Narrative Review Article

Structural Drivers of U.S. Drug Price Disparities: Lessons from Germany and the Role of AI in Reform

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ABSTRACT

The United States leads the world in pharmaceutical innovation, yet it has one of the highest drug prices globally, creating significant barriers to equitable healthcare access. This paper aims to examine the structural mechanisms that drive drug price disparities between the United States and Germany, and to evaluate the potential of artificial intelligence as a complement to pharmaceutical pricing reform. This comparative analysis demonstrates that Germany's centralized pathways, including early benefit assessment, reference pricing, and mandatory price negotiations under the AMNOG framework, constrain launch prices and accelerate post-exclusivity generic competition and price erosion. In contrast, the U.S. system is characterized by fragmented payer negotiation, legal hurdles such as the Medicare Part D non-interference clause, and direct-to-consumer advertising that steers consumers toward higher-priced brand-name drugs. The study evaluates proposals to enable centralized price negotiation and broader biosimilar access and considers emerging AI-enabled efficiencies in drug research and development to reduce drug development costs. Together, these findings suggest a multi-pronged framework for lowering drug costs and increasing access to healthcare while sustaining incentives for innovation.

Keywords: AMNOG; reference pricing; patent evergreening; comparative health policy; generic drugs; biosimilars; Direct-to-consumer; PBMs

INTRODUCTION

While the United States powers global pharmaceutical research and drug development, its pricing institutions translate scientific leadership into unusually high patient costs, leaving millions of Americans unable to afford the medicines their own nation's scientists discovered and brought to market. The disparity in drug pricing raises a striking question: why does a system that excels in pharmaceutical innovation perform so poorly at making these therapies affordable and accessible to patients?

This paper addresses that question through a comparative policy analysis of Germany and the United States. Germany serves as a particularly instructive comparator: as one of the largest and most economically developed nations in the OECD, it shares broadly comparable disease burdens, levels of medical technology, and standards of living with the United States. However, the pricing gap between the two countries is striking: in 2022, manufacturer drug prices in the United States were approximately 2.78 times those in 33 comparable high-income countries, with brand-name originator drugs priced at over four times the international average, and Germany, operating well below that average illustrates precisely the kind of institutional architecture that produces such divergence (1). These price differences have tangible human and public health

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consequences: unlike Germany, where patients face only nominal copayments and no deductibles, U.S. patients are increasingly required to meet high deductibles and pay up to 33 percent coinsurance for their prescriptions (2), creating substantial financial barriers to accessing needed medications (3).

This review examines how institutional design, spanning negotiation frameworks, reference pricing, biosimilar policy, shapes the drug price disparities between U.S. and Germany. Here, "reference pricing" refers to a system in which a drug's reimbursement level is anchored to the average cost of comparable therapies, while "cost-effectiveness" denotes a formal assessment of whether a drug's clinical benefits justify its price relative to existing treatments. "Value-based pricing" encompasses both, linking reimbursement to demonstrated patient benefit rather than manufacturer demand. Further, the paper evaluates the potential of AI-driven development as a complementary mechanism for cost reduction. Specifically, this paper seeks to identify structural and technological reforms that could drive meaningful change in the U.S. pharmaceutical system, making it more equitable, without undermining incentives for innovation.

DATA AND TRENDS

U.S. healthcare spending has risen to levels unmatched by peer nations, creating a fiscal and sustainability crisis. In 2024, healthcare expenditures in the United States reached $5 trillion, representing more than 16 percent of annual GDP and projected to exceed 20 percent of GDP in the coming decade (Figure 1).

