Pharmaceutical Regulation and Incentives for Innovation in an International Perspective

Pierre Dubois*

December 2025†

Abstract

We examine pharmaceutical regulations and incentives for innovation from an international perspective, highlighting the public good nature of healthcare innovation and its cross-border diffusion. We summarize the empirical evidence on how push and pull incentives shape R&D investment, innovation, and global access. We emphasize the role of strategic interdependencies and spillovers, including free-riding in R&D financing, learning-by-doing effects, drug shortages, reference pricing, and parallel trade. We then provide new evidence on the international spillovers of pull incentives on innovation, showing that international cooperation and innovative institutions are necessary to better align national regulations with the global objective of sustaining pharmaceutical innovation.

Keywords: Pharmaceutical Regulation, Innovation, R&D, International Spillovers

JEL codes: L10, L20, I10, I11, I18

*Toulouse School of Economics, pierre.dubois@tse-fr.eu

†I am grateful to Gautam Gowrisankaran, Ilaria Natali, Kevin Outterson, Gosia Majewska, Léa Bignon, Tuba Tunçel, Giulia Tani, Luca Maini, and Darius Lakdawalla for the useful discussions and comments on this chapter. Financial support from the European Research Council and the European Union under ERC grant agreement No. 101141890-EHCI, as well as the ANR under grant No. ANR17-EURE-0010 (Investissements d'Avenir program), is gratefully acknowledged.

1 Introduction

Healthcare depends on complex markets and institutional structures and is shaped by distinct regulatory frameworks and incentive mechanisms that vary significantly across jurisdictions. Each country presents unique features in terms of the organization of health insurance, the delivery of care, and the regulation of pharmaceuticals, which are influenced by the country's epidemiological profile and level of economic development. These national differences directly affect how health systems respond to the challenges and opportunities of pharmaceutical innovation and, in particular, the trade-off between static efficiency and dynamic efficiency. Static efficiency requires maximizing patient welfare given existing knowledge and innovative treatments, thus minimizing the cost of access. Dynamic efficiency must balance spending costs with incentives to innovate. Lakdawalla (2018) provided a thorough review of the broader literature on the economics of the pharmaceutical industry and the different equilibrium mechanisms from the behavior of patients to physicians, all care providers, insurers (private or public) and institutions of regulation.

This paper aims to synthesize the economic literature on pharmaceutical regulation and innovation incentives and provide new insights into the international variation and interdependence of innovation incentives. By comparing different national approaches and analyzing their global spillovers, we seek to inform more coherent and effective pharmaceutical policy design. Finally, we test for these international spillovers and provide new evidence on the global issue of international cooperation in the regulation of pharmaceutical innovation.

Focusing on innovation in healthcare and, in particular, in pharmaceuticals, we explain why understanding the dynamics of drug research and development (R&D) requires an international perspective. Pharmaceutical innovation is a global public good: it is nonexcludable and nonrivalrous. Knowledge created through R&D efforts in one country can benefit populations worldwide, regardless of where the initial investment occurred. This reality generates cross-border spillovers that are beneficial to society but complicate the alignment of national policies with global health objectives.

Healthcare innovation has contributed significantly to improvements in life expectancy and qual-

ity of life over the past century. Advances in pharmaceuticals, such as cardiovascular treatments, antiretrovirals and cancer therapies, have played a central role in reducing mortality and disease burden. However, these benefits come at increasing financial and institutional costs. Scientific breakthroughs, particularly in gene and cell therapy, have increased the potential for transformative health outcomes but have also intensified pressure on the financial sustainability of healthcare systems.

Ensuring continued innovation requires a balance between incentives and access. Mechanisms such as patent protection and market exclusivity offer firms the opportunity to recoup high R&D costs and earn returns on investment (Garthwaite, 2025). However, these mechanisms often lead to high drug prices, raising concerns about affordability, especially in low- and middle-income countries. In response, governments have introduced price regulations, public subsidies, reference pricing, and various demand or supply-side controls. These policies can improve access but may weaken the profitability signals that drive innovation (Lakdawalla et al., 2009; Outterson, 2005a).

The variation in regulatory environments across countries introduces additional complexity. In high-income countries, strong intellectual property (IP) regimes and generous health insurance systems help maintain robust incentives for innovation (Chaudhuri et al., 2006). In contrast, lower-income countries often lack the fiscal or institutional capacity to support similar models. To address this, tools such as differential pricing, voluntary licensing, and international procurement programs have been proposed to expand access while preserving firm incentives. However, concerns about parallel trade and reference pricing often limit their effectiveness, as companies fear losing pricing power in high-income markets.

The incentives driving pharmaceutical innovation are shaped not only by policy but also by strategic firm behavior. Companies respond to international policy differences by adjusting their launch timing, pricing strategies, and supply decisions. For example, when countries adopt reference pricing schemes or allow parallel imports, firms may delay product launches or manipulate list prices to influence benchmarks. Such strategic responses can create inefficiencies in access and investment that spill across borders.

In this context, competition policy also plays a critical role. While intellectual property protections incentivize innovation by granting temporary monopolies, they can also foster anti-competitive practices such as filing follow-on patents to extend exclusivity without meaningful therapeutic benefit (Hemphill and Sampat, 2025) or acquiring future competing products in development (Cunningham et al., 2021). Regulatory frameworks such as the Hatch–Waxman Act in the U.S. and corresponding laws in the EU attempt to balance generic entry with the preservation of innovation incentives (Kyle, 2026). Nevertheless, concerns persist about whether the current system effectively aligns private rewards with public health priorities (Kyle, 2025).

Beyond IP rights, the innovation process is shaped by a wider set of regulations: pricing, reimbursement, advertising, off-label prescribing[1], and even merger control. For instance, advertising regulations differ greatly across countries and can influence consumer awareness, treatment adherence and prescribing behavior. Off-label use and the promotion of such use create further tension between regulatory oversight and clinical flexibility. Understanding these elements is essential for a full picture of the pharmaceutical policy environment.

The global nature of pharmaceutical markets implies that policy decisions in one country can affect R&D incentives globally. For instance, if a major market such as the U.S. imposes aggressive price controls, the reduction in expected profits could deter investment in certain therapeutic areas regardless of policies elsewhere. Conversely, generous pricing in high-income countries can lead to free-riding by others who benefit from innovation without proportionate contribution to its funding (Kyle, 2025). This interdependence, coming from spillovers of different types, including free-riding in R&D financing, learning-by-doing effects, drug shortages, reference pricing, and parallel trade, raises difficult normative and practical questions for policy design.

Empirical research has attempted to quantify how policy interventions influence innovation outcomes. Studies show that larger market size, measured through expected revenues, is positively associated with greater R&D activity. For example, expansions in public insurance coverage, such as Medicare Part D, have been linked to increases in drug development for relevant patient populations

[1]Off-label prescribing refers to the legal practice of prescribing a medication for a use, dosage, route of administration, or patient population that has not been officially approved by regulatory authorities.

(Acemoglu and Linn, 2004; Blume-Kohout and Sood, 2013). However, the high costs of innovation and declining marginal returns pose ongoing challenges, particularly as firms shift toward more specialized and expensive treatments.

Using R&D data on the headquarter location of new drugs registered as well as data on revenues per drugs, we then develop an novel analysis testing for international spillovers on the elasticity of innovation to different regional revenues and provide new evidence on the global issue of international cooperation in the regulation of pharmaceutical innovation. Indeed, innovation elasticities differ by region, and U.S. and EU firms show strong cross-regional spillovers, with U.S. innovation especially tied to U.S. revenue, while Europe is somewhat more responsive to its own market. Firms in the rest of the world mainly react to local revenue, and although U.S. and European innovation respond negatively to revenue of the rest of the world, this is offset by positive responses from locally-based firms.

Recent policy developments underscore the urgency of these issues. The European Commission proposed an overhaul of pharmaceutical regulation in 2025 and the 2022 U.S. Inflation Reduction Act included planned price negotiations under Medicare. Both reflect growing political and economic pressure to reduce drug costs without undermining innovation. These changes highlight the need for a rigorous economic analysis that accounts for international interdependencies and long-term innovation dynamics.

Section 2 discusses why healthcare innovations are public goods and how they diffuse in society with effects on health. Section 3 highlights the different mechanisms financing innovation in pharmaceuticals, including the push and pull incentives provided by different regulations. Section 4 summarizes the many international spillovers of policies, some of which have been emphasized only recently, as well as new evidence on the spillovers across regions due to the main pull incentive provided by expected revenue. Section 5 concludes the study.

2 Health Innovation as a Public Good and its Diffusion

2.1 Health Innovation as a Public Good

Healthcare innovation is a public good. Indeed, once a medical breakthrough, such as a vaccine or drug, is developed, the underlying knowledge can benefit many people without being depleted by individual use (Bryan and Williams, 2021). New knowledge is indeed nonexcludable and non-rivalrous. Although law introduces property and exclusivity rights, these are not permanent. Furthermore, the widespread societal health improvements from innovations such as herd immunity and reduced disease burden create positive externalities that extend beyond direct users.

Moreover, most small-molecule pharmaceuticals, that are low-molecular-weight organic compounds, are knowledge-based innovations with large fixed "invention and validation" costs but relatively low marginal production costs compared with R&D investments. As a consequence, innovations such as pharmaceuticals can diffuse relatively easily because they can be replicated without investing again in the high discovery costs and simply paying for their usually low marginal production costs. As noted below, this has indeed allowed for the diffusion of innovative treatments.

However, medical progress does not always follow this pattern, as biologic drugs and advanced therapies can also involve high production costs. Unlike traditional small-molecule drugs, which are chemically synthesized, biologics are typically large, complex molecules derived from living organisms or their components and are produced using biotechnology techniques such as recombinant DNA technology. Common examples include monoclonal antibodies (used for cancer or autoimmune diseases), vaccines, gene and cell therapies, hormones (such as insulin), and enzyme replacement therapies. Because of their complexity and sensitivity, biologics are usually administered by injection or infusion and require strict handling and storage conditions. They have revolutionized treatment in fields such as oncology, rheumatology, and rare diseases. Innovations with large marginal production costs are thus likely to be less easily disseminated to low-income countries because production costs will make them less affordable even if their invention costs will not be paid by low-income users.

However, many countries are willing to benefit from innovations because they have similar

healthcare needs, exacerbating the need to take an international perspective in the production of such desired global public goods.

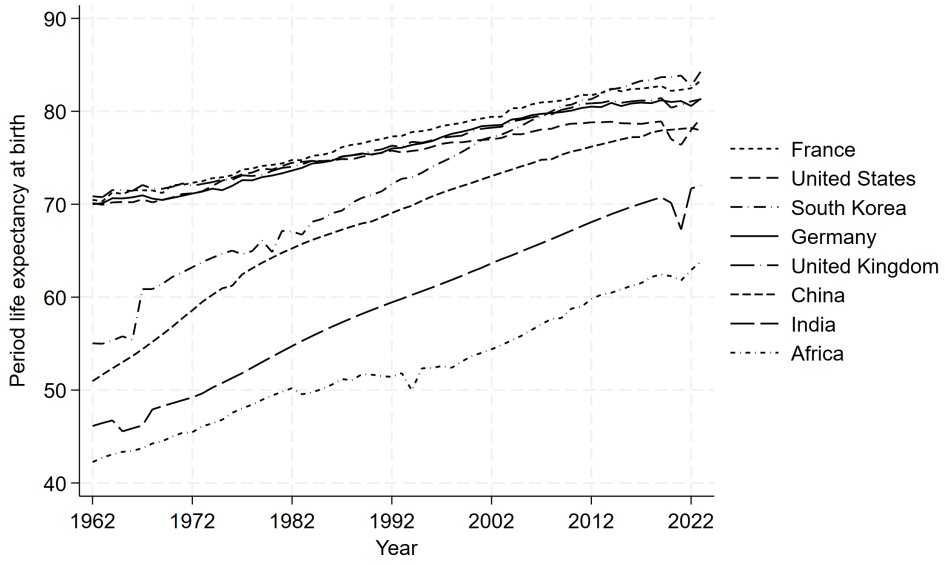
2.2 Evidence of the Effects of Innovations on Health

Historically, innovations in healthcare have generated substantial social welfare gains, with increased life expectancy, better quality of life and reduced mortality.

Innovation expands the healthcare technology frontier and diffuses beyond the regions where it is initially developed and funded. As shown in Figure 1, life expectancy has been rising not only in wealthy countries where innovations are developed but also, with some delay, in lower-income regions. However, determining how much of the lag in life expectancy improvement is due to delays in the diffusion of innovative treatments is challenging, as demographics and health risks vary and evolve across countries, and public health plays a critical role in determining life expectancy. Evidence that pharmaceutical innovation explains some of these improvements exists.

Pharmaceutical innovation has become a cornerstone of global health advancement, delivering transformative treatments across diseases such as cardiovascular diseases, HIV/AIDS, hepatitis C and cancers. Recent breakthroughs such as GLP-1 agonists for obesity further underscore the potential of pharmaceuticals to address emerging global health challenges.

Figure 1: Life Expectancy at Birth Since 1960



Note: The figure was created using data from World in Data.

Lichtenberg (2007) reported that the effects of new prescription drugs between 1990 and 2003 improved longevity and reduced institutional care costs while emphasizing the importance of accounting for other technological advances, such as devices and procedures. Focusing on the U.S., several studies have sought to disentangle the contributions of public health measures, pharmaceuticals, and other forms of medical care to improvements in life expectancy. According to Buxbaum et al. (2020), between 1990 and 2015, life expectancy in the U.S. increased by 3.3 years, with 35% of the gain attributable to pharmaceuticals, 13% to other medical care, and 45% to public health efforts.

Cutler (2008) reported that 20% of the reduction in U.S. cancer mortality between 1990 and 2004 was due to innovative treatments, with the remaining improvements driven by behavioral changes and screening. Dubois and Kyle (2016) further revealed that mortality reductions linked to new drugs vary significantly across cancer types and nations, accounting for 10–30% of mortality reductions. Between 2000 and 2013, on average, one new cancer drug was associated with an 8–9% reduction in mortality from the targeted cancer site.

