NBER WORKING PAPER SERIES

VALUATION OF REGULATORY RISK ON PHARMACEUTICAL R&D

Teresa Corzo Santamaria
Jose Portela
Eduardo S. Schwartz

Working Paper 34863
http://www.nber.org/papers/w34863

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
February 2026

We have no sources of funding. The views expressed herein are those of the authors and do not necessarily reflect the views of the National Bureau of Economic Research.

At least one co-author has disclosed additional relationships of potential relevance for this research. Further information is available online at http://www.nber.org/papers/w34863

NBER working papers are circulated for discussion and comment purposes. They have not been peer-reviewed or been subject to the review by the NBER Board of Directors that accompanies official NBER publications.

© 2026 by Teresa Corzo Santamaria, Jose Portela, and Eduardo S. Schwartz. All rights reserved. Short sections of text, not to exceed two paragraphs, may be quoted without explicit permission provided that full credit, including © notice, is given to the source.

Valuation of Regulatory Risk on Pharmaceutical R&D
Teresa Corzo Santamaria, Jose Portela, and Eduardo S. Schwartz
NBER Working Paper No. 34863
February 2026
JEL No. G1, I18

ABSTRACT

Geopolitical tensions, supply-chain concerns and policy risk have moved to the forefront of the pharmaceutical industry. This paper develops a real options valuation model of drug R&D that captures sequential clinical investment with technical failure, stochastic costs, uncertain cash flows, and optimal abandonment. We incorporate two regulatory shocks: a reduction in effective exclusivity period and a price-control shock that reduces net cash flows. Calibrating to an incremental CNS program, we find that project value at initiation is highly right-skewed: the mean is USD 69.6m but the median is negative, so expected value is driven by rare high-upside outcomes. Regulatory risk mainly compresses this upside. Both reductions in effective exclusivity and price-based interventions substantially weaken investment incentives, even when they occur with moderate probability. Value is strongly convex in exclusivity length, with the final years carrying the highest marginal value. We introduce iso-value maps that summarize how time-based and price-based policies substitute in their impact on project valuation, to clarify the trade-offs inherent in regulatory design: losing two years of exclusivity is comparable to roughly a 30% cash-flow contraction. Using a standard revenue-to-R&D elasticity, these valuation effects imply a 10% to 25%long-run contraction in investment. The framework provides a transparent mapping from policy design to project value and investment incentives.

Teresa Corzo Santamaria
Universidad Pontificia Comillas
Icade School of Economics and
Business Administration
Department of Financial Economics
mcorzo@comillas.edu

Jose Portela
Universidad Pontificia Comillas
Instituto de Investigación Tecnológica (IIT)
jportela@comillas.edu

Eduardo S. Schwartz
University of California, Los Angeles
and Simon Fraser University
and also NBER
eduardo.schwartz@anderson.ucla.edu

Valuation of Regulatory Effects on Pharmaceutical R&D Innovation

January 2026

1. Introduction

U.S. policy shifts, including Medicare price negotiations, supply-chain reshoring, and tariff threats have positioned the global pharmaceutical industry in the spotlight. These headlines also coincide with weaker sector performance and repeated downgrades since late 2024 (Barnes & Raghavan 2025; Bhatt 2025; Lazard 2025; Michielssens 2025).

The industry is large and research-intensive. It spans products from generics to cell and gene therapies. It relies on a global and tightly regulated supply base. It invests heavily in R&D and faces long and risky development cycles. In Europe alone, estimated 2024 output reached €440 billion, with a €220 billion trade surplus, and €55 billion in R&D (EFPIA 2025). Global top 25 large-cap biopharma companies' R&D investments reached $190 billion in 2024, corresponding to an R&D intensity of 25.2%. Typical development lasts 11 to 13 years, with an estimated full cost of about $3.3 billion per new medicine and an overall clinical phase to approval success rate near 7% (IQVIA 2025; Allianz 2025; EFPIA 2025).

The United States is pivotal for launches and profits. It accounted for 54.8% of global pharmaceutical sales in 2024. Among medicines first launched between 2019 and 2023, 66.9% of global sales accrued in the U.S., compared with 15.8% in Europe's five largest markets. The data also indicate U.S. launch leadership. Since 2020, 110 new active substances (NASs) have been introduced in the U.S. but remain unavailable in Europe. Only 14 were launched first in Europe. Revenue exposure amplifies this channel. Non-U.S. health care firms derive about 41% of their revenues from the U.S., making global sector performance vulnerable to shifts in U.S. policy (Barnes & Raghavan 2025; EFPIA 2025; Allianz 2025; LSEG 2025). Goldman and Lakdawalla (2018) estimate that pharmaceutical profits in the U.S. account for 64% to 78% of global profits. This implies that U.S. policy changes can disproportionately affect global expected returns. The US Food and Drug Administration's (FDA) 2024 Site Catalog lists 4,619 registered drug manufacturing sites worldwide. Forty one percent are in the U.S. Quality assurance inspections reached 972 in Fiscal Year 2024, with more than 62% at foreign sites. This indicates deep cross-border interdependence and exposure to reshoring initiatives.

This US centrality has been guided by a distinct regulatory philosophy. The American framework, shaped by the Hatch–Waxman Act (1984), is designed to reward innovation through patent-term extensions and market exclusivity, sustaining high expected returns on R&D. In contrast, European and other developed markets emphasize price controls, reference pricing, and health-technology assessments, which constrain margins but enhance affordability and equity of access. Empirical evidence consistently links these

differences to innovation intensity: firms with greater exposure to price-regulated markets display markedly lower R&D investment, whereas U.S. firms maintain higher profitability, innovation rates, and market capitalization (i.e., Vernon 2005; Golec & Vernon 2010; Eger & Mahlich 2014; EFPIA 2025). This configuration makes current regulatory shifts, including price negotiation, tariffs, and tighter quality oversight, especially consequential.

Several studies have assessed the potential impact of price regulation in the United States, consistently finding substantial effects on revenues, R&D investment, and long-term innovation output. Philipson and Durie (2021) estimate that the introduction of direct price controls would reduce global drug manufacturer revenues by 19–39%, translating into a 29–60% decline in R&D spending over two decades. Ji and Rogers (2024) reach similar conclusions, documenting a 44% fall in revenues and a 53% drop in R&D expenditure. Earlier evidence from Vernon (2005) and Golec and Vernon (2010) likewise demonstrates that tighter price regulation reduces firms' internal cash flows and innovation rates. Against this background, the industry's reaction to the U.S. government's measures is predictable, given the historical link between regulation, investment behavior, and their effects on industry incentives, and both short-term performance and long-term social welfare (e.g., Lo and Thakor 2022; Rogers 2023; Frech et al. 2023). However, most studies operate at the firm or market level. They rarely translate policy shocks into project-level valuation under uncertainty. Yet project valuation is the object that guides portfolio choice, staging, licensing, and abandonment.

In this paper, we quantify regulatory risk at the project level. We quantify how two regulatory events affect the value of an incremental innovation project. The first, Event I, represents a reduction in the effective patent or market exclusivity period, which shortens the time during which a firm can commercialize a drug without generic competition. This event captures potential policy actions that compress the revenue window, such as accelerated generic entry, revised exclusivity terms, or changes in the duration of protection. The second, Event II, models the introduction of direct or indirect price controls, reflecting government negotiation, statutory ceilings, or reference pricing mechanisms that reduce net cash flows. Both events are introduced probabilistically within the model to represent regulatory uncertainty, allowing us to assess how changes in exclusivity duration and pricing policy influence project value, and, consequently, R&D investment incentives. Because policy packages often combine pricing pressure and changes in effective exclusivity, we also summarize the joint effect of these two levers in iso-value (isoline) maps. The contours show which combinations of protected production years and net cash-flow reductions yield the same project value at initiation. This representation is intended to be portable across settings in which regulators and firms negotiate between lower prices and shorter or longer effective market protection.

We adopt a real options valuation (ROV) framework based on Least Squares Monte Carlo (LSM) following Schwartz (2004). The model explicitly represents clinical Phases I–III, capturing the sequential nature of pharmaceutical R&D, and incorporates technical failure through a Poisson process. This approach allows us to simulate the stochastic evolution of costs and cash flows under uncertainty and to value the managerial flexibility to continue or abandon a project as new information arises. In this way we contribute to filling the gap detected by Cassimon et al (2011) related to the lack of model case studies using ROV.

We selected an incremental innovation project in the Central Nervous System (CNS) area to illustrate the model and isolate regulatory effects from radical innovation risk. The CNS field is one of the largest non-oncology therapeutic domains, attracting a substantial share of global clinical trials and R&D investment (e.g., Wong et al. 2019; Wouters et al. 2020). It is also representative of industry dynamics where development timelines are long, attrition rates moderate, and commercial outcomes highly sensitive to policy conditions. Incremental innovation projects in pharma typically involve lower technical and market risk, as they build on validated mechanisms of action and established therapeutic demand. They also account for the majority of new drug approvals (NDA), making them a representative case for assessing regulatory impacts. At the same time, it can be adapted to NMEs or biologics by changing costs, timelines, and success probabilities. Based on prior literature, we can expect a stronger valuation impact in radical innovation settings.

Our model finds a notable valuation impact of regulatory events even when low probabilities are considered. First, project value is highly skewed. Mean value is positive, but the median is negative. Expected value is driven by a thin right tail. Second, regulatory risk reduces value even at moderate probabilities. With a 10% probability of Event I, mean value falls by 6.5%. With a 30% probability of Event II, mean value falls by 16.1%. Third, regulatory risk mainly compresses upside outcomes. Downside outcomes change little, because the shocks hit post-approval cash flows rather than development losses. Abandonment rises modestly, from 5.3% to 6.1% under Event II.

Beyond average effects, the model implies two policy-relevant nonlinearities. Value is convex in effective exclusivity length, with disproportionate weight in the final years. In addition, isoline maps show that some reductions in exclusivity can be comparable to large cash-flow cuts.

Finally, to link valuation to investment incentives, we interpret percentage changes in expected project value as a proxy for revenue changes, holding costs fixed. This is a partial-equilibrium mapping. Using an elasticity of 1.54 (Philipson & Durie, 2021), the valuation losses imply an R&D contraction of about 10%–25% over time. Section 7 reports sensitivity to the low/high elasticities reported in the literature.

Our aim is to provide a transparent and replicable valuation framework that helps stakeholders, investors, companies, and regulators assess the economic consequences of regulatory design on R&D investment and market access. As Lo and Thakor (2023) emphasize, one of the main obstacles to biomedical innovation is the difficulty of assessing and pricing project risk, which complicates capital inflows and widens the sector's funding gap. By offering a tractable approach our model contributes to closing this information gap, facilitating the valuation practice.

The paper is structured as follows. Section 2 describes the regulatory setting and related evidence. Section 3 motivates incremental innovation as the reference case. Section 4 presents the real options approach. Section 5 details the model. Section 6 reports calibration and results. Section 7 provides sensitivity analyses. Section 8 concludes.

2. Regulatory Uncertainty

Due to its specific characteristics, the pharmaceutical industry is tightly regulated. Regulatory agencies, including the U.S. FDA, the European Medicines Agency (EMA), Japan's Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, and China's National Medical Products Administration (NMPA), establish comprehensive rules covering clinical trials, manufacturing quality, pharmacovigilance, pricing, reimbursement, and intellectual property protection. Each carries distinct risk profiles and financial consequences. Firms must incorporate these heterogeneous regulatory maps into their investment decisions and R&D portfolio strategies.

These regulatory frameworks are designed to guarantee the safety and efficacy of pharmaceuticals while reconciling public affordability with the preservation of innovation incentives. Although price-controls and reimbursement limits may expand access to existing medicines and help contain public health expenditures in the short term, such measures might weaken the long-term incentives for R&D (e.g., Vernon, 2005; Frech et al 2023; Ji & Rogers, 2024). A substantial body of empirical work links such interventions to lower R&D intensity and slower innovation dynamics, particularly in markets where price regulation affects a significant share of sales (Vernon 2005; Golec & Vernon 2010; Eger & Mahlich 2014).

As outlined in the Introduction, the U.S. and European systems differ in their regulatory philosophy: the U.S. system intentionally rewards innovation whereas Europe relies heavily on price controls and centralized reimbursement that compress profit margins but increase affordability and equity of access. Among developed economies, the U.S. and New Zealand remain the only countries without statutory or comprehensive federal price regulation of prescription medicines, although New Zealand exercises centralized purchasing control through PHARMAC (Pharmaceutical Management Agency).

In the U.S. there have been attempts of price controls such as the Health Security Act (often called the Clinton health care plan) which was a comprehensive proposal introduced in 1993 (House of Representatives bill, H.R.. 3600 and S.1757) aiming to guarantee universal health coverage, control costs, and restructure insurance markets. However, it was never enacted.