Healthcare costs have increased steadily in both absolute terms and as a share of national income, indicating spending growth that consistently outpaces overall economic expansion. While costs span diagnostics. hospital expenses, and other categories, prescription drugs alone accounted for approximately $500 billion in 2024 (Figure 2). These trends motivate

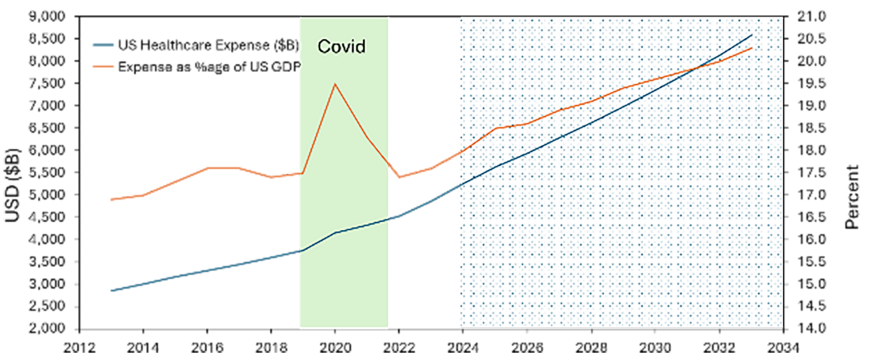

Figure 1. *U.S. National Health Expenditure, 2012–2034. This figure illustrates total U.S. healthcare expenditure in absolute terms (USD billions, left axis) and as a share of gross domestic product (GDP, right axis). Data from 2012 through 2024 reflect actual reported spending; values from 2025 onward represent actuarial projections. The trend demonstrates sustained spending growth that consistently outpaces overall economic expansion. Source: (4).*

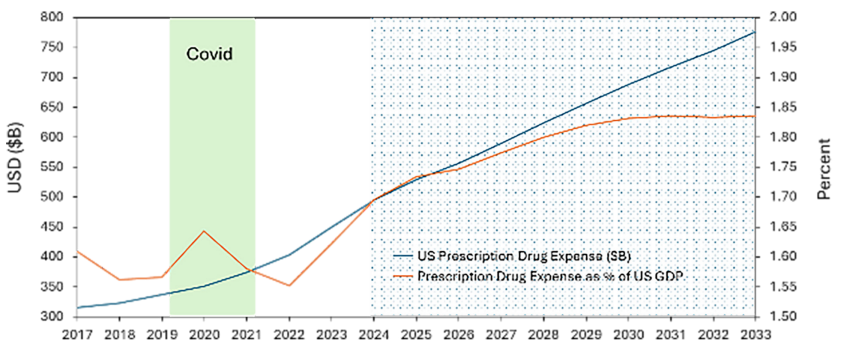

Figure 2. *Trend of U.S. prescription drug expenditure in absolute value (USD billions) and as a percentage of GDP, 2017–2033. Data reflects actual spending through 2024 and CMS actuarial projections thereafter. Source: (4).*

cross-national benchmarking to identify institutional approaches that better regulate pharmaceutical prices. Prices for brand-name originator drugs in the U.S. exceed those of other developed countries by over 400 percent. Even after accounting for rebates, U.S. prices remain approximately 308% higher than the average across 33 OECD nations (3).

Stark pricing differences are observed between the United States and Germany across a wide range of drug classes, underscoring the broader structural issues driving high costs in the U.S. For example, adalimumab (Humira) costs American patients approximately five to seven times more than in Germany. Similarly, semaglutide (Ozempic) and pembrolizumab (Keytruda) is ~3 times more in the US as compared to Germany. Even widely used medications outside of patent protection, such as rivaroxaban (Xarelto) and insulin, show dramatic price disparities, with German patients paying a fraction of U.S. prices (Table 1).

IMPACT OF STRUCTURAL DIFFERENCES IN GERMANY AND US

Unified vs. Fragmented Negotiation

Germany employs a nationally coordinated framework for determining drug prices. Upon market entry, drugs undergo an early benefit assessment under the AMNOG process, administered by the Federal Joint Committee (G-BA) and supported by the Institute for Quality and Efficiency in Healthcare (IQWiG). This evaluation determines whether the drug offers additional therapeutic benefits relative to existing therapies. Following a six-month free-pricing period, statutory health insurers engage in formal price negotiations with the manufacturer to establish a single national reimbursement price that attempts to balance clinical value and budget impact. If an affordable agreement cannot be reached, an independent arbitration board sets the price, which applies uniformly across the statutory insurance system (5, 6). Germany's near-universal statutory coverage, allows insurers to negotiate as a single purchaser, consolidating market power and producing consistent reimbursement rates nationwide.