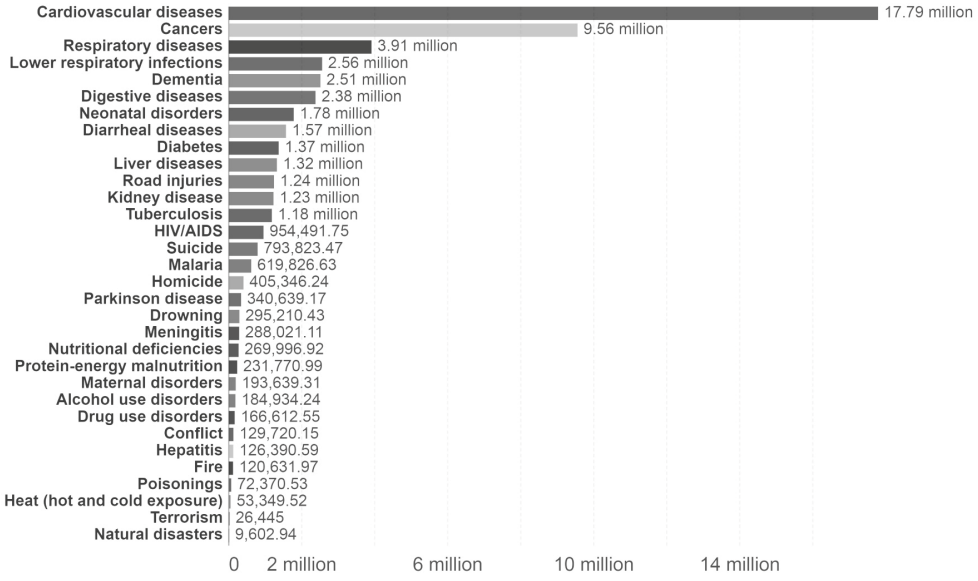
As innovation is highly prevalent among many countries and well above the origin of corresponding investments, improvements in health led by those innovations can be observed in many

countries. In the case of cancer mortality, which is still one of the main causes of death, the impact of innovation can be observed more easily because of mortality data. For example, Lichtenberg (2023) reported that in Spain, pharmaceutical innovation was associated with a 2.77-year increase in the mean age at death from cancer between 1999 and 2016, accounting for 96% of the observed increase. New drug approvals over the 2000–2016 period were linked to a reduction of 333,000 life-years lost before age 75. Lichtenberg (2005a) analyzed the impact of new drug launches on longevity in more than 50 countries and reported that the new drug expenditures associated with an increase in life expectancy were considerably lower than most estimates across many countries of the value of a statistical life-year, justifying the social welfare improvement associated with such expenses.

Despite this progress, as shown in Figure 2, cardiovascular diseases and cancers remain the leading causes of death globally, justifying the social need for further medical progress and innovation.

However, the success of pharmaceutical innovation hinges on sustained investment in research and development, which is incentivized through mechanisms such as intellectual property protections. These policies enable firms to recoup high upfront costs and fund future innovation. As such, striking a balance between accessibility and innovation incentives is crucial to ensuring continued progress in global health outcomes.

Figure 2: Number of Deaths by Cause in 2017



Source: Our World in Data.

2.3 Diffusion Challenges

As a public good, the diffusion of pharmaceutical innovations can be wide and fast, allowing large parts of society to benefit from them. It can occur before or after exclusivity periods of patent protection. After patent protection, generic versions of drugs can be marketed, and competition usually lowers prices, which favors diffusion. However, innovative drug launches are desirable before patent expiration. Cockburn et al. (2016) examined the launch timing of 642 new drugs across 76 countries between 1983 and 2002 and reported that nations with stronger patent protections and fewer price controls experienced significantly faster drug launches. This finding highlights how intellectual property regimes and regulatory environments influence the diffusion of innovation. This finding also shows that despite the public good nature of innovative pharmaceuticals, fast diffusion requires sufficient revenues that only patent rights can secure and that cannot always be provided to generic competing companies depending on the market structure, marginal costs and payer's budgets.

Similarly, Berndt et al. (2011) reported that while the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement harmonized intellectual property protections and accelerated

global drug diffusion, its benefits were globally uneven. Legal compliance alone is insufficient, as broader economic and regulatory barriers must also be addressed.

A key question for the future is whether the diffusion of innovative treatments will remain robust. The low marginal cost of producing standard small-molecule drugs has allowed generics to spread widely, including in developing countries. However, the shift in modern medicine toward personalized treatments, gene and cell therapies, and biologics, which are characterized by significantly higher marginal production costs, may challenge this pattern of diffusion.

3 Financing Health Care Innovation and Regulation

High-cost investments in the R&D of healthcare technologies usually produce public goods whose societal value far exceeds their investment cost but that are difficult to capture without appropriate regulatory frameworks. Even without considering the free-riding problem of financing a public good innovation across multiple payers (countries), market failures may exist for several reasons. There can be a lack of decision to invest in life-saving treatments because it concerns a small population of patients or because of their low ability to pay when the disease strikes predominantly the poorest patients (such as in low-income countries), or when there are externalities such as in the case of vaccines, contagious diseases, and antimicrobial resistance.

To address this fundamental market failure, which leads to underinvestment without public intervention, a combination of push and pull incentives are often put in place to support R&D.

Push incentives include grants and subsidies for basic research, tax credits, and support for biotechnology clusters, all aimed at reducing upfront costs. Pull incentives, in contrast, offer rewards on the basis of the success or adoption of innovations and potential future revenues, relying heavily on the enforcement of intellectual property rights.

There is broad consensus that pull incentives are generally more efficient, although evidence suggests that they work best when complemented by push mechanisms and that push incentives are needed for fundamental research whose benefits are harder to appropriate. Despite their wide use, pull mechanisms carry the persistent risk that regulators or governments may later be tempted

to expropriate innovators or lower the promised rewards once innovation has been obtained. Harmonized intellectual property rights protection has been adopted since the TRIPS agreements to limit this political risk of ex post renegotiation.

While push incentives are unconditional and pull incentives only reward success, Ridley et al. (2025) proposed a new funding mechanism with reimbursement of part of the clinical trial costs in case of failure. In addition to traditional push and pull mechanisms, a mechanism where the funder pays only if the drug fails may be optimal. In a context where there is both moral hazard and adverse selection in development risk, Ridley et al. (2025) showed that this insurance mechanism is optimal when the commercial reward is moderate (not large enough to attract private investment alone but sufficient to incentivize effort) and when clinical trial costs are relatively low. Such a mechanism has not yet been implemented anywhere.

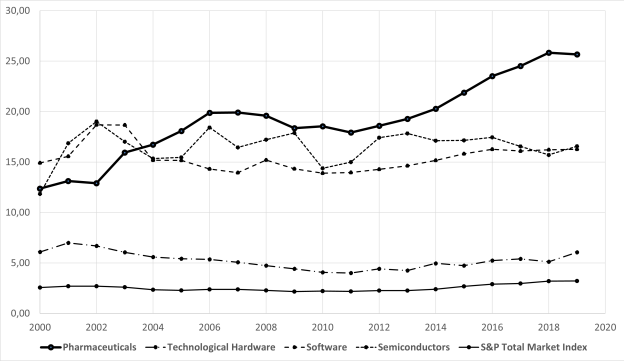
3.1 R&D Investment

Innovation usually requires large investments in R&D, covering everything from fundamental discovery to late-stage clinical trials that test and provide evidence of the efficacy of new treatments.

In the field of health technologies and pharmaceuticals, these investment costs are particularly high because of the high failure rates imposed by strict clinical trial safety and efficacy requirements. As a result, data from publicly traded companies in the U.S. show that compared with other knowledge-based industries, the pharmaceutical sector invests more heavily in R&D, allocating approximately 25% of its revenue to research and development, while other industries such as semiconductors or software invest between 15% and 20%, with other industries investing even less (see Figure 3). However, within the pharmaceutical industry, small and large firms tend to focus on different R&D activities. Small companies devote a larger share of their efforts to discovering and testing new drugs and are often acquired by larger firms. In contrast, large pharmaceutical companies concentrate more on conducting clinical trials and making incremental improvements (line extensions) to existing products. Large companies (with revenues over $1 billion per year) have accounted for more than half of new drug approvals since 2009 and an even larger share of industry revenues, although they have initiated only approximately 20% of the drugs currently in

Phase III trials (Congressional Budget Office, 2021).

Figure 3: Share of Revenue Invested in R&D in Knowledge-based Industries

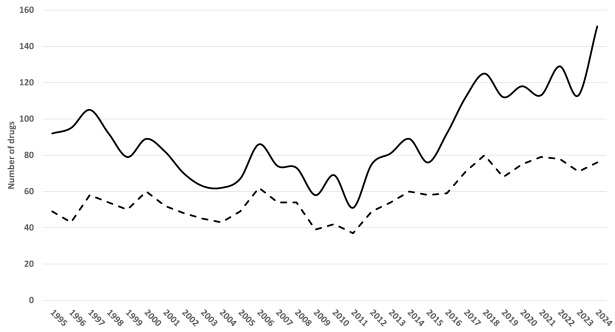


Note: The figure was created using data from Congressional Budget Office (2021) - https://www.cbo.gov/publication/57025#data

Pharmaceutical R&D spending increased by 50% between 2015 and 2019 (Congressional Budget Office, 2021), reaching over $280 billion worldwide by 2024 (Chandra et al., 2024). While the average cost per new drug is also rising, now exceeding $2 billion (DiMasi et al., 2016), the number of new drugs approved per year has recently increased, with approximately 140 new drugs approved annually worldwide (80 in the U.S.) compared to approximately 80 per year (50 in the U.S.) between the mid-1990s and 2010 (see Figure 4). The expected cost of development to obtain approved new drugs is large, as many drug projects fail at different stages of their development and evolution because of insufficient safety or efficacy. Indeed, the failure rates of projects going through preclinical stages (all projects not yet tested in humans) to Phase I (safety, tolerability and dosage determination on a small number of healthy volunteers or patients), Phase II (evaluations of efficacy, safety, and side effects on patients with a target condition) and Phase III (confirmation and comparison with placebo or other standard treatment on a large set of patients to provide data for regulatory approval) are usually high; thus, many projects do not reach drug launch, as reflected by the number of projects per phase in Figure 5 and the success rate in Table 1. On average, only 8.6% of drugs entering Phase I clinical trials are ultimately approved (Dubois and Natali, 2025). While part of this risk is strategic because firms may stop developing projects when competitors seem to be ahead for the same indication (Khmelnitskaya (2023)), most of it is scientific. Around 10% of projects succeeding in their phase III are finally not launched because registration costs

may be prohibitive in cases where revenues finally seem unlikely to cover those costs, for example because other competing projects were launched first. Table 1 shows that the final success rate of development projects is still only 44% on average for projects reaching Phase II, with variation across classes from only 33% for nervous system drugs to 56% for hormone-based drugs.

Figure 4: Newly Registered Drugs per Year



Note: The solid line represents the total number of newly approved drugs worldwide, and the dotted line represents the number of newly approved drugs per year in the U.S. Author's calculation using Citeline Pharmaprojects data.

Table 1: Success Rate by Therapeutic Class and Development Stage

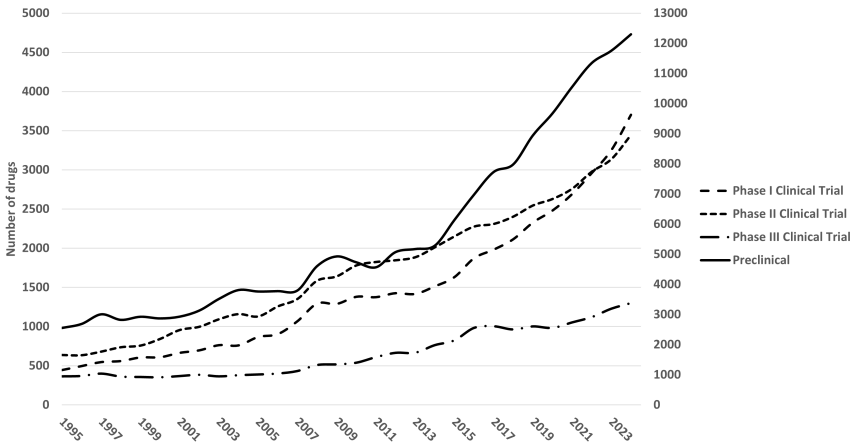
ATC Class		Preclinical	Phase I	Phase II	Phase III	Registered
A	Alimentary tract and metabolism	1.28	7.95	12.12	39.35	88.82
B	Blood and blood-forming organs	3.18	14.06	19.46	46.17	90.93
C	Cardiovascular system	1.19	8.27	14.01	41.63	88.59
D	Dermatologicals	1.52	8.92	11.38	44.20	90.04
G	Genito-urinary system and sex hormones	1.49	7.99	11.49	42.18	89.47
H	Systemic hormonal preparations[2]	2.73	9.08	18.45	56.67	85.67
J	Anti-infectives for systemic use	1.37	10.03	16.96	52.19	87.48
L	Antineoplastic and immunomodulating agents	1.17	6.83	11.61	43.29	89.77
M	Musculoskeletal system	1.01	7.69	13.26	43.24	87.31
N	Nervous system	0.63	5.08	9.04	33.30	88.42
R	Respiratory system	1.34	6.07	8.95	44.88	91.01
S	Sensory organs	1.44	10.96	13.06	41.10	89.45
All		1.53	8.58	13.31	44.02	88.91

Note: The number of drug projects launched out of 100 entering each phase. Author's calculation using Citeline Pharmaprojects data. The statistics are based on the anatomical therapeutic chemical (ATC) class. Registered drugs are approved for market but not yet launched.

Moreover, Figure 5 shows the evolution of active clinical trials by phase over the past 30 years, with a large increase in all phases of trials but even more for preclinical stages since 2015. However, the rate of increase in the number of clinical trials per Phase I, II or III is smaller than that for the

preclinical stages. The more advanced the phases are, the lower the rate of growth, illustrating the growing difficulty and complexity of R&D.