2.1.Regulatory Tools, Profitability and Innovation Incentives

Among the wide array of regulatory tools, price controls, the patent system and market exclusivity periods exert the strongest economic influence.

The seminal paper by Sood et al (2009) provides a systematic review on pharmaceutical regulations across 19 OECD countries. It classifies national regulatory instruments into ten categories, including global budgets, price controls, reference pricing, economic evaluation and generic-promotion policies. This dataset remains a benchmark for empirical research on international price regulation and its economic effects. They document that the majority of regulations reduce pharmaceutical revenues significantly, however, direct price controls are the most popular regulation, and that have the largest impact on revenues. Direct price controls reduce pharmaceutical revenues by 18–26%, with cumulative effects reaching -24% within six years. Through the elasticity of R&D with respect to revenues Philipson and Durie (2021) translate how the price controls affect R&D decisions, studying the HR 3 announced by Biden administration in August 2021. Through the survey of 10 major empirical studies estimating the elasticity of pharmaceutical R&D with respect to revenues, they find that the estimated drop in global drug manufacturer revenue would be on the range 19%-39%, and the price control will lead over time (2021 to 2039) to a decline in R&D from 29.2% to 60%.

Exclusivity mechanisms, such as patents, and market exclusivity periods are essential to sustain private investment in R&D by providing temporary monopolies that offset high development costs.

Patents are private intellectual property rights granted by national patent offices for inventions that meet novelty, non-obviousness, and utility requirements. In pharmaceuticals, patents may cover active ingredients, formulations, or new therapeutic uses. They last 20 years from filing under the World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS 1994) Agreement, but effective market protection is shorter because R&D and regulatory approval can take a decade or more. To compensate for this delay, many jurisdictions provide patent-term extensions: up to five years in the United States under the Hatch–Waxman Act, through Supplementary Protection Certificates (SPCs) in the European Union, and through comparable schemes in Japan, Australia, Canada, and South Korea.

Market exclusivity is a separate, statutory protection granted upon approval by drug authorities such as the FDA or EMA. It blocks generic or biosimilar applications for a

fixed period, even if patents have expired. In the U.S., exclusivities include five years for new chemical entities, seven years for orphan drugs, and twelve years for biologics, resulting in a maximum competition-free period of up to 14 years post-FDA approval. In the EU, the "8 + 2 + 1" framework guarantees up to eleven years of combined data and market exclusivity. These mechanisms provide complementary layers of protection, enabling firms to recoup investment costs and sustain incentives for pharmaceutical innovation.

These mechanisms collectively ensure roughly 11-15 years of effective protection after marketing authorization.

The use of these regulatory tools influence profitability and innovation as has been established by seminal studies. Vernon (2005) demonstrates that lowering U.S. pharmaceutical profit margins to European levels would reduce R&D investment by 23–33%, about half of which derives from reduced internal cash flows. Golec and Vernon (2010) extend this analysis internationally, showing that U.S. firms exhibit higher profitability (17.1% vs 12.2%), greater R&D intensity (9.6% vs 8.9%), and superior stock-market performance than their European counterparts, reflecting more favorable pricing conditions. Eger and Mahlich (2014) confirm that once European sales exceed 33% of a firm's revenue, R&D spending declines non-linearly. These results demonstrate that tighter regulation diminishes both expected returns and the capacity to finance innovation internally. Dubois et al. (2015) advances the empirical understanding of how market size drives innovation incentives in the pharmaceutical sector. Through the estimation of a robust elasticity of approximately 0.23 between market size and innovation, their results show that innovation responds positively but less than proportionally to market expansion, reflecting increasing R&D costs and competitive saturation. Even moderate contractions in expected revenues, such as those resulting from price regulation, can significantly diminish the number of new drug launches globally.

Subsequent studies refine these findings. Shaikh et al. (2021) revisit the classic debate using the ten largest pharmaceuticals firm-level data, showing that regulation reduces revenues and cash flows but that the effect on R&D intensity depends on firm size and internal capabilities—large incumbents can partially offset adverse shocks. Ji and Rogers (2024), analyzing Medicare price reforms for durable medical equipment, find revenue declines of 44%, a 25% fall in FDA device submissions, and a 53% drop in R&D spending, translating into annual innovation losses valued at $46 billion against Medicare savings of $3.8 billion.

Historical and recent U.S. policy proposals illustrate how even the threat of regulation can affect innovation incentives. The Clinton Administration's Health Security Act (1993), though never enacted, caused cumulative abnormal stock returns of -45% for R&D-intensive firms and a 7% to 8% contraction in R&D expenditure (Golec, Hegde &

Vernon 2010). The National Pharmaceutical Council's white paper by Ciarametaro and Buelt (2022) consolidates 19 empirical and theoretical studies published between 2000 and 2020, concluding that price regulation uniformly reduces innovative output, though the magnitude varies by policy design and disease area. They estimate that a 1% contraction in market size may reduce the number of new drug approvals by 0.2% to 6%.

2.2.The Inflation Reduction Act (IRA, 2022) Case

The Inflation Reduction Act (IRA 2022) introduced Medicare price negotiation[1] for high-spending drugs, creating differentiated exclusivity windows—9 years for small-molecule drugs versus 13 years for biologics—and thereby altering R&D incentives. This differential period grants large molecules (biologics) a longer span of unregulated market pricing, thereby preserving stronger investment incentives.

However, the IRA preserves stronger incentives for biologics through a longer unregulated window. Biologics are large and complex molecules produced in living systems. They are harder to design, replicate, and scale than small molecules. Their development costs are higher, and clinical phases can be longer (EFPIA 2025; Wouters et al. 2020).

Conversely, the asymmetry may weaken incentives for small molecules. Philipson et al. (2023) estimate that this asymmetry could reduce new small-molecule approvals by about 79 and new indications by approximately 109 over 20 years, corresponding to an 8% drop in revenues and a 12% cut in R&D spending. Canestaro et al. (2025) observe from their interviews with venture and corporate investors that "early signals of IRA impact on investor strategy include favoring a larger population launch and reduced small molecule investing". Schulthess et al. (2025) and Zheng et al. (2025) report that venture-capital investment has pivoted toward biologics, while small-molecule projects, particularly those targeting Medicare-heavy diseases of aging, are being deprioritized.

Although industry-wide innovation remains robust (Dao & Ledley 2025), its composition is shifting. The IRA effectively transforms Medicare exposure into a policy-specific risk factor: assets targeting elderly populations are now discounted by investors, who reallocate capital toward biologics and non-Medicare markets. The resulting investment distribution implies lower investments in chronic and geriatric diseases, raising long-term welfare concerns.

2.3.Recent Empirical Evidence on Regulatory Impact

This reshaping effect of the R&D pipeline has been also noted in the papers by Krieger et al. (2022a; 2022b). Krieger et al. (2022b) provides evidence that regulatory and market shocks reshape not only the scale but also the direction of innovation. Using project-level

[1] The IRA 2022 introduces limited Medicare negotiations for some drugs, but it does not constitute a comprehensive national price regulation system.

data from the biopharmaceutical industry, they show that negative product shocks, such as FDA Public Health Advisories (PHAs), lead firms to increase overall R&D spending but shift it toward acquisitions of late-stage projects rather than internal early-stage research, particularly when internal pipelines are weak. In Krieger et al. (2022a) the authors document a systematic decline in novel, first-in-class developments, as firms increasingly prioritize incremental and lower-risk projects to mitigate uncertainty. Together, these findings suggest that regulatory pressures and market erosion alter firms' innovation strategies.

Recent structural evidence reinforces this mechanism. Rogers (2023) develops an equilibrium model of innovation under regulatory constraints and finds that price and reimbursement controls not only depress the overall rate of innovation but also alter its direction, reducing incentives for high-risk projects. The model predicts a 20–30% long-run decline in breakthrough innovation and shows that welfare losses may outweigh short-run cost savings when spillover effects are considered. These findings show that the cumulative effect of national pricing policies extends beyond firm behavior, shaping the distribution of R&D effort across countries.

In this broader level, the asymmetry between the largely unregulated U.S. market and the price-regulated European one has macroeconomic implications. Frech et al. (2023) conceptualize pharmaceutical R&D as a global public good financed asymmetrically across nations. Using OECD data, they find that the United States contributes 66–73% of global pharmaceutical quasi-rents that sustain innovation, approximately $289 to $326 billion annually, or $900 to $1,000 per capita, while the rest of the OECD collectively contributes 27% to 33%, averaging $200 per capita. This pattern confirms that other developed economies partially free ride on U.S. incentives, yielding a globally sub-optimal equilibrium in pharmaceutical R&D investment.

Regulatory interventions entail a fundamental trade-off between static and dynamic efficiency. While tighter price controls may improve short-term affordability and budgetary outcomes, they also depress expected returns and, consequently, future innovation. The literature consistently finds that reductions in expected revenues or market size led to fewer clinical trials, fewer new drug approvals, and delayed technological progress raising welfare considerations (e.g., Vernon 2005; Golec & Vernon 2010; Philipson & Durie 2021; Ji & Rogers 2024). EFPIA (2025) data corroborate these trends at the aggregate level: Europe's share of world pharmaceutical R&D spending has fallen to 22.7%, whereas the United States now accounts for 54.8%.

Additionally, pharmaceutical companies consider regulation as a driver to decide where to locate their research and facilities (Gassmann et al 2018).

The literature also emphasizes that regulatory uncertainty amplifies financing frictions in the sector. Lo and Thakor (2022) show that the structural features of drug development

force biopharmaceutical firms to rely heavily on external equity financing, making them especially sensitive to shifts in investor sentiment and policy expectations.

2.4.U.S. Policy Shift and Global Strategic Realignment

All these investigations indicate that regulation, whether enacted or anticipated, functions as a systematic source of financial and R&D risk in the pharmaceutical industry.

In 2025, this risk moved to the forefront. The Trump Administration shifted U.S. drug-pricing policy toward executive action and trade leverage.

Executive Order 14273 set workstreams to revise Medicare negotiation guidance. It also called for reforms to reduce the IRA "pill penalty" for small molecules (Executive Office of the President 2025a). Executive Order 14297 then set a most-favored-nation (MFN) pricing goal (Executive Office of the President 2025b). These MFN initiatives are motivated by the large international price gap. Mulcahy et al. (2021) estimate that, in 2018, U.S. prices were about 256% of prices in other OECD countries, and about 344% for brand-name originator drugs. The Executive Order 14297 also directed agencies to enable direct-to-consumer purchasing at MFN prices and to challenge foreign price discrimination (Executive Office of the President 2025b). In parallel, the Department of Commerce initiated a Section 232 national security investigation on pharmaceutical imports and inputs (U.S. Department of Commerce 2025). This increased the credibility of tariff threats.

The tariff lever is mostly a negotiation tool. It is now paired with voluntary MFN agreements. These agreements focus on Medicaid and cash-pay channels. Pfizer announced the first agreement in September 2025 (Bose & Wingrove 2025). The deal offered tariff relief and included new U.S. investment commitments (Bose & Wingrove 2025). Later White House announcements widened the scope, including GLP-1 (Glucagon-Like Peptide-1) therapies (The White House 2025a). In December 2025, nine more manufacturers joined: Amgen, Bristol Myers Squibb, Boehringer Ingelheim, Genentech, Gilead Sciences, GSK, Merck, Novartis, and Sanofi (The White House 2025b). These deals tie MFN pricing to both existing products and new launches (The White House 2025b). They also link price concessions to onshoring and supply security. The December agreements included large U.S. manufacturing pledges and contributions to a Strategic Active Pharmaceutical Ingredients Reserve (The White House 2025b).

Table 1: U.S. evolving policy levers and likely impacts as of 2025

Policy	Description and Impact
Import-tariff threat on branded drugs (section 232)	Negotiation tool to secure U.S. manufacturing and price concessions; raises uncertainty and capital expenditure needs for firms reliant on offshore production
Voluntary Most Favored Nation Pricing Deals (Medicaid/cash pay; TrumpRx)	Targeted discounts with limited P&L hit versus broad controls; creates reference-pricing pressure for new launches
Adjust IRA timing for pills versus biologics	Policy intent to reduce the small-molecule penalty and stabilize incentives; implementation path remains uncertain
Geopolitical supply-chain push (onshoring; strategic API reserve)	Accelerates U.S. plant plans and stockpiling initiatives; improves resilience but raises near-term costs and execution risk

Sources: Executive Office of the President (2025a; 2025b); U.S. Department of Commerce (2025); The White House (2025a; 2025b); Bose & Wingrove (2025)

In relation to the IRA 2022 reforms discussed above, the current agenda prefers executive leverage. Tariff threats and MFN bargaining replace broad, uniform controls. Uncertainty remains high, because outcomes increasingly depend on bilateral negotiations and trade enforcement rather than uniform statutory rules (Executive Office of the President 2025a, 2025b; The White House 2025b).