By contrast, the U.S. pharmaceutical pricing process is highly fragmented and largely unregulated from the point of launch. Manufacturers may introduce drugs at any price, without mandatory evaluation of comparative clinical benefit or cost-effectiveness relative to existing alternatives. Subsequent negotiations occur between individual insurers, pharmaceutical companies, and pharmacy benefit managers (PBMs), producing wide pricing variations and limited transparency that almost always favor manufacturers and intermediaries. Insurance fragmentation diffuses bargaining power across hundreds of payers, weakening their collective ability to discipline prices (7).

Reference Pricing and Cost-Effectiveness

Germany's use of reference pricing and cost-effectiveness assessments plays a central role in keeping drug prices low. Through the G-BA, each drug is evaluated to determine whether it offers additional therapeutic benefit compared to existing treatments. If no added benefit beyond current standard therapies is demonstrated, the drug is reimbursed at the same level as the average cost of comparable treatments — the reference price (1, 2). This mechanism prevents manufacturers from setting excessive launch prices in the absence of meaningful clinical improvements.

Empirical evidence supports the cost-containment effects of Germany's reference pricing framework. When statins were incorporated into the German reference pricing scheme in 2005, manufacturers largely responded by cutting prices to avoid losing market share, and subsequent research documented a sustained downward trend in statin prices attributable to the policy.

Table 1. *Drug Price Gaps: U.S. vs. Germany. Real-World Drug Price Comparisons (2024).*

Drug	U.S. Price	Germany Price	Notes
Humira (Adalimumab)	~$6,000/month	~$800–$1,200/month	Biosimilar entry allowed faster in Germany
Ozempic (Semaglutide)	~$900/month	~$300–$400/month	Strict cost-benefit pricing by G-BA
Keytruda (Pembrolizumab)	~$12,000/treatment	~$4,000–$6,000/treatment	Subject to HTA and price negotiations
Xarelto (Rivaroxaban)	~$500/month	~$50–$100/month	Reimbursed at reference price in Germany
Insulin (Lantus)	~$300–$400/vial	~$40–$60/vial	Bulk pricing and regulation in Germany

More broadly, reference pricing has driven substantial price convergence across multiple therapeutic classes — including proton pump inhibitors — as utilization shifted toward lower-cost but clinically equivalent alternatives, without meaningful changes in overall utilization (8, 9).

In contrast, the United States lacks a standardized mechanism linking reimbursement to demonstrated therapeutic value. Without formal cost-effectiveness benchmarks, insurers and patients have limited leverage to control overpricing of drugs. Direct-to-consumer advertising by U.S. drug companies drives demand for expensive brand-name drugs, often without full consideration of cost-effectiveness or therapeutic alternatives (10). Germany's prohibition of such advertising is yet another structural cost-containment feature. The tangible difference in Germany and the US of a comparable mechanism underscores how structured government evaluation links reimbursement more closely to clinical value rather than manufacturer's pricing power.

Biosimilar and Generic Drug Utilization

Beyond pricing institutions, differences in post-exclusivity competition further widen the pricing gap. Germany's AMNOG framework, which requires manufacturers to demonstrate added benefit and subjects non-innovative drugs to reference pricing, sharply limits opportunities for patent-based exclusivity extensions and accelerates the shift to lower cost alternatives. More broadly, evergreening strategies, where firms file following patents to prolong monopoly protection, can delay generic entry and sustain high prices, a dynamic well documented in the pharmaceutical sector (11). By constraining the effectiveness of such tactics, Germany's regulatory structure facilitates earlier competition and more rapid price erosion than is typically observed in the United States (11, 12)

Legal and regulatory differences in biosimilar and generic drug access further widen U.S.-German price disparities. For example, drugs such as enoxaparin and teriparatide are recognized as biosimilars by European regulators but have not received biosimilar designation in the United States, despite manufacturers submitting complete comparative analytical and clinical data demonstrating high similarity and therapeutic equivalence. Between 2011 and 2020, Germany authorized 52 biosimilars, Switzerland approved 28, and the U.S. granted approval to only 15 during the same period. Although seven adalimumab biosimilars had received U.S. regulatory approval, none entered the market until 2023, with the first launch (Amjevita) occurring on June 30, 2023 (13, 14).