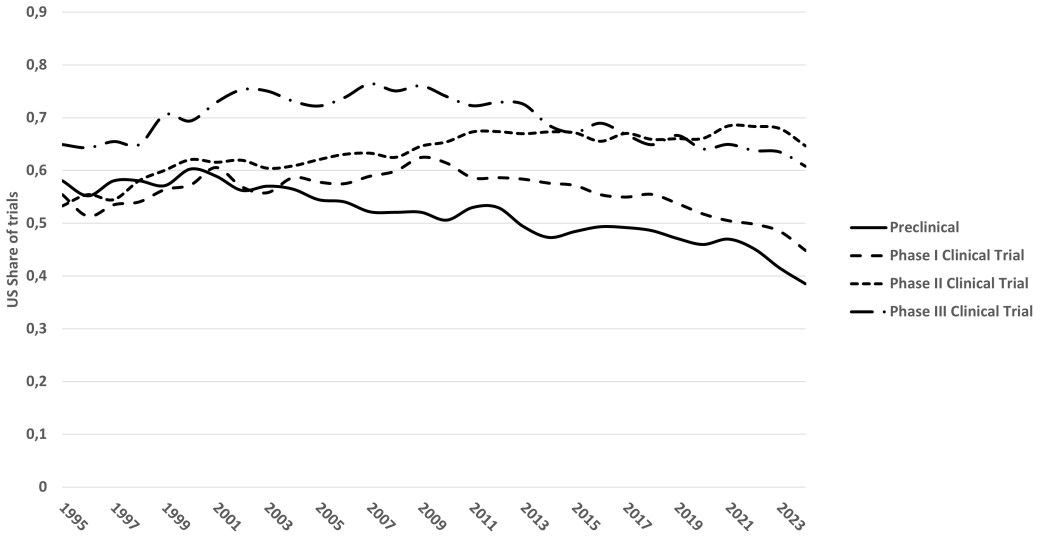
Figure 5: Active Clinical Trials per Phase per Year



Note: The vertical axis for preclinical project counts is on the right, while it is on the left for Phases I, II and III of clinical trials. Author's calculation using Citeline Pharmaprojects data.

While the majority of clinical trials still take place in the U.S., this share has been declining over the past 15 years, except for Phase II trials. Figure 6 shows the share of U.S.-based active clinical trials by phase over the same period. Phase II is a critical stage, focusing on demonstrating real efficacy in patients. As the last relatively lower-cost checkpoint before the expensive Phase III stage (DiMasi et al., 2016), sponsors rely heavily on robust U.S.-based Phase II data, and the U.S. remains key for recruiting well-characterized patient cohorts and accessing top research centers (IQVIA, 2024). Conversely, Phase I trials (focused on safety) are increasingly outsourced outside the U.S. to reduce costs. Countries such as India and China have seen 20–47% annual growth in Phase I trials, whereas U.S. Phase I activity has declined by approximately 6% per year. Moreover, Phase III trials are becoming more global and complex, with companies seeking broader, lower-cost multinational footprints, leading to a decline in the number of U.S.-only Phase III trials. While this may lead to efficiency gains in reducing R&D costs, local positive spillovers of clinical trials may explain location choices in addition to costs. More research on the location choice of clinical trials and their consequences should be conducted to better understand the effects of future policies on these decisions.

Figure 6: Share of U.S. Clinical Trials per Phase per Year



Note: Author's calculation using Citeline Pharmaprojects data.

Types of New Drugs in Development Most new drugs approved focus on treatments for cancer and nervous system disorders (such as Alzheimer's and Parkinson's disease) that are highly prevalent, especially in wealthier countries. Currently, these two therapeutic classes account for more than twice as many clinical trials as the next three areas: vaccines, pain, including arthritis therapies, and dermatological treatments. Moreover, many of the newly approved drugs are specialty drugs or biologics; unlike in the 1990s, when many new drugs were low-cost treatments for large patient populations, they are often high-priced therapies intended for relatively small patient groups. In addition, compared with traditional small-molecule drugs, biologics have lower clinical trial success rates, raising concerns about development costs.

Trends in R&D Costs DiMasi et al. (1991, 2003, 2016) documented a steady evolution in the expected costs of innovation defined as the discounted sum of all costs of a drug project from its start to its possible launch. These expected costs account for the costs of each phase but also for the failure rate of drug projects at any stage. The figures have increased from $230 million in the 80s to $500 million in 2000 to $1.4 billion in 2013. R&D costs have increased by approximately 6.5% per

year over the past 25 years, driving up the cost per drug. This is due to the composition of drugs developed, which are increasingly biologics with lower clinical trial success rates, but also because personalized treatments targeting narrowly defined cancer subtypes make patient recruitment more challenging. In addition, oncology treatments have extended patients' lifespans, requiring longer clinical trials that are costlier to assess outcomes. To mitigate this problem in development, the Food and Drug Administration Safety and Innovation Act of 2012 reinforced the possibility of using surrogate endpoints in clinical trials. This framework allows the approval of drugs for serious or life-threatening conditions on the basis of surrogate or intermediate clinical endpoints (lab markers, imaging results, or biological signs) that are reasonably likely to predict clinical benefits. However, if not confirmed by postmarketing trials, approval may be withdrawn. This policy has helped reduce the tendency to underinvest in longer, clinically valuable treatments (Budish et al., 2015).

3.2 Push Incentives

The positive externalities of innovation imply that R&D efforts are often not commensurate with the social benefits they generate (Bryan and Williams, 2021; Dix and Lensman, 2025). Market failures are therefore highly likely without regulatory intervention. Moreover, capital market imperfections can restrict financing for high-risk, long-horizon biomedical R&D, particularly for rare diseases or in low- and middle-income countries (Lo et al., 2013). These problems are compounded by regulatory uncertainty and misaligned incentives in health systems. Uncertainty and risk in R&D, especially owing to unobservable effort and probabilistic success, further complicate private investment.

To stimulate innovation in the pharmaceutical sector, governments and international organizations often rely on push incentives, which are mechanisms that lower the upfront costs of research and development. These measures help address the early-stage funding gap that private investors are often unwilling to fill because of high uncertainty and long development timelines (Kyle, 2022). The economic rationale behind push incentives is that scientific ideas are difficult for private firms to fully appropriate. Once an idea is created, others can often imitate or build upon it, reducing the innovator's incentive to invest. Public support helps address this market failure, ensuring that

society still benefits from valuable innovations.

A key form of push incentive is the direct financing of fundamental research in cutting-edge areas such as biology, medicine, artificial intelligence for drug discovery, messenger RNA technologies, and gene-editing tools. This fundamental research lays the scientific groundwork from which future therapies and technologies can emerge. Grants are ideal for uncertain research, but effective grant programs require thoughtful design to define the scope, apply peer review, share risks, and focus on translation (Azoulay and Li, 2022).

Subsidies and tax incentives also play major roles. Public agencies such as the U.S. Biomedical Advanced Research and Development Authority (BARDA), philanthropic foundations, and international organizations offer targeted subsidies, especially for clinical trials and high-risk R&D projects. Additionally, tax deductions for R&D expenses reduce firms' financial burdens, encouraging investment in innovative but uncertain areas.

However, push incentives have several limitations. Because funding is provided upfront and not tied to outcomes, there is a risk of moral hazard in the efficient use of resources. This independence from performance can lower the return on public investment compared with outcome-based mechanisms.

Most empirical evidence on the effects of medical research funding comes from the U.S. National Institute of Health (NIH), which accounts for approximately half of global public spending in this area (Moses et al., 2015). Estimates of the return on public funding are strikingly high; for example, Cockburn and Henderson (2000) reported a lower bound of 30%. Olson and Merrill (2011) summarized studies that generally support the hypothesis that push policies increase pharmaceutical innovation.

Recent studies using improved causal inference methods continue to show large NIH effects, with an additional $10 million in funding generating approximately 2.3 more patents on average, without evidence of crowding out and instead showing complementarity, as NIH funding increases total private-sector innovation (Azoulay et al., 2019). Toole (2007) reported that public basic research funded by the NIH significantly stimulates private R&D, with a long-term elasticity of

expenses of 1.69, showing that public research plays a complementary role in pharmaceutical innovation. Stevens et al. (2011) examined the direct contributions of public-sector research institutions (PSRIs), such as universities, research hospitals, nonprofit research centers, and federal laboratories, to the discovery and development of drugs, biologics, and vaccines. They reported that many FDA-approved products have been discovered in part by PSRIs since the biotechnology revolution and the Bayh–Dole Act of 1980, which allowed U.S. universities to retain the patent rights of inventions funded by federal money.

Finally, unlike pull incentives, push policies require immediate budget outlays and acceptance of failure, which can be politically difficult for governments to support. Moreover, administering research grants demands specialized expertise in evaluation and monitoring.

3.3 Pull Incentives

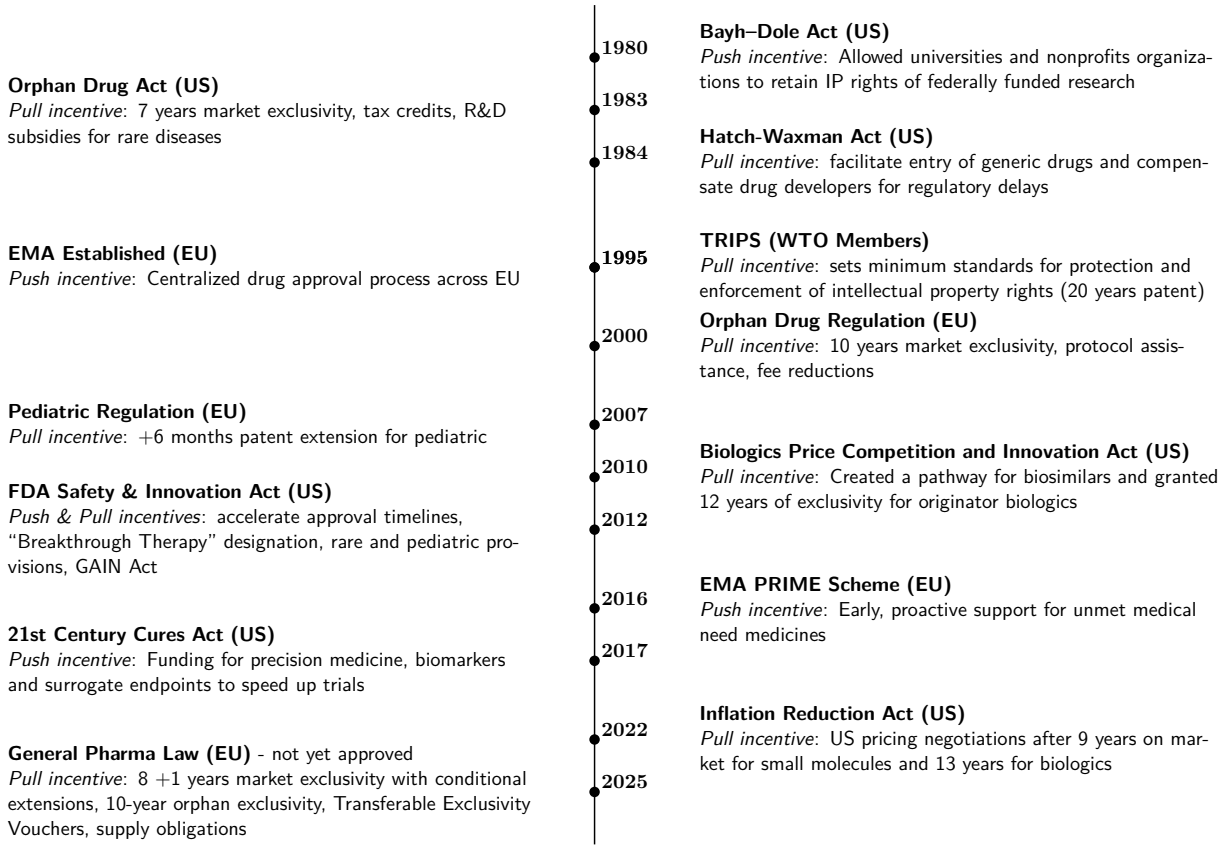
For-profit research attracts R&D. Pull incentives can be more efficient than push incentives because they reward performance rather than inputs, but their effectiveness depends on global factors such as future disease prevalence, demographic trends, regulatory frameworks, intellectual property protection laws, and competition or antitrust policies.

3.3.1 Intellectual Property and Patent Protection

Figure 7 summarizes the main regulatory events since the 1980s, including the recent reforms of the Inflation Reduction Act in the U.S. and the new general pharmaceutical legislation under discussion but not yet implemented in the EU.

In the U.S., a key milestone in intellectual property rights protection was the Orphan Drug Act of 1983, which granted seven years of market exclusivity for designated orphan uses. This was followed by the Hatch–Waxman Act of 1984, which provided up to five additional years of patent protection to compensate for time lost during clinical trials and introduced provisions to support the entry of generic drugs. At the global level, the TRIPS Agreement was signed in 1994 as part of the Uruguay Round of World Trade Organization (WTO) negotiations and came into effect in January 1995. The TRIPS Agreement established minimum standards for various forms

Figure 7: Main Pharmaceutical Regulatory Events



of IP protection, including pharmaceutical patents, requiring WTO member states to provide at least 20 years of patent protection. This marked a significant shift in global IP enforcement, particularly by extending patent protections to pharmaceuticals in developing countries, although transitional provisions and flexibilities were included. Despite the fact that noncooperative national policies lead to an underprovision of global innovation incentives (Grossman and Lai, 2004), the harmonization of intellectual property rights laws (as in TRIPS) is neither necessary nor sufficient for global efficiency.

In 2006, the European Medicines Agency (EMA) pioneered biosimilar guidelines with a centralized procedure, providing a single application, a single scientific assessment, and authorization valid across all EU/EEA countries. In 2010, the U.S. Biologics Price Competition and Innovation Act introduced a regulatory pathway for the approval of biosimilars as interchangeable products. However, as noted by Scott Morton et al. (2018), postexclusivity innovation diffusion is influenced not

only by the expiration of regulatory exclusivity but also by other regulations affecting procurement practices, interchangeability standards, and clinician incentives to prescribe biosimilars.

While TRIPS harmonized patent duration globally, it did not harmonize drug prices. Kyle and Qian (2014) and Cockburn et al. (2016) reported that strong patent protection accelerates drug launches worldwide. Although TRIPS mandated a minimum level of patent protection, member countries retained the right to impose price controls and issue compulsory licenses under certain conditions. Both Kyle and Qian (2014) and Cockburn et al. (2016) found that patents have substantial effects on drug access: without a patent, product launch is unlikely; with a patent, drugs are priced higher but also achieve greater sales. Kyle and Qian (2014) further showed that the price premium for patented drugs is smaller in lower-income countries and in regions with a higher disease burden and that the price discrimination of patented drugs has increased across countries after TRIPS harmonized patent duration.