As noted by Barnes & Raghavan (2025), the sector's valuation dynamics and capital allocation patterns have become highly sensitive to U.S. policy risk. As Lazard (2025) argues to mitigate policy exposure, firms are accelerating domestic manufacturing and adapting portfolios to reduce public-payer pricing exposure.

These shifts have triggered responses abroad. The European Union and Japan pointed to trade frameworks that cap U.S. pharmaceutical tariffs at 15% (Blenkinsop 2025). The United Kingdom pursued alignment through a pharmaceutical pricing agreement in principle. It includes higher net prices for new medicines and exemptions from Section 232 tariffs (USTR 2025). These responses show that U.S. drug policy now transmits through trade as well as regulation.

In this evolving landscape, it is clear that regulatory risk management has become as critical to pharmaceutical success as scientific and commercial execution.

3. Incremental innovation as the reference case

Innovation constitutes a core element of business success and a defining characteristic of the pharmaceutical industry. Accordingly, there is a full area of study related to innovation within organizations. However, defining and measuring innovation remains challenging due to diverse typologies and perspectives in the management literature.

Innovation differs in novelty and in the type of knowledge it requires. A useful distinction is incremental versus radical change. Incremental innovation improves existing technology while preserving core concepts and the prevailing architecture. Radical innovation changes core concepts and can displace existing designs (Henderson and Clark, 1990).

3.1. Definition and scope in pharmaceuticals

Within the pharmaceutical ecosystem, research and policy attention have primarily focused on novel drugs. Novel drugs, whether new molecular entities, NME, or new therapeutic biologics, NBEs[2] represent the highest level of novelty and are considered, by the related literature, radical innovations once approved. For instance, a first-in-class drug is the first therapy with a novel pharmacological mechanism, and a first-in-target drug is the first aimed at a new biological target; these are hallmark radical innovations.

By contrast, incremental innovation encompasses drug developments that do not introduce a NME, NBE, or mechanism of action. These include follow-on products such as new formulations, new therapeutic indications, or "me-too" drugs that enhance existing therapies through better delivery, safety, or dosing profiles. Although these advances build on known science, they can generate substantial economic and welfare value (Bokhari, & Fournier, 2013; Arcidiacono et al., 2013; Okuyama 2024). Incremental innovations typically involve refinement or enhancement of existing drugs' attributes. For example, a follow-on drug might have better safety, improved delivery methods, greater potency, or a more targeted therapeutic profile compared with a pioneering drug in the same class. The principal characteristic is that the new product delivers incremental benefits, like improved efficacy or fewer side effects over predecessors, thereby offering value to patients and competitive advantage to firms. Many studies of pharma innovation build on this idea (e.g., Schuhmacher et al 2016; Okuyama 2017; Johnson 2020). For instance, Okuyama (2024) explicitly defines incremental pharmaceutical innovation as "late-entry" drugs, those launched second or later in a therapeutic class sharing the same mechanism of action as an existing drug. Such late entrants seek to differentiate on specific features like pharmacokinetics, formulation, or modality, rather than inventing an entirely new

[2] To ease the exposition, we will use the terminology adopted by the U.S. FDA; other regulatory agencies employ similar terms to refer to the same concepts.

mechanism. Empirically, Krieger et al. (2023) measure a drug candidate's novelty by its molecular distance from prior drugs and classify "follow-on" drugs with close chemical similarity to known compounds as incremental innovation.

In economic terms, incremental pharmaceutical innovation is a form of sequential innovation within a cumulative research process. Early inventions generate follow-on opportunities, but they also create a problem of how to split rewards between pioneers and improvers. Patent scope matters because it affects whether an improvement infringes and therefore whether licensing is required and on what terms. In this setting, licensing and bargaining shape how returns are divided and thus whether follow-on improvements are privately attractive to develop. These issues are central in analyses of cumulative innovation and sequential patenting (Scotchmer, 1991; Green and Scotchmer, 1995).

In practice, most NDA each year do not correspond to novel drugs but to incremental developments. Regulatory data from the U.S. FDA illustrate this pattern, though they do not represent the global market. Between 2000 and 2022, only about 31% of NDAs by the U.S. FDA were NMEs, fluctuating between 22% and 41% annually (FDA 2022). The remaining approvals consisted of other FDA categories.[3]

Radical pharmaceutical innovations are widely acknowledged to have outsized potential to address unmet medical needs and can dramatically improve health outcomes, firm performance, and societal welfare (e.g., Vernon 2005; Lo & Thakor, 2022; Frech et al 2023; Frankel et al., 2024). By contrast, the welfare implications of incremental innovation are more nuanced.

Empirical evidence shows that incremental innovation can generate meaningful welfare gains through several channels. Entry of follow-on and "me-too" drugs can improve patient-treatment matching, expand choice, and intensify competition within therapeutic classes, thereby reducing prices and increasing consumer surplus (Bokhari & Fournier, 2013; Arcidiacono et al., 2013). At the same time, Arcidiacono et al. (2013) show that me-too entry can raise insurer spending in some settings, reflecting limited price sensitivity and reimbursement design. These effects become particularly salient when incremental innovation is rewarded through market exclusivity. Yin (2023) finds that, in the Selective Serotonin Reuptake Inhibitors market, welfare losses associated with exclusivity extensions for incremental innovations can exceed their benefits. Taken together, these findings indicate that welfare outcomes depend critically on institutional and market conditions.

As mentioned, novel drugs possess clear transformative potential, but their discovery and development involve high costs, significant risk, and long timelines. Consequently, a large body of literature examines the underlying costs and success probabilities of radical

[3] Like "New Uses of Approved Drugs" which are new treatments, modifications or expansions of use, Approved Drugs Expanding for New Pediatric Populations, etc.

innovation. Numerous studies have documented these parameters across therapeutic areas and development stages (e.g., Schuhmacher et al., 2016; DiMasi et al., 2016; Wong et al., 2019; Wouters et al., 2020; Lo & Thakor, 2022; Sertkaya et al., 2024). Estimates place the capitalized cost of developing a new drug between 1 and 3 billion USD (DiMasi et al., 2016; Wouters et al., 2020; Sertkaya et al., 2014), while the probability of success remains low, typically between 7% and 20% of candidates entering Phase I clinical trials achieve approval (e.g., Schuhmacher et al., 2016; Wong et al., 2019; EFPIA, 2025; IQVIA, 2025).

By contrast, many incremental innovations are modifications of known drugs and thus can leverage existing data and experience, often requiring fewer resources. Light (2007) observed that such incremental projects have lower R&D cost than novel drugs, roughly one-quarter the cost on average, because much of the groundwork (basic mechanism, safety profile, etc.) is already laid by the predecessor. Incremental projects may also face a smoother regulatory path: while they must still satisfy safety and efficacy standards, some incremental drug approvals can rely on abbreviated clinical trial requirements. For example, a new formulation or a new indication for an approved drug might not require full Phase I–III trials if sufficient data are available or may only need focused comparative studies. In all cases, however, incremental innovations do undergo rigorous regulatory scrutiny, and many follow-on drugs (especially new usage expansions) still demand substantial clinical testing.

Beyond differences in cost and duration, radical and incremental innovations also diverge in their risk structure. Incremental projects benefit from prior scientific knowledge and established therapeutic pathways, reducing both technical and market uncertainty. As Frankel et al. (2024) note “Firms are better able to evaluate the likelihood of success of incremental drugs because they are related to ideas that have previously been investigated, enabling them to screen out weak candidates.” This results in a higher probability of technical success and a more predictable development process. Other studies similarly indicate that incremental drug R&D carries reduced technical and market risk (e.g., Yin 2023), as these projects build on validated mechanisms and existing demand.

In our analysis, we consider incremental innovation projects that proceed through the full set of clinical trial phases (I–III) as the reference case. However, the valuation framework developed in this paper can be readily adapted to products following abbreviated or modified clinical pathways, ensuring analytical consistency across different regulatory scenarios.

3.2. Incremental innovation as a rational strategic choice

From the firm’s perspective, incremental innovation can be an equilibrium response to uncertainty and financing frictions. Incremental projects are easier to evaluate. They

provide clearer signals and enable faster learning. This raises effective information precision and supports internal capital allocation.

According to Frankel et al. (2023), the dominance of incremental innovation arises from differences in information precision. Incremental projects provide clearer signals of success and enable faster learning, whereas radical R&D is harder to evaluate and generates diffuse knowledge spillovers that firms cannot fully appropriate. This search for internal efficiency comes at the expense of the broader learning externalities produced by radical projects, leading to systematic underinvestment in exploratory research.

Complementarily, incremental innovation is reinforced by the accumulation of tacit knowledge and organizational learning over time. Okuyama (2017) highlights that tacit expertise, embodied in routines, interpersonal communication, and experiential know-how, acts as a critical driver of continuous refinement, allowing firms to reproduce and gradually enhance successful practices. Johnson (2020), in her literature review, further shows that dynamic capabilities, such as learning orientation and knowledge sharing within teams, strengthen coordination and behavioral consistency, thereby institutionalizing improvement cycles. This learning path is consistent with cumulative innovation models discussed above.

Financial and regulatory frictions intensify this bias. Because knowledge assets are non-collateralizable, external investors impose high capital costs on uncertain projects (Lo & Thakor, 2023). Incremental innovations, being more predictable, attract financing more easily. Caggese (2019) formalizes this behavior: under tight financial constraints, firms rationally pursue safer incremental paths, producing the "missing novelty" pattern observed across the industry.

The cumulative nature of innovation creates a well-known policy challenge. Patent systems must balance incentives between pioneering breakthroughs and subsequent improvements. The Hatch–Waxman Act (1984) represents a key policy effort to calibrate this balance by rewarding innovation while enabling timely generic entry. In practice, this framework and related regulatory incentives have strongly shaped firms' innovation strategies. Hemphill and Sampat (2012) show that secondary patenting and generic patent challenges jointly determine the effective duration of market exclusivity. Patent challenges are concentrated on later-expiring and lower-quality patents, which limits the ability of weak follow-on patents to extend exclusivity.

Together, these mechanisms, evaluation efficiency, knowledge accumulation, financial selectivity and policy frameworks, make incremental innovation a rational equilibrium outcome shaped by risk management rather than technological stagnation.

In a related stream, the literature shows that firm size mediates both regulatory and financial vulnerability. Large firms can withstand shocks but tend toward incremental

innovation; small firms drive novelty yet remain financially fragile. This asymmetry shapes the equilibrium structure of the pharmaceutical R&D ecosystem.

Large firms benefit from economies of scale and scope, as their extensive resources, expertise, and infrastructure can enhance development efficiency and allow them to absorb failures better, supporting radical experimentation (e.g., Schuhmacher et al., 2021; Krieger et al., 2022b). However, other studies identify diseconomies of scale: different stakeholders, bureaucracy and complexity in large organizations often raise costs and lower returns. Adams and Brantner (2006) show that larger firms do not necessarily achieve lower R&D costs; in some cases, their per-drug expenditures exceed the industry average. Similarly, Mestre-Ferrandiz et al. (2012) find that results on scale effects are inconclusive, with efficiency gains often offset by higher coordination costs and longer development timelines. Schuhmacher et al. (2021) further show that large pharma firms sustain R&D output through partnerships and portfolio management, whereas smaller firms achieve higher innovation efficiency in early-stage discovery.

According to Okuyama (2024), incremental innovation has become the dominant R&D mode of medium and large pharmaceutical companies, whereas small and medium-sized enterprises (SMEs) increasingly act as originators of radical discoveries, often partnering with or being acquired by larger companies.

Regulatory and financial constraints reinforce these structural differences. The already mentioned studies by Vernon (2005), Golec & Vernon (2010), and Shaikh et al. (2021) show that tighter price regulation and policy uncertainty erode cash flow and profitability, thereby lowering R&D investment, especially among smaller firms with limited internal buffers. Lo and Thakor (2022) further demonstrate that regulatory uncertainty raises discount rates and widens the funding gap, disproportionately constraining early-stage innovators.

Empirical estimates of market-size elasticity (Dubois et al., 2015; Philipson and Durie, 2021) confirm this heterogeneity: a 1% decline in revenue corresponds to roughly a 1.5% reduction in R&D investment, indicating that policy-induced shocks propagate unevenly across firms. Large pharmaceutical companies can absorb such shocks through diversification and financial reserves, whereas smaller firms, constrained by financing capacity, move toward short-cycle R&D.

Agha et al. (2022) add a new dimension providing evidence that insurance and reimbursement designs act as an additional constraint, filtering which incremental projects remain viable. They find that exposure to restrictive pharmacy benefit manager formularies significantly reduced new drug development. A one standard-deviation increase in formulary exclusion risk lowered subsequent development activity by roughly 11%, with the largest contraction in therapeutic classes characterized by many existing products and older, less novel science.