In the U.S., patent thickets — overlapping patents layered around a single drug — significantly hinder timely biosimilar entry, reducing market competition and delaying potential cost savings by up to 17 years (13). In a recent example, AbbVie used patent settlement agreements to extend exclusivity for Rinvoq's biosimilar competitors until at least 2037 (15). The German system facilitates smoother biosimilar adoption because patent protections are more narrowly defined, requiring manufacturers to demonstrate genuine clinically meaningful innovation rather than relying on secondary patents for minor formulation or device changes. This narrower scope limits evergreening, forces competition on therapeutic value, and accelerates biosimilar entry once core patents expire. Regulatory agencies also coordinate with statutory health insurers to encourage substitution of lower-cost biosimilars following exclusivity expiry (16).

These differences carry substantial financial consequences: the median monthly cost for biosimilar treatment in the U.S. was $8,987, compared with $932 in Germany and $1,351 in Switzerland (13). Although generics account for nearly 90% of all U.S. prescriptions, they represent only 17.5% of total drug spending — a figure that highlights the outsized market share of high-priced brand-name drugs (17).

Germany's lower prices stem from three interlocking structural factors: centralized benefit assessment, consolidated bargaining power, and regulatory support for biosimilar substitution. Together, these create conditions under which competition exerts sustained downward pressure on prices while preserving incentives for genuine innovation.

EVALUATION OF ECONOMIC AND TECHNOLOGICAL FACTORS

Having established how Germany's structural features i.e., centralized negotiation, reference pricing, and biosimilar policy, produce systematically lower drug prices, this section examines the economic underpinnings of U.S. market failure, fundamental reasons of high cost and the potential of AI-driven development as an additional lever for cost reduction.

Free Market Failures in U.S. Drug Pricing

In basic economic theory, competitive markets should exert downward pressure on prices. One might therefore expect that the United States' pluralistic

insurance landscape would prove effective at disciplining pharmaceutical manufacturers. In practice, the U.S. system deviates sharply from the conditions required for price discipline. At the launch point, manufacturers can set initial prices with limited evaluation of clinical benefit or cost-effectiveness. Subsequent negotiations within a fragmented insurance framework, mediated by PBMs, dilute collective bargaining power and limit leverage (7).

Patent exclusivity, combined with strategic litigation and delayed generic or biosimilar entry, sustains prices far beyond what a competitive market model would predict (7). In this environment, competition among insurers is stymied by drug-level monopoly protections, resulting in a structural collapse of the price-discipline mechanisms that free markets depend upon.

Impact of Drug Development Costs on Drug Pricing

High drug prices are frequently justified by citing the time, cost and risk of developing new branded drugs. It often requires over 10-15 years of research and clinical testing for a new drug molecule before reaching the market because of extreme scientific complexity, high failure rates, and rigorous regulatory safety standards. Recent estimates indicate that direct spending on a single successful drug averages approximately $172 million, rising to $516 million when failed candidates are included and to nearly $900 million when capital costs are accounted for (18). In oncology, average development costs exceed $1.2 billion. Median annual costs for cancer-related therapies now exceed $142,833, with some treatments approaching or surpassing $800,000 per year (19).