On the other hand, Williams (2013) documented the negative impact of IP protection on follow-on innovation. Specifically, genes covered by Celera's IP portfolio saw 20–30% less scientific research and product development during the protection period than publicly sequenced genes did. Notably, this effect disappeared once the IP restrictions were lifted. However, Sampat and Williams (2019) showed that, on average, patent protection on human genes does not appear to have hindered follow-on innovation.

Moreover, generic entry significantly reduces treatment costs, as shown in Berndt and Dubois (2016), where the design of a country's generic substitution system plays a crucial role in determining cost savings. Across most countries, average daily treatment costs decrease sharply following patent expiry, with the greatest declines observed in markets where pharmacists, rather than physicians, directly substitute.

While patent protection is intended to grant profitable monopoly rights to innovative firms and incentivize R&D, the strength and magnitude of the relationship between potential revenue and innovation remain empirical questions.

Hemphill and Sampat (2025) explored how the patent system both enables and distorts phar-

maceutical innovation. Patents are critical for incentivizing investment in new drugs by granting temporary market exclusivity. However, firms often seek to extend exclusivity through follow-on patents on minor changes, such as new formulations or delivery methods. These practices can delay generic competition and keep drug prices high without delivering corresponding health benefits.

The key question is whether current policies strike the right balance between encouraging innovation and ensuring affordability and access. Budish et al. (2025) showed that heterogeneity in property rights enforceability distorts investment, leading to inadequate incentives.

3.3.2 Alternatives to Patents: Prizes, Advanced Market Commitments, and Transferable Exclusivity Extensions

Uniform intellectual property rights protections, such as fixed-length patents, are unlikely to address market failures effectively for all diseases because the market value of fixed-length exclusivity protection will not allow the full social value of the product to be captured.

Some areas experience significantly greater market failures and a more severe underprovision of socially valuable innovations. For instance, when there is no corresponding demand from payers that reflects the social value of a particular innovation, the standard patent-based monopoly rights mechanism fails to generate sufficient returns, providing too little incentive to justify the initial investment. Lichtenberg (2005b) showed the absence of a link between pharmaceutical innovation and the burden of disease in low-income countries, in contrast to the positive association found in higher-income countries.

Thus, when diseases affect small populations (orphan diseases), patients with a limited ability to pay (in less developed countries), or involve significant externalities (antibiotics, vaccines, and contagious diseases), there is likely to be a substantial gap between the social and private value of innovation with standard IP protection.

For example, the U.S. Orphan Drug Act of 1983 and, later, the EU Orphan Medicinal Products Regulation granted seven and ten years of guaranteed market exclusivity, respectively, along with other advantages such as reduced marketing approval fees, to address this market failure. The U.S. Orphan Drug Act clearly spurred innovation targeting orphan diseases (affecting fewer than 200,000

people in the U.S.), although Gamba et al. (2021) showed through calibrations that the adopted incentives may have widened the gap between more and less rare diseases classified as orphan.

In the case of antibiotics, OECD (2023) evaluated different policies against antimicrobial resistance and report benefits far exceeding their costs. Alternative policies are therefore needed when the societal benefits of innovation substantially outweigh the required investment costs. To address this problem, the U.S. GAIN Act of 2012 provided greater incentives for developing new antibiotic treatments against priority pathogens by extending market exclusivity by five years beyond existing protections. Majewska (2023) showed that these incentives had a positive effect on clinical trial success rates because of increased investment but only for projects using known technologies and that, ultimately, the policy failed to generate many truly innovative antibiotics.

Advanced Market Commitments An alternative to patents consists of cash prizes or advanced market commitments (Kremer, 1998; Kremer and Glennerster, 2004; Kremer and Williams, 2010; Kremer et al., 2020). A sufficiently large cash prize can provide enough revenue for the innovator to cover investment costs without relying on the global demand capacity generated through intellectual property rights. However, this approach does not solve the problem of securing a willingness to pay for the innovation reward and does not address the free-riding problem in funding the prize. Indeed, the financing of a public good benefiting several decision-makers usually suffers from underinvestment because each player is willing to free-ride on others' investments. In areas such as antibiotics, it has proved difficult to find institutions willing to finance such rewards (Outterson, 2005b, 2006). For others, such as the funding of the pneumococcal vaccine by the Vaccine Alliance (GAVI) in 2009 or the COVAX COVID-19 Vaccine advanced market commitment for low- and middle-income countries in 2020, the approach was successful.

Moisson et al. (2023) showed that equilibrium free-riding significantly hinders the financing of socially valuable innovation rewards, even when the benefits are shared globally. Free-riding in the international financing of public goods is thus a key problem for innovation funding in health.

Transferable Exclusivity Extensions Another mechanism involves rewarding inventors with transferable exclusivity extensions (TEE) or "vouchers". In this system, the inventor receives a right to extend an existing drug exclusivity that can be sold to another entity holding an existing intellectual property right.

A TEE voucher mechanism designed to support antimicrobial innovation is currently under consideration in Europe as part of the European Commission's draft reform of pharmaceutical legislation (European Commission, Directorate-General for Health and Food Safety, 2024). In the U.S., an early draft of the bipartisan 2018 U.S. REVAMP Act (Re-Valuing Anti-Microbial Products Act, HR6294) proposed transferable exclusivity vouchers for drugs designated priority antimicrobial products (Boyer et al., 2022) but that were ultimately not applied. Rome and Kesselheim (2020) estimate the financial costs of a one-year transferable exclusivity extension for fast-track drugs (on U.S. data from 2007–2019) without accounting for user welfare.

In addition, "priority review vouchers", inspired by Ridley et al. (2006), have been used in the U.S. since 2007. Although they differ economically from TEEs, they share the underlying concept of rewarding innovation through tradable vouchers. Accelerated approval is clearly a way to improve pull incentives. Chandra et al. (2024) showed that the FDA's Breakthrough Therapy Designation program, which was started in 2012, aimed at speeding up the regulatory review of a new product to market and accelerating access without impairing the quality and safety of approved drugs, showing that regulators' evaluation capacity can be worth investing in to improve access. The tradability of priority review can increase these pull incentives in markets with reduced profitability. Gans and Ridley (2013) provided a detailed analysis of a voucher value depending on tradability and on the characteristics of medical R&D.

While exclusivity extensions impose additional costs on payers by prolonging the market power of the rights holder, Dubois et al. (2022) compared the welfare costs of vouchers with those of cash transfers for equivalent innovation rewards. Vouchers can be more favorable to public finances than cash prizes because the social welfare loss due to the increase in market power can be smaller than the corresponding increase in profits for the rights holder. This occurs when postexclusivity

markets are imperfect and when generics still earn quasirents. A TEE voucher system is preferable to a cash reward at the national level because it transfers rents from generic producers to the innovator. However, the international free-riding problem depends on whether a supranational authority can enforce exclusivity extensions across countries. In the European context, the European Commission can effectively implement exclusivity extensions. The challenge lies in aligning incentives for adopting such a system versus financing an equivalent cash prize collectively among European countries. Cash transfers require funding from general revenues, incurring a shadow cost of taxation that must be distributed according to an agreed-upon sharing rule.

Outterson and McDonnell (2016) and Boyer et al. (2022) emphasized that the length of the exclusivity extension must be calibrated to the investment needs of antibiotic development and that safeguards such as those requiring sufficient advance notice to generic manufacturers before the extension is exercised should be established to prevent market abuse. However, such a mechanism may solve the market failure observed in some markets.

3.3.3 Market Size, Elasticities of Innovation and Empirical Evidence

The literature on market size and innovation has examined how expected future profits influence innovation outcomes, thereby assessing the strength of pull incentives in driving innovation. Since for-profit pharmaceutical firms undertake innovation projects they expect to be profitable, these decisions are shaped by expected market size, which depends on multiple factors. Demographic, socioeconomic, and epidemiological trends determine how many people suffer from a given condition and their ability to pay for treatment. Industry-specific factors such as competition and firm strategies also affect profitability. More market entrants intensify price competition, meaning that larger market sizes are required to recover innovation costs, particularly when alternative substitute molecules exist for patent holders or when there is generic competition after exclusivity expires.

Regulatory policies also influence the market size by affecting generic entry, the scope of approved indications, off-label substitution possibilities (Tunçel, 2025), off-label promotion (Dubois et al., 2024), drug advertising (Lakdawalla et al., 2013; Dave, 2013; Dubois and Pakes, 2025), treatment initiation and drug adherence (Alpert et al., 2023) and reimbursement rules (Dubois and

Lasio, 2018), all of which shape margins and expected profits. Price regulation by governments can reduce prices for pharmaceutical treatments; however, the short-run effect on innovation may be limited because R&D expenditures are already sunk, and such regulation lowers incentives to invest in discovering new treatments. Given that the U.S. accounts for more than 40% of global pharmaceutical revenue, U.S. drug pricing policies are likely to have an outsized effect on global market size, R&D investment, and innovation rates (Garthwaite and Starc, 2023; Ho and Pakes, 2025).

Filson (2012) developed a dynamic structural model to explore the role of market size in innovation through calibrated policy counterfactuals. While such modeling is valuable, most of the literature focuses on estimating the elasticity of innovation with respect to market size, which is a key parameter for assessing the societal cost of price regulation.

Acemoglu and Linn (2004) estimated this elasticity, measured by the number of new chemical entities launched for a given disease class relative to expected market size, proxied by U.S. spending on treatments for diseases in that class. Using demographic shifts interacted with age-specific expenditure shares as an instrument for U.S. revenue, they found an elasticity of 1. Finkelstein (2004) reported a larger value of 2.75 for vaccines. Differences between drugs and vaccines in the innovation process and approval costs likely explain this gap. Acemoglu et al. (2006) also showed that the introduction of Medicare increased pharmaceutical innovation. While the U.S. is the largest pharmaceutical market, with approximately 40% global revenue, revenue from other countries is substantial and growing and can also stimulate innovation.

Dubois et al. (2015) estimated the elasticity of the number of new chemical entities to global expected market size (measured across the 14 largest pharmaceutical markets for 1997–2007) and found a much lower value of 0.23 on average. Their market size measure was instrumented using exogenous changes in GDP, mortality, and demographics to avoid reverse causality. They also estimated that approximately $2.5 billion in additional revenue is required to bring one new drug to market, which is consistent with DiMasi et al. (2016)'s accounting estimates of total development costs. Dubois and Natali (2025) reestimated the elasticity for a more recent and extended time

period and found an average elasticity of 0.30 between the number of new molecules reaching the market in a class and the expected lifetime branded drug revenue of that class. Natural experiments, such as policy interventions, also provide valuable evidence. Studies such as that by Finkelstein (2004); Blume-Kohout and Sood (2013) have examined single-country legislative changes and confirmed the link between market size and innovation.

Some studies have focused on intermediate outcomes, such as the number of new clinical trials, and found significant positive elasticities (Qian, 2007; Yin, 2008, 2009; Kyle and McGahan, 2012; Blume-Kohout and Sood, 2013; Dubois and Natali, 2025). For instance, Blume-Kohout and Sood (2013) showed that the introduction of Medicare Part D substantially expanded demand for prescription drugs among elderly and disabled Americans, generating both current and future positive shocks to market size and a strong increase in clinical trials. Kyle and McGahan (2012) estimated the elasticity of new clinical trials to market size across countries, accounting for the presence of patent protection. Innovation has also been proxied by the number of relevant scientific articles on disease regimens (Lichtenberg, 2005b) or by measures correlated with potential market size, such as Disability-Adjusted Life Years (DALYs) and mortality (Civan and Maloney, 2009). For example, Lichtenberg (2005b) found that a 1% increase in the number of cancer patients leads to a 0.58% increase in chemotherapy regimens, whereas Giaccotto et al. (2005) reported similar findings. Civan and Maloney (2009) observed that a 1% increase in expected U.S. price increases the number of drugs in development by 0.5%, and Lichtenberg (2005b) estimate that a 1% increase in DALYs leads to a 1.3% increase in global drug launches.

The elasticity of innovation to market size reflects the combined effect of the number of clinical trials and trial success rates, which may not be constant as the volume of trials changes. Elasticities for clinical trials can therefore be larger or smaller than those for new drug launches. While one might argue that final innovation outcomes such as the number of new drugs approved are most relevant for patient welfare, clinical trials themselves generate important positive spillovers, as discussed in McKibbin and Weinberg (2021).

Measuring welfare impacts, however, can be complex, as the approval of a new treatment does

not necessarily guarantee access, and welfare effects depend on pricing, substitution effects on existing treatments, potential externalities (e.g., in chronic disease management), and the organization of health insurance systems, which vary significantly across countries. Furthermore, while market size reflects both the potential patient population and payers' willingness to pay, social welfare benefits and innovator profits are not always aligned.

4 International Dimension and Strategic Interdependence

We have shown that innovation in healthcare is a global public good and that different push and pull incentives are used to correct for underinvestment. However, despite the harmonization of patent lengths since the TRIPS agreements, many national policies amended the exclusivity periods either in the U.S. (Hemphill and Sampat, 2025) or in Europe (Kyle, 2026) without clear international coordination. Moreover, marketing authorizations, pricing, reimbursement and push policies remain mostly national and generate international spillovers. Let us now examine the different types of policy spillovers affecting the financing of innovation. These spillovers then affect strategic interactions across countries.