Ultimately, the coexistence of incremental and radical innovation describes and defines the equilibrium of the pharmaceutical industry. Incremental innovation sustains continuous improvement and economic stability, while radical innovation drives transformative advances. As Krieger et al. (2022a) emphasize, this configuration represents not stagnation, but an endogenous equilibrium shaped by firms' responses to systemic risk and capital constraints.

4. Real options and Pharma R&D projects

In the pharmaceutical industry, where uncertainty is high and investment horizons are long, Real Options Valuation (ROV) methods have proven effective by explicitly valuing managerial flexibility. They account for the options to delay, abandon, expand, or adapt projects as new information becomes available. By aligning with the sequential and uncertain nature of pharmaceutical R&D, where each phase can be understood as an embedded option whose exercise depends on intermediate results, ROV provides a superior decision framework compared with conventional net present value (NPV) methods.

Real option analysis builds on option pricing theory from financial economics. Its use in pharmaceutical settings expanded in the late 1990s and early 2000s. Early studies, such as Kellogg and Charnes (2000), Rogers et al. (2002), and Schwartz (2004), showed how R&D can be treated as a sequence of contingent decisions rather than an irreversible commitment.

Several advantages have been emphasized in the literature. By capturing the value of choices such as delaying, expanding, or abandoning projects, ROV protects the downside and quantifies the benefit of managerial flexibility (Cassimon et al 2004; Hartmann & Hassan, 2006). Real options models mirror the stage-by-stage process of drug development. Each phase, discovery, Phases I–III, and regulatory approval, constitutes an option to be exercised if results are favorable or abandoned if not. Cassimon et al. (2004) modeled drug development as a six-fold compound option, demonstrating how each successive decision point adds incremental value when treated as an option. This multi-stage perspective yields realistic valuations for long-term R&D projects exposed to binary outcomes at each stage. Cassimon et al. (2011) extend this compound option approach by separating technical risk from commercial uncertainty, and they document the method in a real-life licensing case study.

Additionally, by capturing upside potential, ROV can validate projects that NPV would reject. This is especially relevant when payoffs are highly skewed and a small probability of blockbuster (sales above 1 billion USD) exists (Rogers et al., 2002; Kellogg & Charnes 2000).

Beyond valuation, an important aspect is that ROV improves understanding of the underlying decision process (Kellogg and Charnes, 2000). It provides a common language and a quantitative framework for communicating the value of R&D projects to stakeholders. The approach reveals value of future opportunities, helping managers assess investments as well as learning and spillover effects. In M&A and licensing contexts, ROV supports negotiations by valuing upside potential, such as new indications or expansion options. In licensing contracts, milestone payments and sales lifecycle assumptions can materially affect how flexibility value is shared (Hoe and Diltz, 2012).

Recent research refines ROV to better match pharmaceutical R&D realities. For example, D'Amico and Villani (2021) allow for dependent success probabilities and random development-stage durations.

Despite support in academic literature, adoption in pharmaceutical firms remains limited. Hartmann and Hassan's (2006) survey identified analytical complexity, data limitations (especially the estimation of project volatility), and organizational resistance as key barriers. Notably, the study emphasized that determining the appropriate volatility for an R&D project is a major challenge, as such projects lack observable market prices. Along the same lines, Cassimon et al. (2011) also emphasize perceived complexity and the lack of well-documented "role model" case studies as impediments to wider use. We contribute to filling this gap by providing a transparent, fully documented application of LSM to regulatory risk.

The literature also offers many ROV implementations, including decision trees, binomial lattices, closed-form compound options, and simulation-based methods. While these models allow more realistic estimates of project value, their diversity complicates direct comparisons and limits the emergence of a consensus approach for practical adoption.

In this paper we use the LSM method developed in the seminal contribution of Longstaff and Schwartz (2001), widely applied across industries beyond pharmaceuticals. LSM has been applied to pharmaceutical contexts, including licensing valuation (Schwartz, 2004; Hoe and Diltz, 2012). LSM allows the valuation of American-style and real options with early-exercise features by regressing simulated continuation values on a set of explanatory functions (also called basis polynomials or approximation functions), which approximate the conditional expectation of future payoffs. This procedure efficiently identifies early optimal exercise policies along simulated stochastic paths. LSM handles multiple and correlated uncertainties and scales well to high-dimensional problems. It is therefore well suited to R&D pipelines with sequential options such as abandonment, deferral, and expansion (Schwartz, 2004; Hoe and Diltz, 2012).

Willigers and Hansen (2008) note that LSM use in pharmaceutical practice has been limited, but they also show that it can outperform expected NPV and binomial approaches in realistic settings. Drawing on Hartmann and Hassan (2006), they attribute this partly

to an incomplete understanding of both ROV concepts and the shortcomings of traditional NPV methods. Through applied examples and comparisons, Willinger and Hansen (2008) demonstrate that LSM offers a realistic, flexible, and computationally tractable framework for valuing pharmaceutical R&D projects. The method surpasses both expected NPV and binomial ROV models by modeling multiple correlated sources of uncertainty, capturing path-dependent managerial decisions, and operating under a coherent risk-neutral valuation framework. The modular structure of LSM further enables integration into existing corporate valuation systems, making it a practical step forward for resource allocation and capital budgeting in drug development.

In this paper, we follow Schwartz (2004) and model pharmaceutical R&D using stochastic state variables. The project is structured across three development phases. After development, the product enters a commercialization stage following regulatory approval. The model incorporates a probability of failure following a Poisson process. The LSM framework allows us to clearly assess the impact of two regulatory events, which are introduced probabilistically into the model.

5. The model

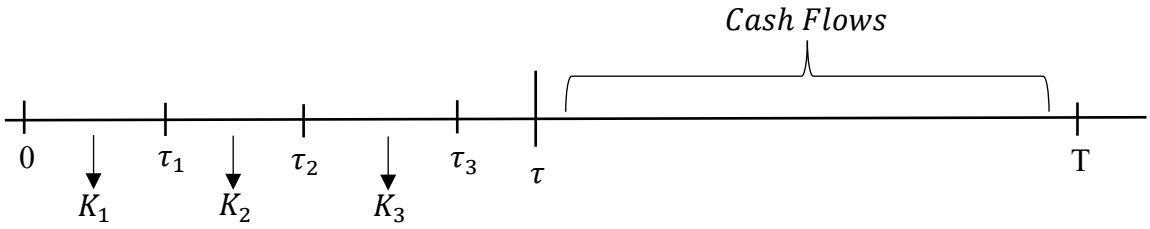
The pharmaceutical R&D process must go through several stages to bring to market a new drug: discovery research, preclinical testing in animals, and clinical testing in humans in three phases. Phase I for safety, Phase II for efficacy for a given indication, Phase III for efficacy for larger populations and against alternatives. Interested readers are referred to Wong et al. (2019), Lo and Thakor (2022) for further details of the full process a firm must go through to successfully develop a new drug.

Finally, subsequently to these R&D stages, the new product must receive the corresponding agencies' approvals in order to be marketed and distributed. During the process of developing a new drug, companies work closely with the national agencies. For example, the FDA interferes right after the preclinical tests, where the FDA's Center for Drug Evaluation and Research (CDER) determines if the new drug is suitable for use in clinical trials with humans, then receives annual reports, and the project is specially discussed before entering phase III (Gassmann et al 2018). Similar processes are followed in different jurisdictions. This close supervision minimizes the risk of failing to obtain the corresponding final approval by the national agency, although the approval process still experiences uncertainties, such as review time delays or approval/rejection decisions, affecting market entry, etc. (Gassmann et al 2018; Chorniy et al 2019). The vast majority of R&D projects fail for reasons related to safety, efficacy, or commercial viability.

In our model we consider the discovery and preclinical phases to belong to the general R&D business model of a pharma company, and therefore we do not include them in the valuation of a particular project. Thus, we focus on the clinical phases, and we study a

drug development program which is the investigation of a particular drug for a single indication. We start at time 0, when the patent is granted and the company decides to start the formal phases of the clinical trials in humans.

We model the R&D stage, when investments are made, as a three-stage sequential process. The timeline of the pharmaceutical project, including the investment and the production stages, is as follows:



Where, $\tau_1$is the end of phase I, and τ_2 and τ_3 are the end of phase II and phase III respectively. The investment stage ends in τ_3, and the production stage starts at τ. The time difference $\tau - \tau_3$ is the time passed of regulatory approval when the company is working on the compliance process but is not investing in R&D. Therefore, the company is paying the R&D costs, only during the investment stage up to time τ_3. To start investing in phase II and III trials, the results of the research in previous phases must have been successful, and the corresponding time τ_1, τ_2 or τ_3 is reached. If the project is completed the company will receive the net cash flow, C, during production time. The cash flows considered in this model and its estimations are all net of the monetary outflows derived from the project under analysis over the given period. The final moment T is fixed at time τ and corresponds to the moment the patent or the market exclusivity period end. After T there are no cash flows corresponding to this drug, since generics at lower price enter the market.[4]

Based on this framework, we build a stochastic model of the process, considering the expected costs to completion and the expected cash flows during production as random variables that follow stochastic processes described below, as well as the time to complete each phase. The regulatory approval time is assumed to be fixed at the median time previous studies document, but random time of approval could be easily incorporated into the analysis.

5.1. Investment Cost Uncertainty

The expected costs to completion K_1, K_2, K_3 are assumed to follow different dynamics in each phase of the R&D project. We follow Pindyck's (1993) investment of uncertain cost

[4] A residual value could be easily incorporated in the analysis

framework by treating the remaining R&D cost as a stochastic process. Ongoing investment drives the cost-to-complete downward, while random shocks make it fluctuate:

$$
\begin{aligned}
Phase\ I &\begin{cases} dK_1 = -I_1 dt + \sigma_1 (I_1 K_1)^{\frac{1}{2}} dz_1 \\ dK_2 = \sigma_2 (I_2 K_2)^{\frac{1}{2}} dz_2 \\ dK_3 = \sigma_3 (I_3 K_3)^{\frac{1}{2}} dz_3 \end{cases} \\
Phase\ II &\begin{cases} dK_2 = -I_2 dt + \sigma_2 (I_2 K_2)^{\frac{1}{2}} dz_2 \\ dK_3 = \sigma_3 (I_3 K_3)^{\frac{1}{2}} dz_3 \end{cases} \\
Phase\ III &\begin{cases} dK_3 = -I_3 dt + \sigma_3 (I_3 K_3)^{\frac{1}{2}} dz_3 \end{cases}
\end{aligned} \tag{1}
$$

Where I_1, I_2, I_3 are the rates of investment of the cost processes, and $\sigma_1, \sigma_2, \sigma_3$ are dimensionless parameters capturing the relative magnitude of the diffusion term in each phase. $dz_{1,} dz_{2,} dz_3$ are standard Brownian motions uncorrelated with the market portfolio.[5] Note that investment occurs only in the corresponding phase, but uncertainty affects all current and subsequent phases.

The formulation considers that the expected costs of one phase are only being reduced when the corresponding phase is active. The evolution of the costs through time is the key determinant of the changes of phases and the three relevant timepoints during the process. Phase I transitions to phase II at τ_1, which is defined as the instant where $K_1(t)$ reaches zero, i.e., $K_1(\tau_1) = 0$. Phase II transitions to phase III at τ_2, which is defined as the instant where $K_2(t)$ reaches zero, i.e., $K_2(\tau_2) = 0$. Finally, the investment stage is completed when $K_3(t)$ reaches zero, i.e., $K_3(\tau_3) = 0$. Consistent with Pindyck (1993), each development phase ends when its remaining cost is fully expended. Phase durations are therefore endogenously determined and stochastic, with an expected length equal to $\frac{K_i(0)}{I_i},\ i \in \{1,2,3\}$.

Under this specification, the link between the variance of the cost to completion, and the scaled volatility parameter is given by equation (2) which can be used to infer values for this volatility parameter:

$$
Var\left(\widetilde{K}_i\right) = \frac{\sigma_i^2 K_i^2}{2 - \sigma_i^2}\ for\ i \in \{1,2,3\} \tag{2}
$$

[5] Cost uncertainty does not have a risk premium associated to it, since they are assumed to be uncorrelated with the market. Correlated shocks to the investments could easily be incorporated into the analysis.

The σ_i^2 parameters, bounded between 0 and $\sqrt{2}$, provide a relative measure of volatility that incorporates the heteroscedastic structure of the multiplicative model.

To take into account that many projects fail during the investment phase, we assume a Poisson probability λ_1 per unit of time that the project will be abandoned due to technical failure, competitor entry, catastrophic events etc., all other causes different than market failure. If the event related to λ_1 occurs, the project is stopped, its value will jump to zero, and investments made to that moment become a loss.