Artificial Intelligence as a Lever for Cost Reduction

Building on the structural reforms discussed above and the high cost of drug development, emerging applications of artificial intelligence offer a complementary pathway to reduce development costs and accelerate innovation. AI can scan millions of potential compounds in a fraction of the time required by conventional methods. Machine learning systems — such as DeepMind's *AlphaFold* for protein-structure prediction — narrow viable drug candidates, reducing years of trial-and-error research that typically inflates development costs. AI-driven models can use large-scale genomic and real-world clinical datasets to predict how drugs will perform across diverse populations, minimizing failed trials and wasted resources (20). One example is the rBio platform developed by the Chan Zuckerberg Initiative, which uses large-scale biological simulations to model drug interactions with human cellular and organ-level systems, identifying potential toxicities or inefficiencies before costly animal testing or clinical trials (21).

The later stages of development, particularly clinical trials, also stand to benefit. Algorithms that match individual patient profiles to trial eligibility criteria improve recruitment by identifying candidates who would otherwise be overlooked. AI enables real-time monitoring of treatment outcomes through wearable-device metrics and digital trial dashboards, allowing researchers to flag early signs of toxicity and adjust protocols more rapidly. These tools reduce dropout rates, improve accuracy, and shorten timelines. Estimates have revealed that AI-enabled trial design can reduce patient dropout by 10–20 percent, while companies such as *Insilico Medicine* and *Exscientia* have demonstrated preclinical development cycles as short as 18–24 months for candidates that traditionally require 4–6 years (22). Collectively, these advances could shorten development timelines from over a decade to a few years and reduce costs by as much as 70 percent.

Importantly, cost reductions generated by AI will not automatically translate into lower prices for patients without accompanying policy intervention. Efficiency gains must be paired with mandatory transparency requirements, post-launch price-justification rules, and penalties for unjustified price increases to ensure that savings are passed on rather than absorbed as profit. Incentives such as tax credits for AI adoption or streamlined regulatory approval for AI-optimized drugs could encourage U.S. companies to integrate these technologies. Together with stronger price negotiation mechanisms and broader biosimilar access, AI-driven innovation can function as a structural complement to pricing reform rather than a substitute for it.

CONCLUSION

This analysis has demonstrated that drug prices in the United States are substantially higher than in comparable high-income countries such as Germany, driven not only by innovation costs but by intentional structural choices: the absence of centralized negotiation, unrestricted launch pricing, weak cost-effectiveness requirements, and permissive direct-to-consumer advertising. Germany's experience shows that a centralized approach, encompassing government-led benefit assessment, unified insurance negotiations, value-based reimbursement, and strict marketing restrictions, produces stronger price

control and broader patient access to clinically necessary medications. By consolidating bargaining power at a national level, Germany prevents manufacturers from setting prices unilaterally and ensures reimbursement rates reflect actual therapeutic value. AI, in turn, offers a mechanism for reducing development inefficiencies that, when paired with policy reform, could lower the underlying cost pressures that are used to justify high launch prices in the current framework.

Several targeted reforms follow from these findings. First, the U.S. should consolidate negotiating authority. For example, by empowering Medicare to negotiate uniform, evidence-based prices on behalf of the entire patient population. This single structural change would directly address the fragmented bargaining power that currently allows manufacturers to maintain high prices across a fractured payer landscape. Second, the U.S. should implement formal reference pricing and cost-effectiveness assessments, requiring proof of clinical value before reimbursement levels are set. Germany's decades-long experience demonstrates that such evaluations lower costs while maintaining access. Third, reforms to promote faster generic and biosimilar entry are critical. Limiting patent evergreening, reforming FDA exclusivity frameworks, streamlining approval pathways, and incentivizing prescribers through cost-sharing differentials would generate stronger post-exclusivity competition and reduce costs without undermining pharmaceutical innovation. Complementary limits on direct-to-consumer advertising would further reduce manufacturer influence over prescribing behavior. Fourth, to address the cost pressures on the development side, the U.S. should create policy incentives — such as tax credits, research subsidies, or expedited approval for AI-optimized drugs — to encourage companies to integrate AI into development pipelines. Taken together, these reforms offer a feasible, evidence-based pathway to reduce pharmaceutical spending while preserving the United States' global leadership in biomedical innovation.

CONFLICT OF INTEREST

The author declares no conflicts of interest related to this work

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