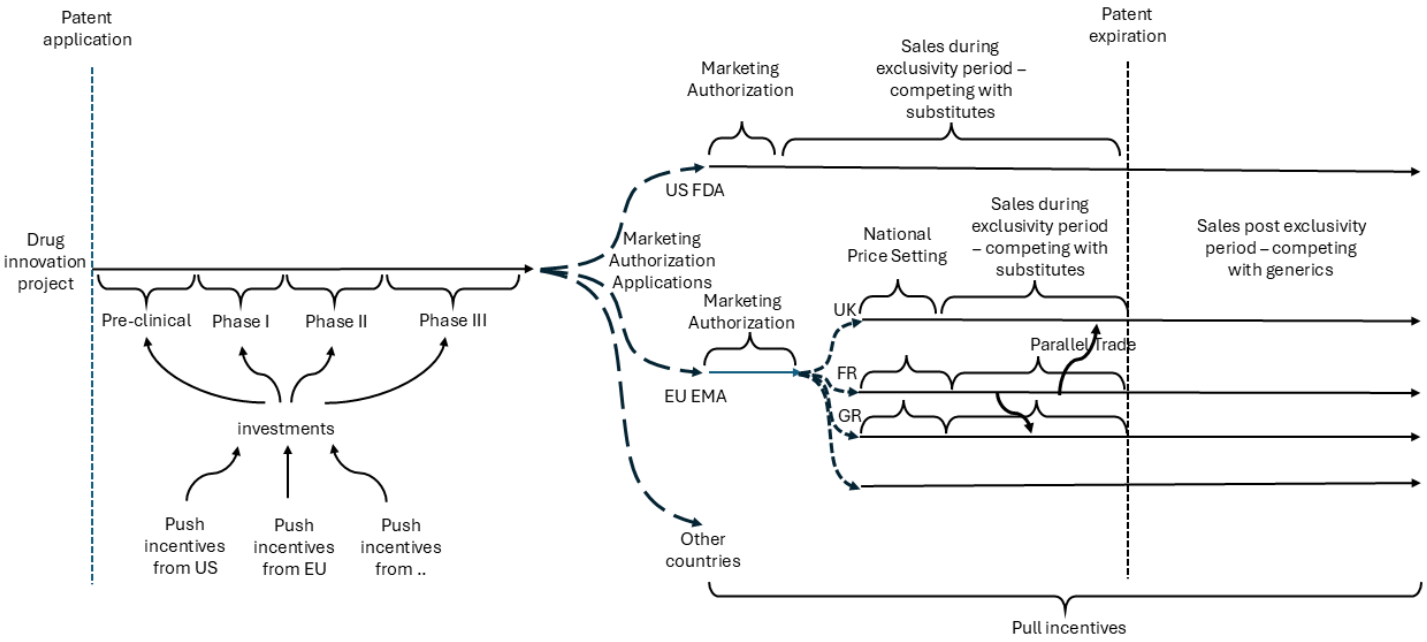
These spillovers of national policies have been recently underscored and were first modeled and discussed by Egan and Philipson (2013). More recently, Frech et al. (2023) reported that while U.S. contributions to global pharmaceutical innovation through high drug prices and quasirents are greater than their share of GDP, other countries make meaningful contributions compared to their GDP, but global R&D investment remains suboptimal with respect to independent national policies.

Kyle (2025) discussed how government policies in one country can create spillover effects for others, particularly in terms of price levels for branded drugs. As market size affects innovation incentives, small markets often free-ride on U.S. incentives because price increases in small markets are unlikely to significantly change global R&D; however, if the U.S. changes its pricing policies, it can meaningfully affect worldwide innovation because of its market size (Ho and Pakes, 2025).

We now examine the different types of spillover effects given the general timeline of a drug

development project interaction with various funders and payers from early development to later launch and pricing as shown in Figure 8.

Figure 8: Timeline of a Pharmaceutical Project from Patenting to Launch in Several Countries



4.1 Local Spillovers

Using the 1980 Bayh–Dole Act as a natural experiment that gave universities intellectual property rights over federally funded inventions, Hausman (2022) showed how U.S. universities contribute to local economic growth by fostering industry agglomeration through knowledge spillovers, beyond spurring patenting, licensing, and university–industry collaborations.

There are also specific spillovers that may be more local but important. McKibbin and Weinberg (2021) examined whether biomedical research reduces local mortality through knowledge spillovers. Using data linking publications, NIH grant funding, and U.S. administrative death records across 38 disease categories from 1999 to 2017, the authors estimated that a 1% increase in local disease-related publications reduces local mortality from that disease by 0.35%. The findings suggest that local populations benefit from proximity to research through earlier adoption of medical advances,

underscoring the public health value of disseminating biomedical knowledge beyond commercial applications.

If taken into account by policymakers, these types of positive local spillovers that favor R&D do not spread across borders and should mitigate the willingness to free ride over others' effort for innovation.

4.2 Government Subsidy International Spillovers

As initially emphasized by Egan and Philipson (2013), free riding in financing innovations may appear both in push and pull incentives. Kyle et al. (2017) showed that international free riding occurs in push incentives because R&D subsidies are crowded out across countries. They found that a 10% increase in U.S. government funding for research against a disease leads to a 2–3% reduction in funding for that disease by other governments.

As world profits drive innovation, pharmaceutical revenue is affected by the healthcare policies of other countries; thus, the short-run–long-run trade-off between static efficiency and dynamic efficiency is affected by other countries' policies. As such, the level of reimbursements determining the size of pull incentives can be "strategic substitutes" and generate "free riding". Egan and Philipson (2013) examined how medical innovation, which is influenced by global market incentives, links domestic healthcare systems internationally. The returns to medical innovation are global, creating positive and normative interdependencies between countries' healthcare reimbursement policies. Using pharmaceutical reimbursement data from 26 developed countries from 1996 to 2010, they found that countries lower their reimbursements in response to others' higher spending, confirming strategic substitution. They predicted that the development of emerging markets such as the BRICS (Brazil, Russia, India, China, and South Africa), despite increasing market size, may lead to more free riding. Similarly, Pertile et al. (2018) empirically analyzed the prices of 70 cancer drugs across 25 OECD countries (2007–2017), showing that countries with large market shares tend to lower prices when others raise their own, relying on external incentives to sustain innovation, while smaller countries aim for the lowest possible access price.

As a consequence, they challenge the hypothesis that larger markets automatically lead to more

innovation.

4.3 The Causes of International Spillovers

We now turn to the main sources of international spillovers that have been identified in the literature. Some causes are related to supply-side externalities in the costs of production capacity or in marginal costs because of learning-by-doing in production or drug shortages. Then, we turn to spillovers created by regulatory rules concerning the pricing and trade of drugs.

4.3.1 Learning-by-Doing

Pharmaceutical innovation once focused on small-molecule drugs that are inexpensive to manufacture after development, yielding low, stable marginal costs and limited economies of scale. With little benefit from shared facilities or expertise, demand in one country had minimal impact on global costs.

However, over time, the industry shifted to more complex treatments, such as biologic drugs made from living cells. These elaborate therapies are becoming increasingly prevalent in developed countries, representing 40 and 45% of pharmaceutical sales in the EU and the U.S., respectively, in 2023 (IQVIA, 2025). They are also more expensive than traditional molecules because of their complex manufacturing process. The latter makes production experience valuable, leaving scope for returns to experience to decrease future marginal costs. This is particularly important for healthcare systems, as biologics can have substantial marginal costs and thus require high prices. Indeed, Bignon and Dubois (2025) showed that learning-by-doing in biologic drug production reduces marginal costs, generating a new type of international spillover. Moreover, unlike small molecules, biologic drugs cannot have a generic version and biosimilar drugs are defined as bioequivalent, not identical. As a result, the imperfect substitutability of biologics and biosimilars after exclusivity can limit biologic diffusion.

Using data on the production process of biologic drugs and consumption for the top 25 pharmaceutical markets, Bignon and Dubois (2025) estimated a model of drug demand and pricing to recover marginal cost estimates from Bertrand–Nash pricing conditions in Sweden, a small market

where pricing does not affect future costs. The marginal cost estimates were used to recover the primitives of the production model and the learning-by-doing in the production of tumor necrosis factor (TNF)-α inhibitors, which are biologic agents used for several chronic inflammatory diseases. The results suggested that the marginal costs decrease by approximately 10% each time experience doubles, with a 46% decrease over three years. Concentrated production generates spillovers across countries; thus, demand improves future global efficiency. Biosimilar penetration at the country level shapes these gains, which increase with market size. While learning-by-doing suggests that delaying biosimilar entry results in lower marginal costs upon entry, these delays slow efficiency gains in other countries.

A study by Scott Morton et al. (2018) found that in Europe, the extent of price reductions and biosimilar market penetration after entry depends heavily on market size and institutional frameworks. In contrast, Feng et al. (2024) observed that in the U.S., branded biologic manufacturers engage in more aggressive price competition with biosimilars than branded small-molecule drugmakers do with generics, primarily because of fewer competitors, imperfect therapeutic equivalence, and persistent perceptions of quality differences. While this limited competition slows biosimilar adoption, it simultaneously increases the financial incentives for biologic innovation by prolonging the commercial dominance of originator products.

4.3.2 Drug Shortages

Another type of externality across countries arises when one considers drug availability and the capacity of supply chains of production to fulfill international demand.

Drug shortages are indeed a widely documented problem worldwide. Acosta et al. (2019) cited studies describing the occurrence of drug shortages in many regions (Europe and Latin America), as well as country-specific analyses covering the U.S., France, Spain, Ireland, Brazil, Venezuela, Australia, and a few Asian countries. Most of the studies focused on the U.S. showed a sharp increase in the number of shortages observed in the early 2010s.

Although generic drugs typically operate in a competitive environment in the U.S., Conti and Wosińska (2025) reported that the price rigidity of contracts between drug buyers (group purchas-

ing organizations and hospitals) and suppliers prevents short-term price increases in response to shortages. As a result, when demand surges or supply falters, higher prices that could incentivize increased production or entry do not materialize. As the market often fails to reward reliability and quality, manufacturers have little incentive to invest in resilient infrastructure and maintain a consistent supply. The lack of spare capacity limits the ability to perform regular maintenance, increasing the risk of disruptions. Without backup production lines, any disruption can translate into a shortage. Galdin (2025) showed that contracts valuing reliability can significantly improve supply resilience and consumer welfare.

Using Medicare reduced prices reimbursed to the practitioners administering the drugs in 2003 and 2005, Yurukoglu et al. (2017) reported that sterile injectable products had longer shortages for drugs that were more exposed to this reduction. However, quantitative evidence on drug shortages is very limited. Although measures of shortage reports are very useful, they are likely noisy with possible misreporting and do not measure the magnitude of shortages.

While shortages occur in the U.S. because of the inability to reward reliance, they also occur in countries with nationally regulated prices where demand and supply cannot equalize at an equilibrium price that would vary according to shocks in demand coming from epidemiological variations and shocks on supply coming from transitory changes in production capacity.

Dubois et al. (2023) presented a quantitative framework to detect and evaluate drug shortages using sales data and shows evidence of international spillovers. The results first showed that lower prices in France increase the probability and amount of shortages but that prices in the UK of the same drugs also increase the amount of shortages when they occur. This means that when supply capacity is insufficient compared with demand, competition across countries for available units implies that higher prices elsewhere increase the shortage of drugs in a given place, creating negative spillovers across countries. However, Dubois et al. (2023) also showed that higher prices in other countries can lower the frequency of shortages in France, thus resulting in a positive spillover, which is likely to occur through manufacturing capacity. Indeed, capacity building depends on world-level expected demand and price regulation. Higher prices exert a positive spillover over

other countries as they increase capacity choices by manufacturers.

Drug shortage risk may thus exert an economic force that goes against the free riding incentives to lower the prices of drugs as much as possible given the prices in other countries.

4.3.3 International Reference Pricing

While spillovers across countries can result from national policies without explicit rules linking different markets, some regulations explicitly refer to other countries and create important international spillovers.

Indeed, while international price differences across countries can be explained by differences in income, disease prevalence and willingness to pay for different treatments, they are regularly used as a justification by regulatory institutions to develop external reference pricing where the reimbursement price of a drug depends on the regulated prices of other countries. Reference pricing is widely used in Europe (Maini and Pammolli, 2023), even sometimes when price regulation already sets price caps (Dubois and Lasio, 2018).

While external reference pricing likely reduces international price differences when drugs are present, it has been shown that it causes companies to delay or avoid launching products in low-price countries (Danzon and Chao, 2000; Danzon et al., 2005; Kyle, 2007). This is because a low price in one country might lower the allowed price in richer referencing countries, inducing referenced countries to suffer reduced or delayed access to new treatments because of decisions made elsewhere. Maini and Pammolli (2023) reported that external reference pricing delays drug entry up to 1 year in low-price EU markets.

External reference pricing is mostly used within the European Economic Area but has since been considered by the U.S. As the U.S. spends twice as much as European countries per inhabitant in pharmaceuticals, mostly because of substantially higher prices, price controls have been increasingly called for with H.R.3 Lower Drug Costs Now Act of 2019 and H.R. 5376 Build Better Back Act of 2021, which was not implemented until the Inflation Reduction Act of 2022 and a U.S. presidential executive order in 2025. Salter (2015) discussed international reference pricing for the U.S. as a way to reduce pharmaceutical spending, using experience in other developed countries as evidence

of price reduction effects. Weiss et al. (2016) noted that the U.S. government may reduce the differential pricing that exists with respect to other markets by using an international reference pricing policy (although price controls may be achieved only following rereferencing, as the U.S. is typically a first-launch market). Such a policy was implemented on a small scale in the 1990s when the U.S. Federal Government included a most favored customer clause on pharmaceutical product prices supplied to Medicaid. While firms had to provide Medicaid at their lowest price, Scott-Morton (1997) showed that the rule resulted in higher prices of generics to some non-Medicaid consumers of pharmaceuticals. Feng et al. (2023) used variation induced by the Affordable Care Act in 2010 to show that the effects of the Medicaid best-price clause extended to the net price of branded drugs for non-Medicaid payers.

The advantage of an international reference pricing regulation implemented by the U.S. is that it only requires ex post control that U.S. prices should not be higher than prices for the same drugs in referenced countries without paying for a health technology assessment. However, equilibrium effects do not guarantee that U.S. prices would decrease to the level of European prices ex ante. Grennan (2013), Gowrisankaran et al. (2015), and Dubois et al. (2022) estimated a bargaining model to simulate a counterfactual international reference pricing policy in which the U.S. prevents higher prices than those in the reference countries. Using Canada as a reference country, they showed that firms internalizing the restrictions would manage to negotiate higher prices in the reference country while slightly lowering U.S. prices. The magnitude of these effects depends on the specific structure of the policy. In particular, the effect is stronger when the U.S. refers to a group average of several countries. In comparison, direct bargaining on the prices of drugs, which is the policy adopted in the Inflation Reduction Act, is more likely to reduce prices than international reference pricing is. Instead of relying on drug value evaluation in reference countries, direct bargaining depends on the need of the U.S. population when negotiating. Dubois et al. (2022) showed the negative pricing externalities of international reference pricing on the reference countries, whereas additional negative impacts on delayed entry in the referenced countries also occurred (Danzon and Chao, 2000; Danzon et al., 2005; Maini and Pammolli, 2023).