5.2. Cash flow uncertainty

Cash flow follows a stochastic process, which during the investment period (from 0 to τ) is assumed to follow the following geometric Brownian motion:

$$\frac{dC}{C} = \alpha_I dt + \emptyset d\omega \tag{3}$$

where $d\omega$ is an increment to a Gaussian Wiener process which is uncorrelated with the uncertainty in the expected costs to completion. The drift, α_I, in the cash flow reflects the average return (rate of growth) expected, during the investment stage, to be obtained from the particular project under analysis. This cash flow changes as more information are obtained through investment and through an increased knowledge of the market for the product.

Since future cash flows are derived from revenues contingent on market performance, they are exposed to systematic risk and therefore command a risk premium, consistent with standard asset pricing theory. Therefore, for valuation purposes we use the risk-adjusted process

$$\frac{dC}{C} = \alpha_I^* dt + \emptyset d\omega \tag{4}$$

where $\alpha_I^* = \alpha_I - \eta$, is the risk-adjusted drift, and η the risk premium associated with the cash flow process.

Once the company starts the production stage, the dynamics of the cash flow start to grow. At the production stage (from $\tau \; to \; T$) cash flows are assumed to follow the following stochastic process, similar to equation (3) but with different drift.

$$\frac{dC}{C} = \alpha_p dt + \emptyset d\omega \tag{5}$$

The drift $\alpha_p$now incorporates the market entry dynamics, reflected in a higher growth rate than that used during the investment stage, to capture the fact that sales initially start small (C is the cash flow to be received the first year of production) but grow over time until reaching the potential commercial value of the new drug, as determined by the market size S.

At this stage, the risk-adjusted process becomes:

$$\frac{dC}{C} = \alpha_p^* dt + \emptyset d\omega \tag{6}$$

where $\alpha_p^* = \alpha_p - \eta$, is the risk-adjusted drift and being η the said risk premium.

Assuming that the Intertemporal Capital Asset Pricing model of Merton (1973) holds, the risk premium is equal to the beta of the successful project, β, times the market risk premium $(r_m - r)$. We use equation 7 for its estimation:

$$\eta = \beta(r_m - r) \tag{7}$$

5.3.Value once the investment has been completed

As explained, during the production period the initial cash flow will be growing at a growth rate higher than the risk-free rate until it reaches its potential market size S at T. Empirical evidence shows that most chronic-use small molecule drugs, such as oral agents for cardiovascular or neurological conditions, tend to reach peak sales between years 7 and 12 of their patent life, approaching the expiration of market exclusivity (Dubois et al 2015).

This value is assumed to be reached at time T (the final year of the patent or the exclusivity period, $C(T) = S$), after which the residual value is assumed to be zero.

Standard arguments and derivations (i.e., can be consulted in Schwartz 2004) lead us to the following solution for the present value of the cash flows at time τ, $V(C, \tau)$:

$$V(C, \tau) = \frac{C}{\alpha_p^* - r}\left[e^{(\alpha_p^* - r)(T-\tau)} - 1\right] \tag{8}$$

where $\alpha_p^* > r$

Then, to account for the time of the regulatory approval, the value at time τ_3 is obtained by discounting the value at time τ at the risk-free rate:

$$V(C, \tau_3) = V(C, \tau)e^{-r(\tau - \tau_3)} \tag{9}$$

The value $V(C, \tau)$represents the present value of the cash flows at time τ up to time T. Once the investment has been completed, this value, interestingly, no longer depends on volatility and is linear in the cash flows. This contrasts with the investment period, during which uncertainty is at its maximum and we need to take into account the volatilities of the investment processes to value the project.

5.4.Value with regulatory event once the investment has been completed

We introduce in the model the probability of a regulatory event occurring during the production stage. According to the literature reviewed in the regulatory framework

section, two types of regulatory events stand out as significantly modifying the project outcomes.

1) Patent or market exclusivity time reduction: Event I that decreases the life of the patent/exclusivity period to time T* with probability $\lambda_{2,T*}$. If the protected time is reduced from T to T*, the value of the project at τ will be:

$$V(C,\tau) = \frac{C}{\alpha_p^* - r}\left[e^{(\alpha_p^* - r)(T^* - \tau)} - 1\right] \quad (10)$$

Equation (10) is similar to equation (8), except that the final time is modified to T*.

2) Price-control event whether direct price-control or reference price-control: Event II that decreases the amount of the cash flow to a fraction φ of C with probability $\lambda_{2,C*}$. The new cash flow will be $C^* = \varphi C$, and the value of the project at τ will be:

$$V(C,\tau) = \frac{C^*}{\alpha_p^* - r}\left[e^{(\alpha_p^* - r)(T - \tau)} - 1\right] \quad (11)$$

In this case, Equation (11) is similar to equation (8), except that the cash flow is modified to C^*.

In all scenarios, to account for the approval period, we obtain $V(C,\tau_3)$ by discounting $V(C,\tau)$ from τ to τ_3 at the risk-free rate before estimating the project's value during the trials phases.

5.5.Valuation procedure: Least Squares Monte Carlo (LSM) approach

To solve this problem and to obtain the valuation of the investment at the initial time, we use the LSM method developed by Longstaff and Schwartz (2001). The method first consists of performing a large number of simulations for all the relevant random variables in the problem. Once the main variables are simulated, the procedure consists in obtaining the value of the project for each simulation considering the realized events on that path. Finally, the estimated value of the project at the starting time is obtained by averaging the different results for each path.

The relevance of the real options approach is that, for each path, the company is allowed to discontinue the investment on the project when the expected value is less than the investment needed to continue the process.

For each simulated path, the value of the project at any given time t and phase i, is defined as $F(t)$=$F_i(\cdot\,,t)$, which depends on the state variables affecting each phase and the following boundary conditions imposed:

- At time $t = 0$, $F(0) = F_1(K_1, K_2, K_3, C, 0)$.
- In stage 1: $F(t) = F_1(K_1, K_2, K_3\,, C, t)$
- At the transition from phase 1 to phase 2:

$$F(\tau_1) = F_1(0, K_2, K_3, C, \tau_1) = F_2(K_2, K_3, C, \tau_1)$$

- In phase 2: $F(t) = F_2(K_2, K_3, C, t)$
- At the transition from phase 2 to phase 3:

$$F(\tau_2) = F_2(0, K_3, C, \tau_2) = F_3(K_3, C, \tau_2)$$

- In phase 3: $F(t) = F_3(K_3, C, t)$
- At the conclusion of phase 3: $F(\tau_3) = F_3(0, C, \tau_3) = V(C, \tau_3)$.

The preceding framework ensures continuity between the phases.

Starting from the end of the simulated path (time τ_3), the value of the project $F(\tau_3)$ is set to $V(C, \tau_3)$.

Then, the simulation moves backward in time to obtain the estimated value of the project $F(t)$ before termination by discounting back the values and considering the costs incurred at each time step $Ii{\cdot}d$t. To obtain the continuation value at intermediate points, the LSM approach (Longstaff and Schwartz 2001) is applied, which consists of the following:

1. For each simulation path j, the realized value $F_j(t + dt)$ is known and recorded along with the corresponding state variables $K_{1j}(t), K_{2j}(t), K_{3j}(t), C_j(t)$.
2. Then, the expected continuation value at t is approximated as a function of state variables using a polynomial regression:

$$\hat{F}_j(t) = \sum_k \beta_k \phi_k\big(K_1(t), K_2(t), K_3(t), V(t), S(t)\big)$$

   where ϕ_k are basis functions and β_k are the regression coefficients. These coefficients are estimated by regressing the future project values $F_j(t + dt)$ discounted to the time instant t, i.e. $F_j\,(t + dt) \cdot e^{-r \cdot dt}$ against the state variables at time t. Then, the expected continuation value $\hat{F}_j(t)$ is obtained by evaluating the fitted value of the polynomial regression.
3. At this moment, the abandonment condition is verified for each path. Throughout the process, the abandonment policy is the one that maximizes the value of the project, therefore, abandonment occurs when $\hat{F}_j(t) < I_i \cdot dt$, as the expected value of the project is less than the investment needed to be made for continuing. If abandoned, the value is then set to zero, $F_j(t) = 0$.
4. If abandonment is not executed, then, the value of the project is obtained as the expected continuation value subtracting the investment for the next step: $F_j(t) = \hat{F}_j(t) - I_i \cdot dt$.
5. Finally, the possibility of a catastrophic event is evaluated. With probability λ_1 the value of path is updated as $F_j(t) = 0$.

This process begins at time τ_3 and goes back in time to $t = 0$, hence, obtaining for each simulation path the value of the project under uncertainty including optimal abandonment if necessary.

Finally, the final value of the project at time zero for simulation j, F_j^0, is calculated by beginning at time zero and progressing forward along each path until time t^*, which is whether a catastrophic event occurs, or abandonment decision is taken, whichever occurs first. The resulting value at this time $F_j(t^*)$ is then discounted back to time zero subtracting the costs incurred until reaching t^*, also discounted back to time zero. If the optimal stopping time is at time zero, the project's value is zero. It is important to note that this calculated project value F_j^0 typically differs from the value $F_j(0)$, as only the optimal stopping times determined by the algorithm are considered, rather than the expected values.

The final value of the project at time 0 is obtained by averaging these F_j^0 values across all *N* paths taken:

$$F_0 = \frac{\sum_j^N F_j^0}{N} \tag{12}$$

This framework provides a robust way to analyze the present value of the R&D project, integrating the uncertainty of outcomes, the stochastic nature of costs, and the strategic decisions faced by stakeholders.

6. Parameters selection and estimation results

6.1. Parameters selection

We use as an illustrative base case an incremental innovation in a drug targeting the CNS, which serves as our representative example of non-oncology programs. Estimating parameters for this type of innovation is challenging for two reasons. First, most research on pharmaceutical R&D costs focuses on NMEs and first-in-class products, making comparable estimates for incremental innovations scarce. Second, incremental innovation encompasses a heterogeneous range of developments which complicates cost generalization. Model calibration relies on parameter estimates derived from previous empirical studies. It is complemented by expert consultations with industry executives and with the R&D department at Laboratorios Farmacéuticos ROVI (developer of OKEDI).[6] These consultations were used to validate plausible parameter ranges and to interpret the simulation outputs.

As noted by Wouters and Kesselheim (2024), quantifying the cost of new drug development remains a central concern for industry, policymakers, and scholars, as it

[6] https://www.rovi.es/en; Okedi is a medicine used to treat schizophrenia in adults: https://www.ema.europa.eu/en/medicines/human/EPAR/okedi

directly affects price negotiations, incentive design, and assessment of the investment required to achieve clinically meaningful advances. However, substantial heterogeneity persists in reported R&D expenditure data (Lo and Thakor 2022).

The benchmark study by DiMasi et al. (2016) reports that, in 2013 USD (adjusted to 2023 USD for comparability), total R&D costs per approved drug range from USD 1.3 billion to 3.4 billion. Wouters et al. (2020) estimate, specifically for CNS drugs, mean costs of USD 765.9 million (range USD 323 - 1473.5 million). Both analyses include expenditures on failed trials and the expected return to investors. More recent estimates by Sertkaya et al. (2024) report, for CNS drugs, mean expected costs (including the cost of failure) of USD 463.7 million (range USD 302.5 - 714.3 million) and USD 894.6 million (USD 526.1 - 1550.3 million) when capitalized. However, these studies, like most of those reviewed by Schlander et al (2021) focus primarily on novel chemical or biological compounds representing first-time approvals, rather than incremental or follow-on innovations.

Light (2007) provides an important correction to the general interpretation of the figures on costs, emphasizing that "most new drug products have much lower R&D costs than NMEs because they are incremental improvements on existing drugs… Their average direct cost may be only about one-fourth that of an NME." Hence, incremental innovations can be associated with 25% of the development cost of radical innovations. Consistent with this, we assign our benchmark case an estimated cost of approximately USD 160-170 million.

Following Sertkaya et al. (2024), we allocate R&D expenditures across clinical phases I, II and III as 8.6%, 19.4%, and 72%, respectively, consistent, also, with EFPIA (2025) figures.

We infer cost volatility from the ranges reported in previous studies for CNS development, obtaining standard deviations equivalent to 46%–37% of mean costs (including capitalized values) and 27% for non-capitalized figures. Since Phase II typically exhibits higher uncertainty due to higher attrition rates (e.g., Wong et al 2019; Sertkaya, 2024), and incremental innovation entails lower technological and regulatory risk than radical innovation, we adjust volatility downward to 25% for Phases I and III and 30% for Phase II.

We set the expected median durations for each clinical phase based on the evidence available in the literature. Wong et al. (2019) report median values of 1.6 years (Phase I), 2.9 years (Phase II), and 3.8 years (Phase III) across all therapeutic areas. When isolating CNS programs, these shorten to 0.92, 2.55, and 2.83 years, respectively. However, Schlander et al. (2021) find that CNS projects often exhibit longer development timelines than other therapeutic areas, with durations of up to 9.6 years reported in the literature

they review. All cited studies report median durations, reflecting that the distribution of development time is positively skewed and leptokurtic.

