenue compression under MFN translates directly into reduced investment in innovation.⁴

Table 2: Geographic stratification of MFN effects

Market Category	Key Markets	MFN Exposure	Strategic Trajectory
High-price basket-bilateral protection	UK (Dec 2025 deal) ^{17,18}	Negotiated carve-out; 3-yr tariff exemption	Maintained presence
High-price basket - no protection	Germany, Switzerland, Japan	High-income, high-volume markets → launch sequencing decisions subject to close MFN impact monitoring ^{1,7,9}	Prioritised early launch to anchor benchmarks
Lower-price basket	Spain, Czech Republic, Ireland, Norway	Direct Method I exposure ^{7,9}	Elevated delay pressure

Poland warrants specific attention: at £50,700/QALY - the highest ICER threshold internationally¹⁴ - combined with non-basket status and a 38M population, it presents the strongest structural case for relative manufacturer prioritisation among non-basket EU markets. Its informal IRP referencing basket country prices creates indirect exposure,^{16,17} but the high threshold provides pricing discipline that partially mitigates this. Whether this incentive translates into materially faster access depends on healthcare budget constraints and reimbursement velocity. The Czech Republic is the only Central/Eastern European country in the basket, exposing it to direct launch delay pressure despite its small market size.^{7,9}

UK-US deal: Announced on December 1, 2025, the agreement raises the NICE threshold to £25,000-£35,000/QALY, reduces the VPAG rebate cap to 15%, and secures 0% pharmaceutical tariffs for three years.^{10,17,18} However, the new threshold midpoint (£30,000) represents only 62% of the inflation-adjusted benchmark (£48,300/QALY) and 90% of the international average^{14,19} - it raises the ceiling but does not resolve the access velocity problem that the ABPI identifies as the main structural constraint.¹¹ Whether Germany, France, or Canada pursue analogous agreements will determine if this becomes systematic architecture or remains exceptional.

Discussion

For decades, US and ex-US pricing teams operated in separate silos. That separation has ended.¹ A constrained launch in a single reference basket country can cascade through IRP networks and reappear in US benchmarking under GLOBE or GUARD;^{1,5} and because GLOBE benchmarks lock-in at drug entry for five years,⁷ modest early ex-US price differences translate into materially larger US exposure over time. US MFN policies focus on net pricing while international IRP systems rely largely on list prices¹ - meaning actions taken to manage US net exposure can indirectly pressure ex-US list prices, creating a self-reinforcing compression cycle.

MFN amplifies rather than corrects the global imbalance in health expenditure. The EUCOPE data confirm a structural shift toward “launch in fewer places with more caution,”⁴ and R&D compression further compounds access inequity: the US Chamber of Commerce (2025) projects a potential 75% reduction in clinical trial activity if MFN is fully implemented without offsetting fiscal incentives.¹² European markets are consequently moving from a predictable anchor to an unpredictable risk factor.

Conclusion

MFN is functioning as designed domestically - however, domestic success and global equity are not complementary outcomes under the current architecture; they are in structural tension. Manufacturer survey data confirm systematic planned withdrawal from EU27 markets,⁴ pricing decisions in reference basket countries now feed directly into US benchmarking,^{1,2} and MFN as currently structured redistributes access risk from US patients to ex-US patients while suppressing R&D investment.

Three structural gaps require resolution: equity must be built into MFN as an explicit design parameter; Method II voluntary submission must be actively incentivised to reward early launch; and R&D investment must be supported through offsetting fiscal mechanisms. If left unaddressed, geographic delay in lower-price basket markets, trial reallocation to emerging markets, and selective EU withdrawal become self-reinforcing and increasingly difficult to reverse.

Abbreviations: CE: Cost-Effectiveness; CMS: Centers for Medicare & Medicaid Services; GLOBE: Global Benchmark for Efficient Drug Pricing; GUARD: Guarding U.S. Medicare Against Rising Drug Costs; HTA: Health Technology Assessment; ICER: Incremental Cost-Effectiveness Ratio; IRA: Inflation Reduction Act; IRP: International Reference Pricing; LMIC: Low- and Middle-Income Country; MFN: Most-Favoured-Nation; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-operation and Development; PPP: Purchasing Power Parity; QALY: Quality-Adjusted Life Year; R&D: Research and Development; VPAG: Voluntary Pricing and Access Agreement