4.3.4 Parallel Trade

Parallel trade typically generates the flow of drugs from lower-price countries to higher-price countries. Reference pricing (or most favored nation clauses) takes effect when a country with an initially higher price refers to a country with an initially lower price. Both policies reduce international price differences across countries, but they lead to different equilibria.

With reference pricing, prices may converge to a single level once the policy is applied. The new equilibrium price lies between the initial high and low prices and depends on the demand structure and market size of each country, as shown in Dubois et al. (2022). In contrast, parallel trade does not necessarily equalize prices across countries because of trade costs and potential differences in consumer preferences for parallel-imported goods. Furthermore, the negotiation between a pharmaceutical company and a buyer may be influenced by the mere threat of parallel imports, even if such imports are never actually used in equilibrium.

Within the European Economic Area, pharmaceutical products are subject to the free movement of goods, and cross-border trade is fully legal. However, drug pricing remains under national jurisdiction, and price differences between countries are substantial. Thus, parallel trade within the European Economic Area generates cross-country externalities that tend to reduce international price discrimination, thereby exerting economic effects across national markets. As a result, parallel trade has increased, now exceeding 6 billion euros per year (European Federation of Pharmaceutical Industries and Associations, 2023), with highly heterogeneous national market shares in Europe, reaching up to 25% in some countries. To limit the scope for parallel trade, as firms may want to price discriminate across countries of different incomes and willingness to pay for drugs, they employ nonprice strategies such as product differentiation and packaging modifications to hinder arbitrage opportunities (Kyle, 2011).

The overall effect of parallel trade on innovation remains ambiguous. Grossman and Lai (2008) examined the relationships among parallel imports, price controls, and innovation incentives in pharmaceuticals, challenging the conventional view that parallel imports undermine intellectual property rights and reduce incentives for innovation. They showed that when parallel imports

are permitted, governments tend to adjust domestic price controls upward to ensure continued supply. This reduces the South's capacity to "free-ride" on the North's innovation efforts, thereby enhancing overall global incentives for innovation. The actual magnitude of this effect, however, is an empirical question.

Despite the significant price dispersion across EU countries, Ganslandt and Maskus (2004) reported that parallel imports may have reduced drug prices by 12–19% for segments subject to parallel import entry in Sweden. Moreover, there are large differences in the penetration of parallel imports across otherwise similar countries, driven by variations in the regulation of pharmacy margins (Kanavos et al., 2004; Kanavos and Vandoros, 2010).

Using a structural model of demand estimated with data from the German market for oral antidiabetic drugs, Duso et al. (2014) suggested that parallel imports reduced the prices of on-patent drugs by 11%, although the impact on consumer surplus was modest. The effect of parallel imports on drug prices, however, depends critically on country-specific regulations affecting pharmacies. Examining parallel imports in Norway, Dubois and Sæthre (2020) investigated how cross-country price differences create incentives for retail pharmacies to sell parallel imports. Modeling wholesale price negotiations between pharmacy chains and either manufacturers or parallel traders using a Nash–bargaining framework, they showed that parallel imports enable pharmacy chains to capture a large share of industry profits at the expense of manufacturers. In the atorvastatin market (marketed by Pfizer under the brand name Lipitor during 2004–2007), the manufacturer's profits would have doubled (+104%) in the absence of parallel trade. This profit shift toward retailers is driven by the increased competition between the manufacturer and parallel importer, resulting from the ability of pharmacy chains to shift sales in response to profitability differences, and by the improved bargaining position provided by the option to sell parallel-imported drugs. Dubois and Sæthre (2020) also reported that banning parallel trade in Norway would significantly increase manufacturer profits in Norway while slightly reducing profits in the source country (France). This suggests that the existence of parallel trade results in higher prices and profits in France than would otherwise be the case.

Finally, Dubois and Sæthre (2020) found that reducing the reimbursement price in Norway decreases the manufacturer's overall profits by less than the reduction in health insurance expenditures, with the loss falling mainly on parallel traders and retailers. This would allow both manufacturers and taxpayers to be better off if a lump-sum transfer compensated for the lower price. These results suggest that if parallel trade cannot be banned, implementing two-part tariff pricing could harmonize prices across countries to limit parallel trade while enabling wealthier countries to contribute to financing innovation through ex post lump-sum transfers to secure access.

4.4 Correlation of Pharmaceutical Revenues per Unit across Countries and Launch Orders

To further examine the potential spillover effects of pharmaceutical pricing across countries, we first analyze how the average manufacturer's wholesale revenue per unit for newly launched molecules in each country compares across markets. In particular, we investigate how these revenues correlate with the sequence of launches between the U.S. and other countries. Of course, these average wholesale revenues per unit depend on regulated prices in some countries or multiple buyer prices in others, depending on insurers, hospitals, or pharmacy systems.

We examine the average wholesale revenue per unit of each molecule launched between 2001 and 2021 using IQVIA data from 21 European countries (Austria, Belgium, Bulgaria, the Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Norway, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland, Turkey, and the UK) and 22 countries across the rest of the world (Argentina, Australia, Belarus, Brazil, Canada, China, Ecuador, Egypt, Indonesia, Japan, Korea, Malaysia, Mexico, Morocco, New Zealand, Pakistan, Philippines, Russia, Singapore, South Africa, Ukraine, and Venezuela). For each molecule entering sometime between 2002 and 2021, we observe the first year of launch in each country and compute the mean wholesale revenue per standard unit of that molecule in each country during the first year of launch. For simplicity, we compute the average wholesale revenue per unit for Europe and the rest of the world, as well as that for the U.S., across all launched molecules with a common first year of launch worldwide and then compute the ratio of these means between the U.S. and Europe or between the U.S. and the

rest of the world. Hence, for each molecule i launched in each country n at time t_{in}, we observe the mean wholesale revenue per unit in that country during their year of launch w_{int} and compute the mean for each region z over molecules in a class c whose first launch was at t as follows:

$$w_{z,ct} = \frac{\sum_{\{i \in c | \min_n\{t_{in}\}=t, n \in z\}} w_{int}}{\sum_{\{i \in c | \min_n\{t_{in}\}=t, n \in z\}}}$$

Table 2: Descriptive Statistics of the Wholesale Revenue per Unit Ratios by Order of Launch

Launch order:	US-W-EU			US-EU-W			W-US-EU			W-EU-US		
ATC class	N	$\omega_{US,EU}$	$\omega_{US,W}$	N	$\omega_{US,EU}$	$\omega_{US,W}$	N	$\omega_{US,EU}$	$\omega_{US,W}$	N	$\omega_{US,EU}$	$\omega_{US,W}$
A	43	3.244	2.088	29	2.604	3.809	77	3.851	0.781	22	0.636	0.546
B	18	2.618	1.968	12	1.526	2.312	42	1.918	0.840	11	0.835	0.818
C	20	3.249	1.888	32	2.356	3.907	31	2.163	0.914	6	0.559	
G	12	4.291	3.253	16	2.216	3.341	3	1.037	0.995	0		
H	0			8	1.108	1.200	6	3.202	0.000	5	0.658	0.432
J	26	2.301	1.777	29	1.353	3.244	53	1.701	0.896	24	0.772	0.942
L	33	1.799	1.541	44	1.474	2.005	186	2.180	0.823	46	0.808	0.646
M	20	2.575	1.934	13	1.941	2.077	8	4.126	0.000	6	0.606	
N	29	2.960	2.040	28	1.852	2.503	57	3.166	0.901	20	0.737	0.204
R	19	3.762	2.868	20	3.731	4.085	30	4.074	0.000	4	0.573	
S	17	6.552	4.611	14	4.201	7.415	10	2.364	0.933	7	0.652	0.012

Note: Author's calculation. For each possible launch order (we never observe launches that occur in the EU first during that time period), N indicates the number of molecules launched in the class during that time period (2003–2021), $\omega_{US,EU}$ represents the mean ratio of the wholesale revenue per unit in the first year of launch between the U.S. and EU, and $\omega_{US,W}$ represents the mean ratio of the wholesale revenue per unit in the first year of launch between the U.S. and the rest of the world.

Table 2 shows for each ATC class c, the mean ratio across regions z and z' of the wholesale revenue per unit for the molecules launched in various orders of regions ($\omega_{z,z'} = \frac{1}{T}\sum_t \frac{w_{z,ct}}{w_{z',ct}}$). It shows how the relative per unit revenue between the U.S., the EU, and the rest of the world vary depending on whether a molecule is first introduced in the U.S., in Western markets, or elsewhere. Compared with both the EU and the rest of the world, the U.S. consistently maintains higher per unit revenue ratios, although the magnitude of the gap varies with the launch sequence. The table also shows that the prices in the U.S. are on average higher than those in the EU or in the rest of the world when the new molecule is first launched in the U.S., but that is not true when the molecule is launched first in the rest of the world or when it is launched after launching in the EU (in second or third position). However, we can also see that the large majority of launches occur

first in the U.S. and that they are rarely launched in Europe before they are launched in the U.S. While it is difficult to determine whether there is any causal impact of the order of launches on prices or of prices on the order of launches, this table clearly shows that the order of launches is correlated with the price levels across countries, which hints at the strategic decisions of companies.

4.5 Market Size and Innovation from an International Perspective

We have shown that many externalities exist across countries in their policy decisions on pharmaceutical revenues, which are therefore likely to affect innovation. In section 3.3.3, we summarize the effect of pull incentives on innovation and, in particular, the estimates of the elasticity of innovation with respect to market size.

Instead of estimating the elasticity of innovation with respect to global market size as in Dubois et al. (2015), we estimate these elasticities to regional market sizes, that is, the way expected regional pharmaceutical revenues affect innovation outcomes. Moreover, we measure innovation using the number of drugs registered by certain health authorities (usually the FDA, the EMA, or both) rather than the number of launched drugs, which can be subject to strategic delays. Looking at the distribution across regions of expected revenue, we can measure how regulatory externalities across countries affect the rate of innovation. Specifically, we study how the expected revenues for drugs in a given therapeutic area influence the number of newly registered drugs in that class. Our dependent variable is the logarithm of the number of newly registered compounds worldwide in a given therapeutic class c and year t, N_{ct}, or N_{zct} the number of those registered by a company whose headquarters is in region $z \in \{U.S., EU, W\}$, where US stands for the United States, EU stands for the European Economic Area (including the UK), and W stands for the rest of the world.

We aim to estimate the following equation:

$$\log N_{ct} = \beta \log R_{ct} + \alpha_c + \gamma_t + \epsilon_{ct} \tag{1}$$

where $R_{ct} \equiv \sum_{j \in c} \sum_{\tau=0}^{T} \delta^{\tau} \pi_{\tau} R_{jt+\tau}$ denotes the expected global revenue for all drugs in class c and year t, $\pi_{\tau,c}$ is the estimated probability of launch in τ years after registration at t, $R_{jt+\tau}$ is the total predicted global revenue of drug j during year $t+\tau$ and δ is the yearly discount factor (using

$\delta = 0.90$).

We also estimate the following equation:

$$\log N_{zct} = \sum_{z \in \{US,EU,W\}} \beta_z \log R_{zct} + \alpha_c + \gamma_t + \epsilon_{ct} \tag{2}$$

where R_{zct} is the expected year t global revenue for all drugs in class c whose headquarters is in region z, as well as the same equation when the dependent variable is the total $\log N_{ct}$.

The estimated probability of reaching the market in τ years, $\pi_{\tau,c}$, for a registered drug at t is allowed to vary by ATC class, but the variation is in fact minimal, and on average, the probability of being launched in one year is 0.60, while that in 2 years is 0.20, that in 3 years is 0.096, and that in 4 years is 0.047, and only 3% take more than 5 years to be launched. Therapeutic class α_c and year fixed effects γ_t control for time-invariant factors common to molecules within the same therapeutic class and for time-varying shocks affecting all drugs uniformly. Details on the data are provided in Appendix A.2.

We estimate equations (1) and (2) via OLS and two-stage least squares. We use instrumental variables to leverage variations in expected future revenue that arise from predicted demographic shifts, future disease-specific mortality rates, or existing competition within a pharmaceutical class. These factors are correlated with expected revenues but not with shocks to innovation, creating more future spending since they are not known at the time we predict future revenue.

Table 3 shows the elasticity of the number of registered drugs within a pharmaceutical class and the expected revenues for drugs registered in that class. The OLS results in Column (1) show an elasticity of 0.44. Column (2) shows the 2SLS results when the number of competing branded and generic products existing in the current class at the time of registration of the innovation is used as an instrumental variable. Column (3) shows the 2SLS results when the demographic and mortality predictions of the diseases targeted by the drugs in the pharmaceutical class considered are used as instrumental variables. Compared with the OLS results, both show greater elasticity, with elasticities between 0.57 and 0.67.

Table 3 shows the elasticity of innovation with respect to the revenue from the three defined

Table 3: Elasticity of Newly Registered Drugs to the Expected Revenue in the Class

Dependent variable	OLS	2SLS	2SLS	OLS	2SLS	2SLS
$\log N_{ct}$	(1)	(2)	(3)	(4)	(5)	(6)
β	0.447***	0.686***	0.588***			
	(0.019)	(0.081)	(0.038)			
β_{US}				0.283***	0.424*	0.609***
				(0.036)	(0.182)	(0.080)
β_{EU}				0.202***	0.147*	0.029
				(0.025)	(0.072)	(0.046)
β_{W}				-0.047	0.107	-0.120
				(0.037)	(0.175)	(0.077)
Year Fixed Effects	Yes	Yes	Yes	Yes	Yes	Yes
ATC Class Fixed Effects	Yes	Yes	Yes	Yes	Yes	Yes
$\chi^2(df)$		0 (1)	.1 (1)		.2869 (1)	11.89 (11)
p-val		.9269	.8051		.3499	.0703
N	964	785	964	964	785	964

Note: Robust standard errors in parenthesis. * for $p < .05$, ** for $p < .01$, and *** for $p < .001$. Overidentifying restrictions test shown when 2SLS is used.

regions (U.S., Europe, and the rest of the world). The OLS results in Column (4) show a positive elasticity with respect to the revenue in the U.S. and Europe but not with respect to that in the rest of the world. The 2SLS estimates in Columns (5) and (6) show that the elasticity is positive and significant with respect to the U.S. and Europe revenue but is stronger with respect to the U.S. revenue alone.