To calibrate success probabilities, we adopt the comprehensive estimates of Wong et al. (2019). In their sample, CNS programs represent about 15% of all industry-sponsored trials, making CNS the largest non-oncology therapeutic category after infectious and metabolic diseases. While challenging in terms of efficacy and patient heterogeneity, CNS development faces lower attrition risk than oncology programs and can be characterized as moderate risk within the non-oncology domain. Wong et al. (2019) report an overall POS of 19.3% from Phase I to approval for CNS drugs, the lowest among non-oncology areas, where success rates range between 20% and 25%. Wouters et al. (2020) estimate a POS of 15%, and Sertkaya et al. (2024) report 11.4% based on BERD (Business Enterprise Research and Development, OECD metric) survey data. In our illustration, we adopt 40% as a representative median estimate for incremental innovation, acknowledging its lower risk compared to radical innovation.[7] This probability of success takes into account both, λ_1 the failure probability, and the abandonment rate due to expected costs exceeding projected cash flows.

The valuation also accounts for an average regulatory-approval lag of 18 months, consistent with Gassmann et al. (2018), Wong et al. (2019), and Chorniy et al. (2021). Against the benchmark valuation, the two regulatory-event scenarios are analyzed:

- Event I. Reduction of patent or exclusivity term, modeled as a two-year reduction, consistent with the potential effects of the IRA 2022. Such changes have been very rare in the pharmaceutical industry's historical record (and hence in the literature). We therefore assign a 10% probability to this event. Ongoing political discussions, including the Trump administration's review of the IRA and related investigations, provide relevance for this assumption.
- Event II. Price-control scenario, modeled as a reduction in net revenues (cash flows) due to government negotiation or statutory limits like fixed ceilings, reference pricing, negotiated price caps, etc.

  Philipson and Durie (2021), analyzing the Biden Administration's proposed H.R. 3 bill, find a substantial impact of price controls on revenues. They estimate a decline of 19–39%, drawing on Stengel et al. (2020), who project potential reductions extending to 34–44%. Although H.R. 3 was not enacted in its original form, its key provisions later informed the IRA 2022.

  Previous literature (e.g., Vernon 2005; Sood et al. 2009; Golec and Vernon 2010; Ji and Rogers 2024) reports comparable results when contrasting price-regulated

[7] This calibration choice is also consistent with qualitative practitioner discussions with senior industry R&D leaders, at Laboratorios Farmacéuticos ROVI, who emphasized the lower attrition profile of follow-on CNS programs relative to first-in-class CNS NMEs.

European markets with the largely unregulated U.S. system, with estimated revenue declines ranging between 18% and 44%, depending on policy design, market exposure, and enforcement scope. The consensus range across these studies suggests an average 20–35% contraction in revenues following the introduction of direct price controls. We consider here a 25% reduction in cash flow.

Given that drug pricing regulation has become a key concern for pharmaceutical executives, with 47% of C-suite leaders identifying pricing as the industry's most critical issue (Deloitte 2025), and considering the increasing policy uncertainty generated by ongoing legislative and executive interventions (Lazard 2025; Michielssens 2025; Carnegie et al. 2025), we assign a 30% probability to this event.

To estimate the risk premium, we compute the average beta relative to the corresponding national benchmark indices for the 50 world's leading pharmaceutical companies, excluding firms that are not publicly listed. The resulting mean beta of 0.56 confirms that the pharmaceutical sector exhibits a defensive profile.[8] With a market risk premium of 5%, the resulting η obtained from equation 7 is 2.8%. This risk premium is consistent with prior valuation models for pharmaceutical R&D such as Schwartz (2004).

The initial expected cash flow is set to 20 Million USD.

All parameters used are summarized in Table 2.

[8] Among the estimated betas we find very low values such as Takeda Pharmaceutical (0.06) and Eisai (0.07) and high values for UCB (2.09) and Moderna (1.18). Clearly, beta estimates based on pure-play firms focused on a single drug would be more accurate estimates.

Table 2: Parameters used for the simulation of the benchmark case and the two regulatory events. The investment cost adds to 160 M USD.

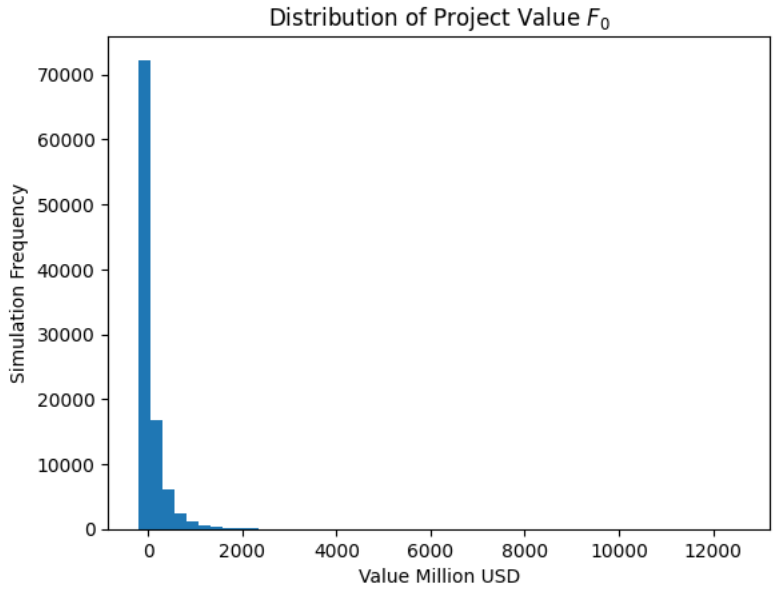
Costs		
Initial expected total costs in phase I [Million USD]	K_1	13.76
Initial expected total costs in phase II [Million USD]	K_2	31.04
Initial expected total costs in phase III [Million USD]	K_3	115.2
Rates of cost per year in phase I [Million USD]	I_1	8.6
Rates of cost per year in phase II [Million USD]	I_2	10.7
Rates of cost per year in phase III [Million USD]	I_3	30.3
Annual volatility of the Cost to completion in phase I	$\sigma(\widetilde{K}_1)$	25%
Annual volatility of the Cost to completion in phase II	$\sigma(\widetilde{K}_2)$	30%
Annual volatility of the Cost to completion in phase III	$\sigma(\widetilde{K}_3)$	25%
Annual Volatility of costs in phase I	σ_1	27%
Annual Volatility of costs in phase II	σ_2	25%
Annual Volatility of costs in phase III	σ_3	18%
Regulatory Agency Approval Time (years)	$\tau - \tau_3$	1.5
Poisson probability of failure event at investment stage (monthly)	λ_1	0.81%
Risk-free rate: long term, annual	r	3%
Time from approval to end of patent protection (years)	$T - \tau$	10
Value of the Cash Flow		
Initial Expected Cash Flow (annual in Million USD)	C	20
Risk-neutral drift at investment stage (annual)	α_I^*	2.2%
Risk-neutral drift during production (annual)	α_p^*	15%
Volatility of the Cash Flow process (annual)	$\emptyset$	30%
Regulatory Events		
Event I. Time reduction to T* (years)	T - T*	2
Probability of Regulatory Event I Total period	$\lambda_{2,T*}$	10%
Event II. Cash Flow reduction to C*	φ	0.75
Probability of Regulatory Event II Total period	$\lambda_{2,C*}$	30%
Numerical procedure parameters		
Number of paths simulated	N	100,000
Maximum time for the simulation (years)	Tmax	25
Simulation time step (years)	dt	1/12

We calibrate the model during the investment phase to a monthly failure rate λ_1 of 0.81%.

6.2. Estimation results

In Figures 1a, 1b, 1c and 1d, we present, for the base case, the distribution of the Project Value, in million USD, for the simulated paths at time zero F_0, an example of a simulated path resulting in success, an example of a simulated path ending in failure, and an example of a simulated path leading to abandonment, respectively. These figures illustrate the stochastic range of project outcomes. The spread of F_0 shows substantial variability due to compounded cost and cash flow uncertainty.

Figure 1a: Distribution of simulated project values F_0 at t=0



In Figures 1b - 1d, the black dot at time zero indicates F_0 for that simulation. is positive for the successful path and negative for failed or abandoned paths, reflecting R&D costs incurred before failure or abandonment. The examples demonstrate the LSM's dynamic decision logic: continue, fail, or abandon depending on expected continuation value.

Figure 1b: Example path resulting in success.

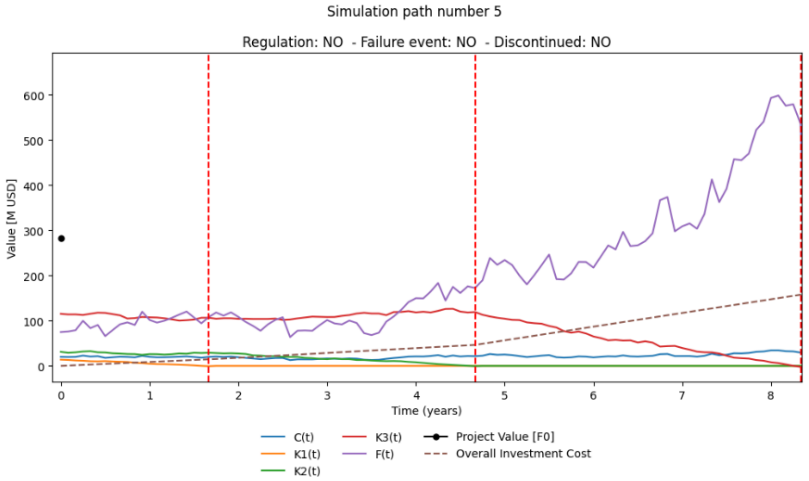


Figure 1c: Example path ending in technical failure

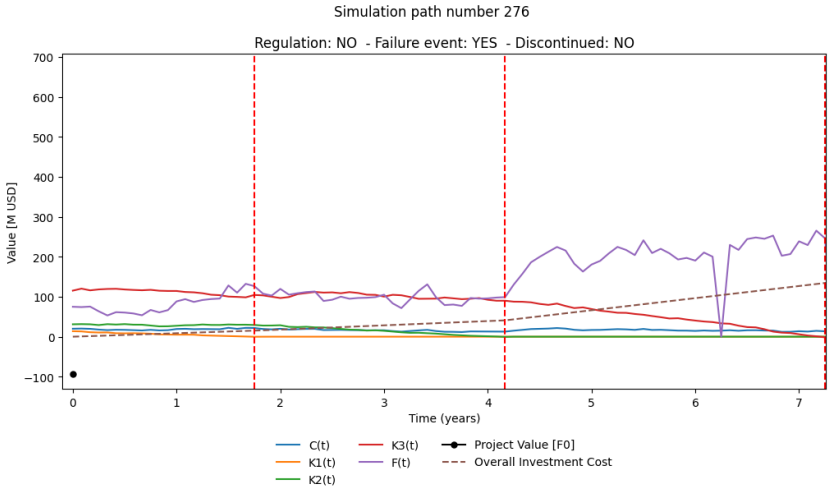
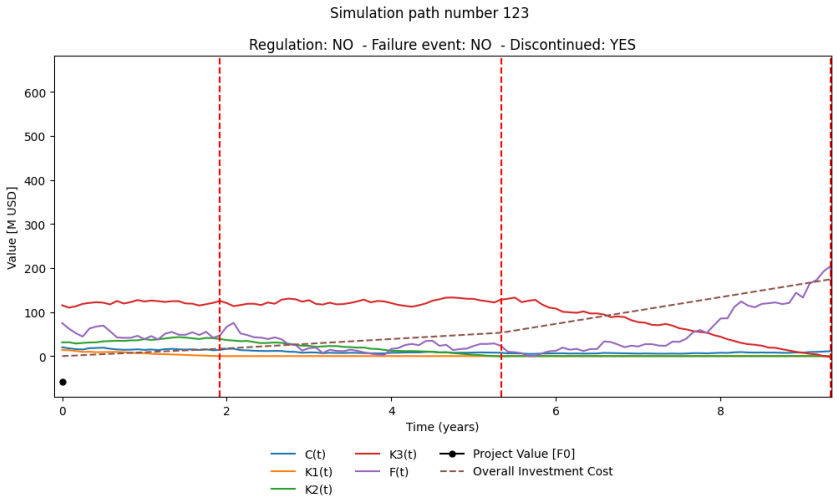
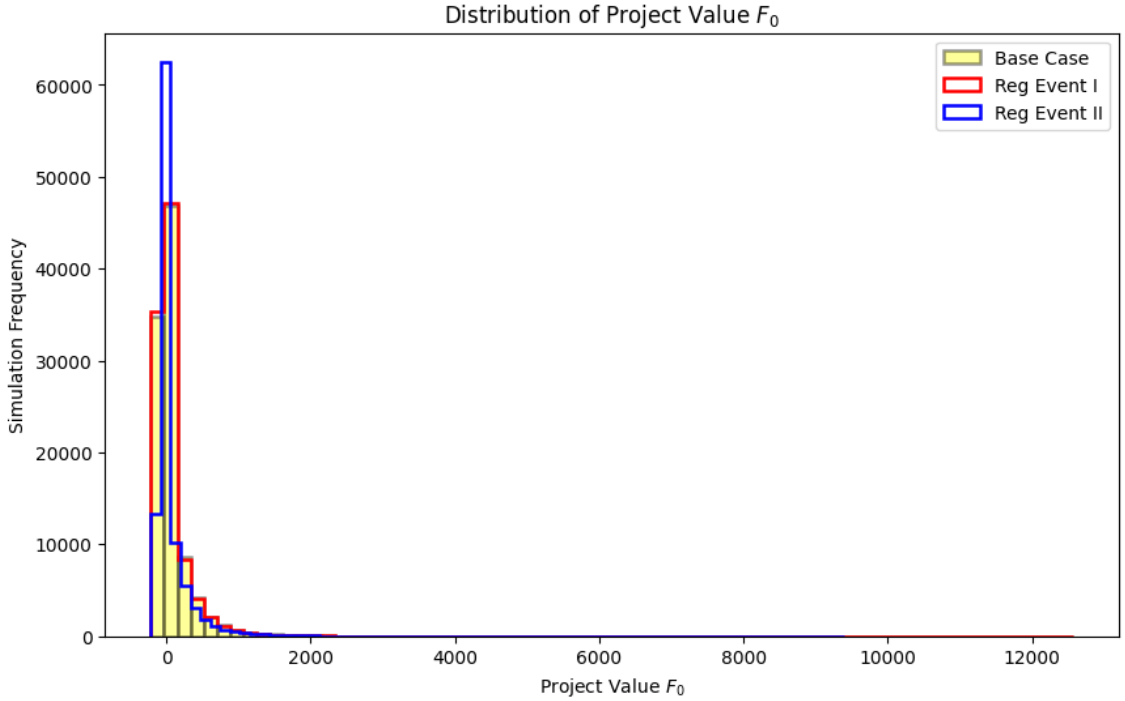


Figure 1d: Example path abandoned optimally



In Figure 2, we plot the histograms of the Project Value for the simulation paths at time zero F_0 distributions corresponding to the base case, as well as to Event I (from T to T*), and Event II (from C to C*) scenarios. In Table 3, the results of the estimation for the three cases are detailed.

Figure 2: Histogram comparison of project value F_0 distributions across the three scenarios.



Both regulatory shocks shift the distribution of F_0 leftward, indicating lower expected value and higher downside probability. The effect is more pronounced for Event II.

To better visualize and assess the results, Figure 2 is expanded. Figure 3a focuses on the upper tail of the F_0 distribution capturing the top 40% of simulated outcomes. It highlights the loss of upside potential under regulatory events. This implies that policy risk reduces the probability of blockbuster-like outcomes. Table 3 quantifies this contraction. This contraction of upside potential reinforces the adverse impact of uncertainty on long-term R&D strategies.

Figure 3a: Upper tail (above the 60th percentile) of F_0 distribution for the base case and the regulatory events: Event I (from T to T^*) and Event II (from C to C^*).

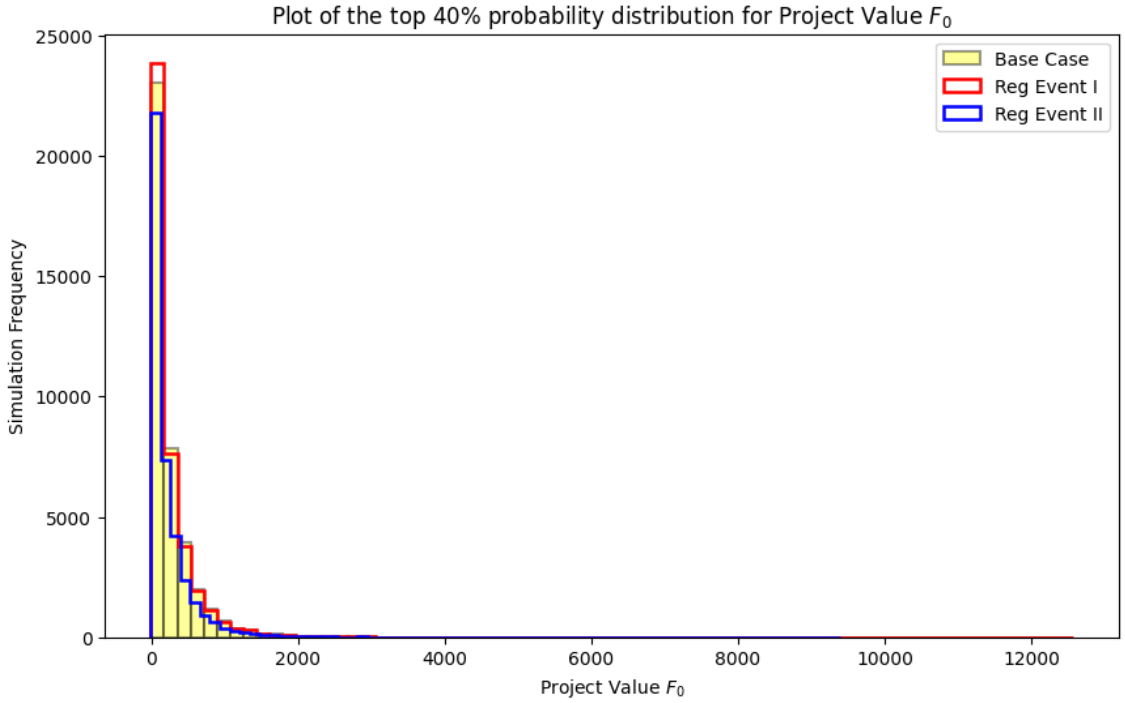


Figure 3b: Lower part (below the 60th percentile) of the project value F_0 distribution for the base case and the regulatory events: Event I (from T to T^*) and Event II (from C to C^*).

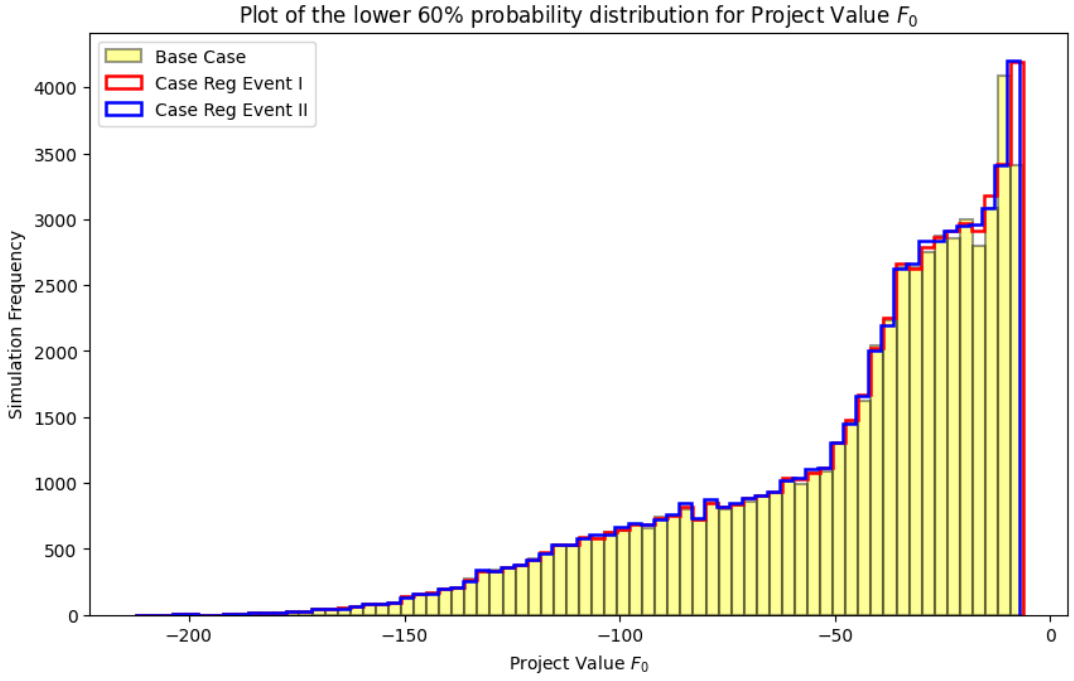


Table 3 reports the numerical summary of simulation outcomes shown graphically, the mean F_0, abandonment rates, and event probabilities for the comparison of the base case and the two regulatory events. The distribution of F_0 is highly right-skewed. We therefore report the median and tail percentiles (P5 and P95) in addition to the mean. All reported percentage changes reflect probability-weighted valuation effects, unless otherwise stated (e.g. iso-value comparisons in Figures 8 and 9).

Table 3: Estimation results from 100,000 simulations. All monetary values are in USD million. Values are rounded to one decimal place. Event probabilities are model inputs (Event I: 10%; Event II: 30%).

	Project Value F_0 (mean)	Median F_0	Tail percentile P5	Tail percentile P95	Abandonment rate	Simulations with $F_0 > 1$ billion	Max Value F_0	Min Value F_0
Base case	69.6	-14.7	-109.7	541.1	5.3%	1527 (1.5%)	12567	-212.7
Event I (T*)	65.1	-15.0	-109.8	524	5.6%	1421 (1.4%)	12567	-212.7
% change versus base	*-6.5%*				*+5.7%*	*-6.8%*		
Event II (C*)	58.4	-15.7	-109.9	494.7	6.1%	1275 (1.3%)	9385	-212.7
% change versus base	*-16.1%*				*+15.1%*	*-16.4%*	*-25.3%*	

In all three cases, the median τ_3 is 8.41 years, and the total failure probability (λ_1) adds to 53.8%, as these results pertain to the investment stage and are not affected by the regulatory events. Regulatory risk impacts on the distribution of post-approval cash flows, rather than through changes in development time or technical success rates. Optimal abandonment is 5.3% in the base case (5.6% under Event I; 6.1% under Event II). The implied probability of reaching approval and entering the production stage is 40.9%, 40.6%, and 40.1%, respectively.

In the base case, the mean project value F_0 is 69.6m. The distribution is highly right-skewed. The median is negative (–14.7m), while the 5th percentile is -109.7m and the

95th percentile is 541.1m. This pattern implies that expected value is driven by a thin upper tail: e.g., only 1.5% of simulations exceed the blockbuster-level project (USD 1 billion), yet the maximum outcome reaches more than 12.3billion, whereas the worst outcome is a loss of 212.7m. In our calibration blockbuster potential declines to 1.4% under Event I and to 1.3% under Event II.

Importantly, the regulatory events are modeled as probabilistic shocks (10% chance for Event I, 30% for Event II), so their effects on F_0 are probability-weighted rather than absolute. Even at these probabilities, policy interventions reduce expected value and primarily compress the upside. A two-year reduction in exclusivity (Event I) lowers project value by 6.5%, while a 25% cut in effective cash flow (Event II) reduces value by 16.1%.

The upper tail contracts under both shocks: the 95th percentile falls from 541.1m (base) to 524m (Event I) and 494.7 m (Event II), and the maximum value drops to about 9.2 billion under Event II. By contrast, downside outcomes are essentially unchanged, because the shocks affect post-approval cash flows rather than investment stage dynamics: the minimum remains –212.7m and the 5th percentile stays near –110 m across scenarios.

Abandonment remains low but increases under regulatory risk, from 5.3% in the base case to 5.6% under Event I and 6.1% under Event II. The absolute change is small, but the relative increase is non-trivial (+5.7% and +15.1%). This pattern is consistent with a real-options interpretation: policy risk mainly reduces expected upside, while managerial flexibility limits immediate project termination, except for marginal cases near the continuation threshold.

To map valuation effects into innovation effects, we treat the percentage change in expected F_0 as a proxy for the percentage change in expected revenues, holding costs fixed. Applying a central elasticity estimate of 1.54 between revenues and R&D spending, (Philipson & Durie 2021) we find the valuation losses observed under Event I and Event II (6.5% - 16.1%) imply an R&D contraction of about 10% - 24.8% over time. Philipson and Durie's (2021) calibration synthesize ten prior elasticity findings, which range from 0.22 to 5. The implied R&D contraction ranges from 1.4% - 3.5% (elasticity of 0.22) to 32.5% - 80.5% (elasticity of 5.0). They emphasize that the 1.54 elasticity is conservative, as it includes studies based on non-U.S. markets; in fact, they argue that applying U.S. specific data, where pharmaceutical profit margins are typically higher, would likely yield an even greater elasticity.