Table 4 shows the elasticities of the innovation from companies with headquarters located in the U.S., Europe or the rest of the world with respect to the revenue from each of these regions. The results are shown for both the OLS and 2SLS estimations. The 2SLS results amplify most of the effects observed with the OLS estimations, except for those for innovation in the rest of the world. The U.S. and EU markets seem to have strong positive spillovers across regions, while the rest of the world mostly responds to local expected revenue. The elasticity of innovation in the U.S. or Europe reacts positively to the expected revenue in the U.S., with greater elasticity in the U.S. than in Europe. We also note that the elasticity of innovation from European companies is greater with respect to European expected revenue than with respect to expected U.S. revenue but with a smaller

Table 4: Elasticity of Newly Registered Drugs by Region to the Expected Revenue in the Class

			OLS			2SLS
	(1)	(2)	(3)	(4)	(5)	(6)
Dependent variable	$\log N_{USct}$	$\log N_{EUct}$	$\log N_{Wct}$	$\log N_{USct}$	$\log N_{EUct}$	$\log N_{Wct}$
β_{US}	0.169**	0.092	0.506***	0.433***	0.381***	-1.219
	(0.052)	(0.052)	(0.061)	(0.080)	(0.088)	(1.086)
β_{EU}	0.095**	0.238***	-0.050	0.192***	0.417***	-1.324
	(0.033)	(0.038)	(0.040)	(0.037)	(0.051)	(0.836)
β_W	-0.096	0.006	-0.113	-0.294***	-0.307***	3.637*
	(0.051)	(0.050)	(0.061)	(0.080)	(0.075)	(1.755)
Year Fixed Effects	Yes	Yes	Yes	Yes	Yes	Yes
ATC Class Fixed Effects	Yes	Yes	Yes	Yes	Yes	Yes
$\chi^2(df)$				23.2 (18)	25.4 (16)	3.2 (1)
p-val				.18121	.06252	.07544
N	751	776	655	751	776	655

Note: Robust standard errors in parenthesis. * for $p < .05$, ** for $p < .01$, and *** for $p < .001$. Overidentifying restrictions test shown when 2SLS is used.

difference than the symmetric elasticities in the U.S. Finally, perhaps surprisingly, the elasticity of innovation from companies headquartered in Europe or the U.S. with respect to the expected revenue in the rest of the world is negative but compensated by the positive elasticity of innovation coming from the rest of the world[3]. Overall, the fact that each innovation from companies in a given region reacts more to the expected revenue coming from that region reflects the fact that local positive spillovers create additional incentives to invest when the expected revenue is coming more from the company's headquarters location. Positive local spillovers may include clinical knowledge spillover and local manufacturing externalities. Lower elasticities and even negative elasticities may result from international free riding in push incentives.

5 Conclusion

Pharmaceutical innovation, as a global public good, presents complex challenges at the intersection of regulation, incentives, and international coordination. This paper has reviewed the economic literature and empirical evidence on how regulatory environments ranging from intel-

[3]See appendix A.2 for the list of countries included.

lectual property protections and price regulations to push and pull incentives shape investment in pharmaceutical R&D. A key tension persists between static efficiency (access and affordability) and dynamic efficiency (sustaining innovation), which is further complicated by cross-border spillovers, strategic firm behavior, and policy interdependence.

While strong intellectual property regimes and market-based incentives have historically underpinned biomedical advances, especially in high-income countries, this reliance has exposed the global innovation system to fragilities. Free-riding, strategic delays in drug launches, and fragmented procurement systems reduce the effectiveness of current incentive structures. Emerging trends such as biologics, high-cost gene therapies, and drug shortages demand rethinking traditional policy levers, especially as the marginal cost structure shifts, which may make the diffusion of innovation more uneven.

The empirical findings underscore the central role of market size and expected revenue in driving innovation but also reveal growing disparities across therapeutic areas. Moreover, international policies such as reference pricing and parallel trade, while often aimed at promoting affordability, risk undermining innovation incentives when not coordinated across borders.

Finally, we emphasize how pharmaceutical innovation is shaped by international spillovers and strategic interdependence across countries and find that while the U.S. and EU markets create strong positive cross-regional incentives for innovation, firms in the rest of the world respond mainly to their own local revenue. Interestingly, U.S. innovation is particularly sensitive to domestic revenues; Europe shows more balanced responsiveness, and revenues from the rest of the world sometimes generate negative spillovers for U.S. and European firms, although this is offset by positive effects from firms headquartered outside these regions.

Moving forward, international cooperation will be essential. Mechanisms such as the shared financing of innovation rewards, coordinated exclusivity extensions, and supranational procurement programs could reduce inefficiencies and spread costs more fairly. Building institutions that balance affordability with the need for sustainable R&D investment should be at the center of global health policy. Only through such coordination can societies ensure that pharmaceutical innovation

continues to deliver transformative benefits across borders.

Bibliography

Acemoglu, D., D. Cutler, A. Finkelstein, and J. Linn (2006). Did Medicare Induce Pharmaceutical Innovation. *American Economic Review, Papers and Proceedings*, 103–107.

Acemoglu, D. and J. Linn (2004). Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry. *The Quarterly Journal of Economics 119*(3), 1049–1090.

Acosta, A., E. P. Vanegas, J. Rovira, B. Godman, and T. Bochenek (2019). Medicine Shortages: Gaps Between Countries and Global Perspectives. *Frontiers in Pharmacology 10*(July), 1–21.

Alpert, A., D. Lakdawalla, and N. Sood (2023). Prescription drug advertising and drug utilization: The role of medicare part d. *Journal of Public Economics 221*, 104860.

Azoulay, P., J. S. Graff Zivin, D. Li, and B. N. Sampat (2019). Public R&D Investments and Private-sector Patenting: Evidence from NIH Funding Rules. *The Review of Economic Studies 86*(1), 117–152.

Azoulay, P. and D. Li (2022). Scientific Grant Funding. In A. Goolsbee and B. F. Jones (Eds.), *Innovation and Public Policy*, pp. 117–150. Chicago: University of Chicago Press.

Berndt, E. and P. Dubois (2016). Impacts of Patent Expiry on Daily Cost of Pharmaceutical Treatments in Eight OECD Countries, 2004-2010. *International Journal of the Economics of Business 23*(2).

Berndt, E. R., I. M. Cockburn, and N. Blalock (2011). Diffusion of new drugs in the post-trips era. *International Journal of the Economics of Business 18*(2), 203–224.

Bignon, L. and P. Dubois (2025). Biologic Drugs and Learning-by-Doing. Working paper, chapter of Léa Bignon's PhD thesis.

Blume-Kohout, M. E. and N. Sood (2013). Market Size and Innovation: Effects of Medicare Part D on Pharmaceutical Research and Development. *Journal of Public Economics 97*, 327–336.

Boyer, B., A. Kroetsch, and D. Ridley (2022). Design of a transferable exclusivity voucher program. Duke Margolis Center for Health Policy white paper.

Bryan, K. A. and H. L. Williams (2021). Innovation: Market Failures and Public Policies. In K. Ho, A. Hortaçsu, and A. Pakes (Eds.), *Handbook of Industrial Organization*, Volume 5, pp. 281–362. Elsevier.

Budish, E., M. M. Durvasula, B. N. Roin, and H. L. Williams (2025). Missing markets for innovation: Evidence from new uses of existing drugs. Working Paper 34222, National Bureau of Economic Research.

Budish, E., B. N. Roin, and H. Williams (2015). Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials. *American Economic Review 105*(7), 2044–85.

Buxbaum, J. D., M. E. Chernew, A. M. Fendrick, and D. M. Cutler (2020). Contributions Of Public Health, Pharmaceuticals, And Other Medical Care To US Life Expectancy Changes, 1990-2015. *Health Affairs 39*(9), 1546–1556.

Chandra, A., J. Drum, M. Daly, H. Mirsberger, S. Spare, U. Neumann, S. Martin, and N. Kirson (2024). Comprehensive measurement of biopharmaceutical R&D investment. *Nature Reviews Drug Discovery 23*(9), 652–653.

Chandra, A., J. Kao, K. L. Miller, and A. D. Stern (2024). Regulatory Incentives for Innovation: The FDA's Breakthrough Therapy Designation. *The Review of Economics and Statistics*, 1–46.

Chaudhuri, S., P. K. Goldberg, and P. Jia (2006). Estimating the Effects of Global Patent Protection in Pharmaceuticals: A Case Study of Quinolones in India. *American Economic Review 96*(5), 1477–1514.

Civan, A. and M. T. Maloney (2009). The effect of price on pharmaceutical r&d. *The B.E. Journal of Economic Analysis & Policy 9*(1).

Cockburn, I. M. and R. M. Henderson (2000). Publicly Funded Science and the Productivity of the Pharmaceutical Industry. *Innovation Policy and the Economy 1*, 1–34.

Cockburn, I. M., J. O. Lanjouw, and M. Schankerman (2016). Patents and the Global Diffusion of New Drugs. *American Economic Review 106*(1), 136–164.

Congressional Budget Office (2021). Research and development in the pharmaceutical industry. Report 57126, Congressional Budget Office.

Conti, R. M. and M. E. Wosińska (2025). The economics of generic drug shortages: The limits of competition. *Journal of Economic Perspectives 39*(2), 79–102.

Cunningham, C., F. Ederer, and S. Ma (2021). Killer Acquisitions. *Journal of Political Economy 129*(3), 649–702.

Cutler, D. M. (2008). Are we finally winning the war on cancer? *Journal of Economic Perspectives 22*(4), 3–26.

Danzon, P. M. and L.-W. W. Chao (2000). Cross-national price differences for pharmaceuticals: how large, and why? *Journal of Health Economics 19*(2), 159–95.

Danzon, P. M., Y. R. Wang, and L. Wang (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.

Dave, D. M. (2013). Effects of Pharmaceutical Promotion: A Review and Assessment. *NBER Working Paper 18830*.

DiMasi, J. A., R. W. Hansen, and H. G. Grabowski (2003). The price of innovation: new estimates of drug development costs. *Journal of Health Economics 22*, 151–185.

DiMasi, J. A., R. W. Hansen, and H. G. Grabowski (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics 47*, 20–33.

DiMasi, J. A., R. W. Hansen William E Simon, H. G. Grabowski, and L. Lasagna (1991). Cost of innovation in the pharmaceutical industry. *Journal of Health Economics 10*, 107–142.

Dix, R. and T. Lensman (2025). Combining Complements: Theory and Evidence from Cancer Treatment Innovation. Job market paper, Massachusetts Institute of Technology.

Dubois, P., O. de Mouzon, F. Scott-Morton, and P. Seabright (2015). Market Size and Pharmaceutical Innovation. *The RAND Journal of Economics 46*(4), 844–871.

Dubois, P., A. Gandhi, and S. Vasserman (2022). Bargaining and International Reference Pricing in the Pharmaceutical Industry. NBER Working Paper 30053.

Dubois, P., E. P. Gentry, and T. Tuncel (2024). Strategic Submissions: A Cross-Country Analysis of Supplemental Drug Approvals. *Toulouse School of Economics Working Paper 1459*.

Dubois, P. and M. Kyle (2016). Are Cancer Drugs Worth the Price? The Effects of Pharmaceutical Innovation on Cancer Mortality Rates. CEPR Discussion Paper 11487.

Dubois, P. and L. Lasio (2018). Identifying Industry Margins with Price Constraints: Structural Estimation on Pharmaceuticals. *American Economic Review 12*(108), 3685–3724.

Dubois, P., G. Majewska, and V. Reig (2023). Drug Shortages: Empirical Evidence from France. TSE Working Paper 23-1417, Toulouse School of Economics.

Dubois, P., P.-H. Moisson, and J. Tirole (2022). The economics of transferable patent extensions. Technical Report TSE Working Paper 1377.

Dubois, P. and I. Natali (2025). Pull Incentives, Market Size and Pharmaceutical Innovation: From Early Preclinical Research to Drug Launch. *TSE Working Paper*.

Dubois, P. and A. Pakes (2025). Pharmaceutical Advertising in Dynamic Equilibirum. *Working Paper*.

Dubois, P. and M. Sæthre (2020). On the Effect of Parallel Trade on Manufacturers' and Retailers' Profits in the Pharmaceutical Sector. *Econometrica 88*(6), 2503–2545.

Duso, T., A. Herr, and M. Suppliet (2014). The Welfare Impact of Parallel Imports: A Structural Approach Applied to the German Market for Oral Anti-Diabetics. *Health Economics 23*(9), 1036–1057.

Egan, M. and T. J. Philipson (2013). International Health Economics. NBER WP 19280.

European Commission, Directorate-General for Health and Food Safety (2024). Proposal for a regulation laying down union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the european medicines agency. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52023PC0193.

European Federation of Pharmaceutical Industries and Associations (2023). The Pharmaceutical Industry in Figures, 2023. Technical report, EFPIA.

Feng, J., T. Hwang, J. Klimek, and L. Maini (2024). Biosimilar Entry and the Pricing of Biologic Drugs.

Feng, J., T. Hwang, and L. Maini (2023). Profiting from most-favored-customer procurement rules: Evidence from medicaid. *American Economic Journal: Economic Policy 15*(2), 166–97.

Filson, D. (2012). A Markov-perfect equilibrium model of the impacts of price controls on the performance of the pharmaceutical industry. *RAND Journal of Economics 43*(1), 110–138.

Finkelstein, A. (2004). Static and dynamic effects of health policy: Evidence from the vaccine industry*. *The Quarterly Journal of Economics 119*(2), 527–564.

Frech, H. E., M. V. Pauly, W. S. Comanor, and J. R. Martinez (2023). Pharmaceutical Pricing and R&D as a Global Public Good. NBER Working Paper 31272.

Galdin, A. (2025). Resilience of Global Supply Chains and Generic Drug Shortages. Working paper, Dartmouth College, Tuck Business School, Hanover, NH, USA.

Gamba, S., L. Magazzini, and P. Pertile (2021). R&d and market size: Who benefits from orphan drug legislation? *Journal of Health Economics 80*, 102522.

Gans, J. S. and D. B. Ridley (2013). Innovation incentives under transferable fast-track regulatory review. *The Journal of Industrial Economics 61*(3), 789–816.

Ganslandt, M. and K. E. Maskus (2004). Parallel imports and the pricing of pharmaceutical products: evidence from the european union. *Journal of Health Economics 23*, 1035–1057.

Garthwaite, C. (2025). Economic markets and pharmaceutical innovation. *Journal of Economic Perspectives 39*(2), 3–26.

Garthwaite, C. and A. Starc (2023). Why drug pricing reform is complicated: A primer and policy guide to pharmaceutical prices in the us. In M. S. Kearney, J. Schardin, and L. Pardue (Eds.), *Building a More Resilient US Economy*, Chapter Chapter. Washington, DC: Aspen Institute.

Giaccotto, C., R. E. Santerre, and J. A. Vernon (2005). Drug Prices and Research and Development Investment Behavior in the Pharmaceutical Industry. *Journal of Law and Economics 48*(1), 195–214.

Gowrisankaran, G., A. Nevo, and R. Town (2015). Mergers When Prices Are Negotiated: Evidence from the Hospital Industry. *American Economic Review 105*(1), 172–203.

Grennan, M. (2013). Price Discrimination and Bargaining: Empirical Evidence from Medical Devices. *American Economic Review 103*(1), 145–177.

Grossman, G. M. and E. L. C. Lai (2004). International Protection of Intellectual Property. *American Economic Review 94*(5), 1635–1653.

Grossman, G. M. and E. L.-C. Lai (2008). Parallel imports and price controls. *The RAND Journal of Economics 39*(2), 378–402.

Hausman, N. (2022). University innovation and local economic growth. *The Review of Economics and Statistics 104*(4), 718–735.

Hemphill, C. S. and B. N. Sampat (2025). Patents, innovation, and competition in pharmaceuticals: The hatch-waxman act after 40 years. *Journal of Economic Perspectives 39*(2), 27–52.

Ho, K. and A. Pakes (2025). Policy options for the drug pricing conundrum. *Proceedings of the National Academy of Sciences 122*(9), e2418540122.

IQVIA (2024). Global Trends in R&D 2024: Activity, Productivity, and Enablers. Institute Report.

IQVIA (2025). Assessing the Biosimilar Void in the U.S. Technical report.

Kanavos, P., J. Costa-Font, S. Merkur, and M. Gemmill (2004). The Economic Impact of Pharmaceutical Parallel Trade in European Union Member States: A Stakeholder Analysis. Research report, London School of Economics and Political Science, London.

Kanavos, P. and S. Vandoros (2010). Competition in prescription drug markets: Is parallel trade the answer? *Managerial and Decision Economics 31*(5), 325–338.

Khmelnitskaya, E. (2023). Competition and attrition in drug development.

Kremer, M. (1998). Patent buyouts: A mechanism for encouraging innovation. *Quarterly Journal of Economics 113*(4), 1137–1167.

Kremer, M. and R. Glennerster (2004). *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases*. Princeton, NJ: Princeton University Press.

Kremer, M., J. Levin, and C. M. Snyder (2020). Advance market commitments: Insights from theory and experience. *AEA Papers and Proceedings 110*, 269–73.

Kremer, M. and H. Williams (2010). Incentivizing innovation: Adding to the tool kit. In J. Lerner and S. Stern (Eds.), *Innovation Policy and the Economy*, Volume 10. University of Chicago Press.

Kyle, M. (2026). Potential and Effective Exclusivity of New Drugs in Europe. In J. M. Barnett and B. Heiden (Eds.), *Bringing Medicines to Life: How Intellectual Property Enables Innovation in the Life Sciences*. Cambridge University Press. forthcoming.

Kyle, M. and Y. Qian (2014). Intellectual Property Rights and Access to Innovation: Evidence from TRIPS. Technical report.

Kyle, M. K. (2007). Pharmaceutical price controls and entry strategies. *The Review of Economics and Statistics 89*(1), 88–99.

Kyle, M. K. (2011). Strategic responses to parallel trade. *B.E. Journal of Economic Analysis & Policy 11*(2).

Kyle, M. K. (2022). Incentives for pharmaceutical innovation: What's working, what's lacking. *International Journal of Industrial Organization 84*, 102850.

Kyle, M. K. (2025). Lessons for the united states from pharmaceutical regulation abroad. *Journal of Economic Perspectives 39*(2), 53–78.

Kyle, M. K. and A. M. McGahan (2012). Investments in Pharmaceuticals Before and After TRIPS. *Review of Economics and Statistics 94*, 1157–1172.

Kyle, M. K., D. B. Ridley, and S. Zhang (2017). Strategic interaction among governments in the provision of a global public good. *Journal of Public Economics 156*(C), 185–199.

Lakdawalla, D., N. Sood, and Q. Gu (2013). Pharmaceutical advertising and Medicare Part D. *Journal of Health Economics 32*(6), 1356–1367.

Lakdawalla, D. N. (2018). Economics of the Pharmaceutical Industry. *Journal of Economic Literature 56*, 397–449.

Lakdawalla, D. N., D. P. Goldman, P. C. Michaud, N. Sood, R. Lempert, Z. Cong, H. De Vries, and I. Gutierrez (2009). U.S. pharmaceutical policy in a global marketplace. *Health Affairs 28*(1), 138–150.

Lichtenberg, F. R. (2005a). The impact of new drug launches on longevity: evidence from longitudinal, disease-level data from 52 countries, 1982-2001. *International Journal of Health Care Finance and Economics 5*(1), 47–73.

Lichtenberg, F. R. (2005b). Pharmaceutical innovation and the burden of disease in developing and developed countries. *The Journal of Medicine and Philosophy 30*(6), 663–690.

Lichtenberg, F. R. (2007). The impact of new drugs on us longevity and medical expenditure, 1990–2003: Evidence from longitudinal, disease-level data. *American Economic Review 97*(2), 438–443.

Lichtenberg, F. R. (2023). The relationship between pharmaceutical innovation and cancer mortality in spain, from 1999 to 2016. *Value in Health 26*(12), 1711–1720.

Lo, A. W., R. MacLean, J. Weng, and V. Surana (2013). Venture capital meets science: Funding high-risk biomedical innovation. *Nature Biotechnology 31*(10), 997–1000.

Maini, L. and F. Pammolli (2023). Reference pricing as a deterrent to entry: Evidence from the european pharmaceutical market. *American Economic Journal: Microeconomics 15*(2), 345–83.

Majewska, G. (2023). Incentivizing novelty in antibiotic development. *Toulouse School of Economics, Job Market Paper*.

McKibbin, R. and B. A. Weinberg (2021). Does research save lives? the local spillovers of biomedical research on mortality. NBER Working Paper 29420.

Moisson, P.-H., P. Dubois, and J. Tirole (2023). The (Ir)Relevance of the Cooperative Form. TSE working Paper 23-1453.

Moses, Hamilton, I., D. H. M. Matheson, S. Cairns-Smith, B. P. George, C. Palisch, and E. R. Dorsey (2015). The Anatomy of Medical Research: US and International Comparisons. *JAMA 313*(2), 174–189.

OECD (2023). *Embracing a One Health Framework to Fight Antimicrobial Resistance*. OECD Health Policy Studies. Paris: OECD Publishing.

Olson, S. and S. Merrill (Eds.) (2011). *Measuring the Impacts of Federal Investments in Research: A Workshop Summary*. Washington, DC: The National Academies Press.

Outterson, K. (2005a). Pharmaceutical arbitrage: Balancing access and innovation in international prescription drug markets. *Yale Journal of Health Policy, Law, and Ethics 5*, 193–230.

Outterson, K. (2005b). The Vanishing Public Domain: Antibiotic Resistance, Pharmaceutical Innovation and Intellectual Property Law. *University of Pittsburgh Law Review 67*.

Outterson, K. (2006). Patent Buy-Outs for Global Disease Innovations for Low-and Middle-Income Countries. *American Journal of Law & Medicine 32*(2-3), 159–173.

Outterson, K. and A. McDonnell (2016). Funding Antibiotic Innovation with Vouchers: Recommendations on how to Strengthen a Flawed Incentive Policy. *Health Affairs 35*(5), 784–790.

Pertile, P., S. Gamba, and M. Forster (2018). Free-riding in pharmaceutical price regulation: Theory and evidence. Discussion Papers in Economics 18/04, Department of Economics and Related Studies, University of York, York, UK.

Qian, Y. (2007). Do National Patent Laws Stimulate Domestic Innovation in a Global Patenting Environment? A Cross-Country Analysis of Pharmaceutical Patent Protection, 1978–2002. *The Review of Economics and Statistics 89*(3), 436–453.

Ridley, D., P. Sun, and C. Xu (2025). Optimal Push, Pull, and Failure Funding for Global Health. Fuqua School of Business, Duke University.

Ridley, D. B., H. G. Grabowski, and J. L. Moe (2006). Developing Drugs For Developing Countries. *Health Affairs 25*(2), 313–324.

Rome, B. N. and A. S. Kesselheim (2020). Transferrable Market Exclusivity Extensions to Promote Antibiotic Development: An Economic Analysis. *Clin Infect Dis. 71*(7), 1671–1675.

Salter, M. (2015). Reference Pricing: An Effective Model for the U.S. Pharmaceutical Industry? *Northwestern Journal of International Law & Business J. Int'l L. & Bus. Northwestern Journal of International Law & Business 35*(2).

Sampat, B. N. and H. L. Williams (2019). How do patents affect follow-on innovation? Evidence from the human genome. *The American Economic Review 109*(1), 203–236.

Scott-Morton, F. (1997). The Strategic Response by Pharmaceutical Firms to the Medicaid Most-Favored-Customer Rules. *The RAND Journal of Economics 28*(2), 269.

Scott Morton, F., A. D. Stern, and S. Stern (2018). The Impact of the Entry of Biosimilars: Evidence from Europe. *Review of Industrial Organization 53*(1), 173–210.

Stevens, A. J., J. J. Jensen, K. Wyller, P. C. Kilgore, S. Chatterjee, and M. L. Rohrbaugh (2011). The role of public-sector research in the discovery of drugs and vaccines. *The New England Journal of Medicine 364*(6), 535–541.

Toole, A. A. (2007). Does Public Scientific Research Complement Private Investment in Research and Development in the Pharmaceutical Industry? *Journal of Law and Economics 50*(1), 81–104.

Tunçel, T. (2025). Should We Prevent Off-Label Drug Prescriptions? Empirical Evidence from France. *The Review of Economic Studies 92*(3), 2027–2070.

Weiss, J., P. Hakim, and R. Degun (2016). Impact of Implementing International Reference Pricing on Pharmaceutical Prices for United States Medicare. *Value in Health 19*(3), A89.

Williams, H. L. (2013). Intellectual property rights and innovation: Evidence from the human genome. *Journal of Political Economy 121*(1), 1–27.

Yin, W. (2008). Market incentives and pharmaceutical innovation. *Journal of Health Economics 27*(4), 1060–1077.

Yin, W. (2009). R&D policy, agency costs and innovation in personalized medicine. *Journal of Health Economics 28*(5), 950–962.

Yurukoglu, A., E. Liebman, and D. B. Ridley (2017). The Role of Government Reimbursement in Drug Shortages. *American Economic Journal: Economic Policy 9*(2), 348–382.

A Data

A.1 Match between ICD classes and ATC classes

The mortality data across years and countries are available per disease category as classified using the ICD-10 classification. Of course, disease categories and drug categories (ATC classes) are different, but one can attribute to each ATC class a "most likely" disease category in the ICD-10 classification, as shown in Table 5 from Dubois et al. (2015).

Table 5: International Classification of Diseases and ATC Drug Categories

ATC Class	ICD10		Disease Title
	Chapter	Blocks	
A14, A16	IV	E00-E90	Endocrine, nutritional and metabolic diseases
Other A	XI	K00-K93	Diseases of the digestive system
B	III	D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
C	IX	I00-I99	Diseases of the circulatory system
D	XII	L00-L99	Diseases of the skin and subcutaneous tissue
G	XIV	N00-N99	Diseases of the genitourinary system
H	IV	E00-E90	Endocrine, nutritional and metabolic diseases
J	I	A00-B99	Certain infectious and parasitic diseases
L	II	C00-D48	Neoplasms
M	XIII	M00-M99	Diseases of musculoskeletal system and connective tissue
N1, N2, N3	VI	G00-G99	Diseases of the nervous system
N4, N5, N6, N7	V	F00-F99	Mental and behavioral disorders
P	I	A00-B99	Certain infectious and parasitic diseases
R	X	J00-J99	Diseases of the respiratory system
S1	VII	H00-H59	Diseases of the eye and adnexa
S2	VIII	H60-H95	Diseases of the ear and mastoid process

A.2 Sources of the data

Proprietary data called "Pharmaprojects" from Citeline track the history and evolution of all pharmaceutical projects from early registration of the preclinical trial phase to market authorization. These data are exhaustive and very detailed.

Despite providing only aggregate sales values and quantities for each drug by different types of users (hospital, pharmacy-specialized distribution channels in the U.S.), the IQVIA MIDAS proprietary data are international and exhaustive. These data have the advantage of guaranteeing

good harmonization across countries in terms of the coding variables.

The list of countries included in the rest of the world for which revenue data are available is Argentina, Australia, Belarus, Brazil, Canada, China, Ecuador, Egypt, Indonesia, Japan, Korea, Malaysia, Mexico, Morocco, New Zealand, Pakistan, Philippines, Russia, Singapore, South Africa, Ukraine, and Venezuela. The list of countries in the rest of the world that have some registered drugs from companies headquartered in those countries is as follows: Argentina, Australia, Canada, Cuba, Hong Kong, China, India, Indonesia, Japan, Mexico, New Zealand, Russia, Singapore, South Korea, Taiwan, Thailand, and Uruguay.

We also use information on population and mortality from the World Health Organization (WHO).