In the following section, we examine the model's sensitivity to the key parameters considered.

7. Sensitivity analysis

To assess the robustness of the results reported in the previous section, we perform a sensitivity analysis with respect to key model parameters. In particular, for the three cases under analysis, we vary total investment cost K, the initial expected cash flow at launch, and the probability and magnitude of the two regulatory events (Figures 4–7).

Figure 4: Plot of project value F_0 with respect to investment cost K variations [125 to 330 M]. All amounts in millions USD.

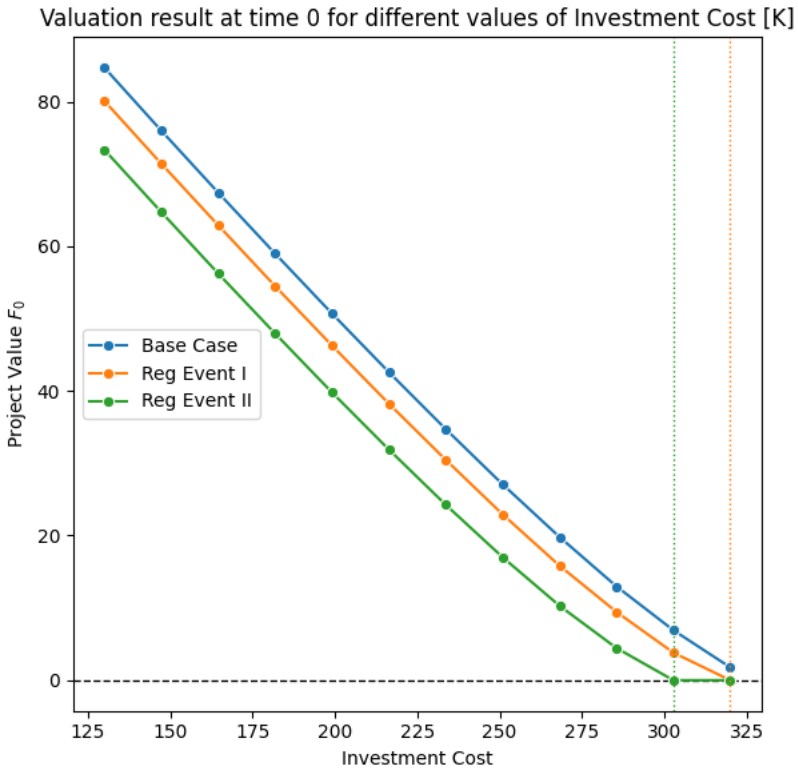
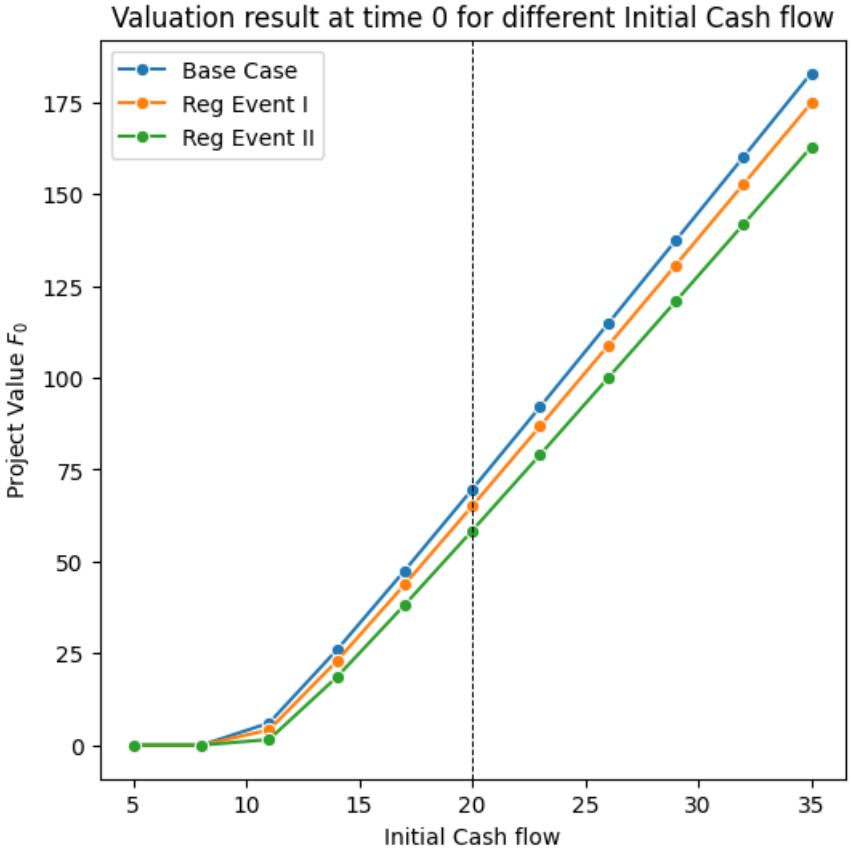


Figure 4 varies total investment cost K over a wide range to identify break-even thresholds. Project value declines monotonically with K in all scenarios. These results reveal a high elasticity of value to cost. Under Event I and Event II, the break-even cost (320m and 302m) are lower than in the base case (325m), reflecting the tighter feasibility frontier.

Figure 5 varies the initial annual cash flow at launch, C_0, from 5 to 35 million USD. Project value increases strongly with C_0 in all scenarios. A lower C_0 increases the likelihood that the project falls below the economic break-even region

Figure 5: Variation of project value F_0 with respect to the estimated initial cash flow [5 to 35 M]. All amounts in millions USD.



Valuation is highly sensitive to revenue expectations, and any regulatory environment that compresses net cash flows effectively raises the minimum commercial performance required to justify the investment. A 10% drop in C_0 decreases mean F_0 by 21.3%.

Next, we analyze the sensitivity of project value with respect to the regulatory events themselves, both in terms of their magnitude and probability of occurrence.

Figure 6 varies the effective exclusivity duration from 6 to 15 years around the 10-year benchmark. We consider Event I probabilities between 5% and 30%. The figure is expressed in terms of effective exclusivity duration, not the reduction $T - T^*$. As discussed in the regulatory section, it is common for the exploitation period to exceed 10 years, often averaging around 11 years, with a maximum of 14 in U.S. and 15 years in Europe.

Figure 6: Variation in the duration of Event I scenarios, shortening or extension of the production stage relative to the base case [−4 to +5 years], with different probabilities [5% to 30%] assigned Event I.

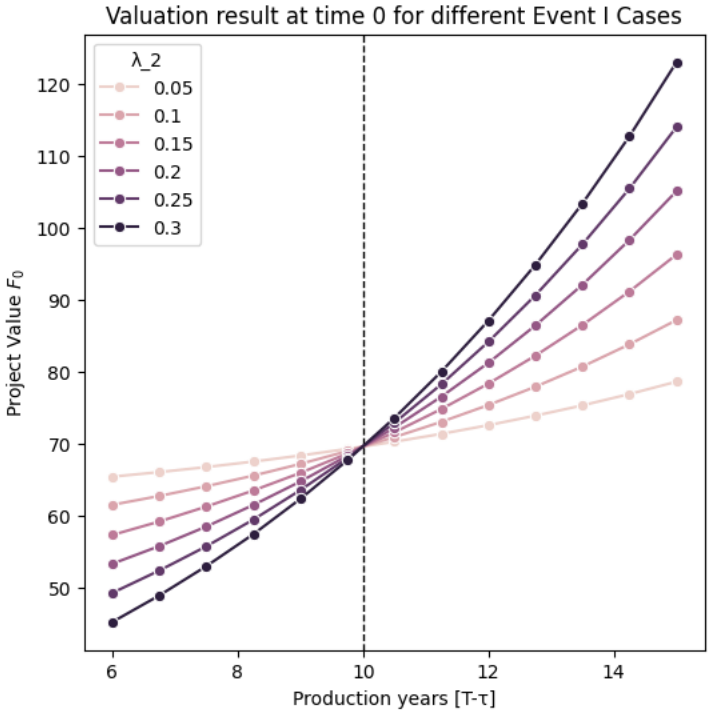
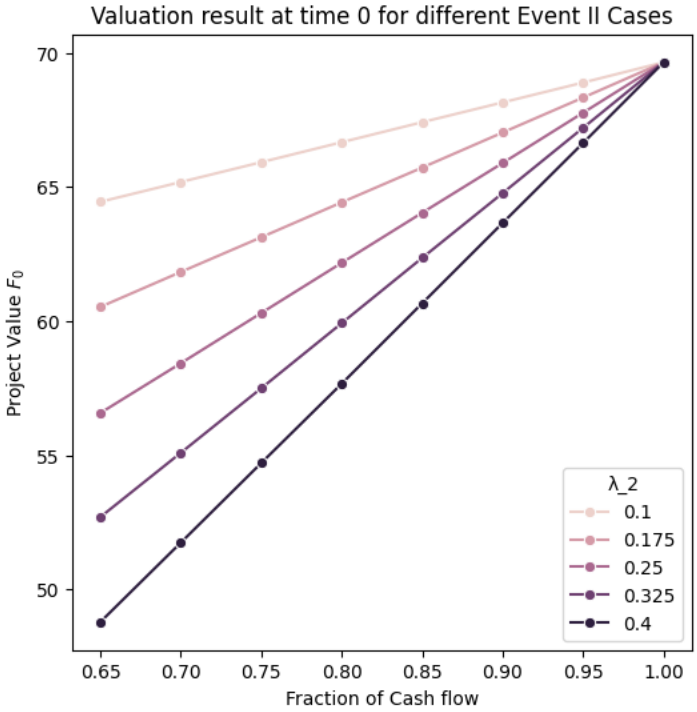


Figure 6 displays a convex relationship between project value and effective exclusivity duration. We find that extending protection beyond 10 years significantly increases project value, while reductions of 2 to 4 years cause steep losses, particularly at higher event probabilities. The curvature illustrates the nonlinear dependence of valuation on patent life, where the marginal loss in value grows disproportionately with more severe or likely interventions, and emphasizes the high marginal value of the final years of market exclusivity.

In Figure 7 we analyze the corresponding sensitivity to Event II, varying both the severity of the cash flow reduction (from 0% to −35%) and its probability (10%–40%). Small price cuts have limited impact when their probability is low, but the loss in value accelerates as reductions deepen and policy intervention becomes more likely. For combinations of larger price reductions and high event probabilities, the project's expected value falls substantially.

Figure 7: Cash flow variation relative to the base case [0% to −35%], with different probabilities assigned to the event [10% to 40%].

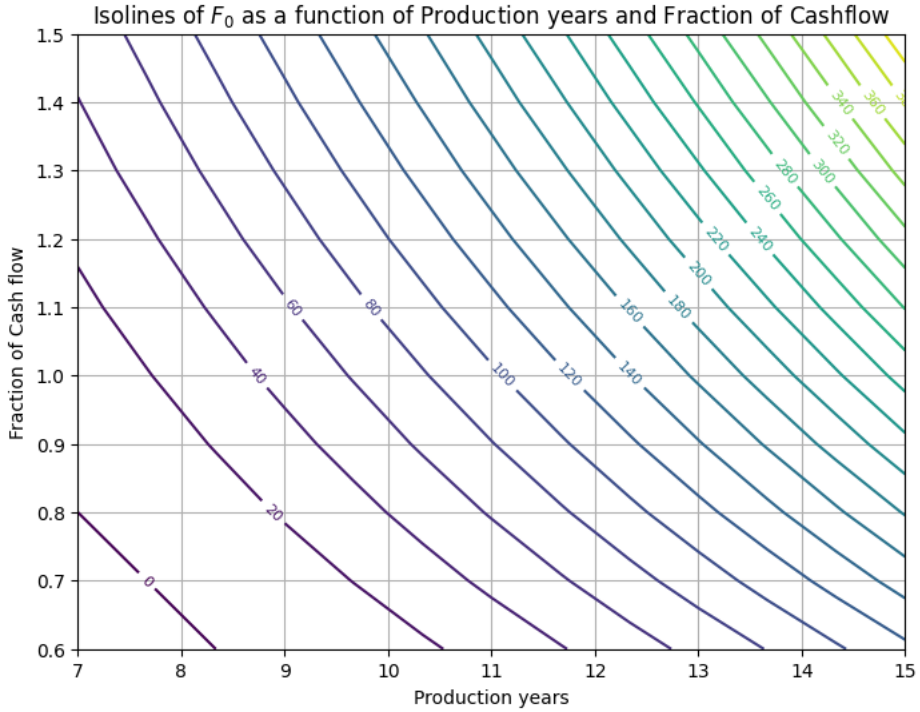


A relevant question is the interaction effect on the value of the project F_0 between the number of Production Years for the product and the Fraction of Cash Flow that would be received in those years. Policy discussions often treat these two levers as substitutes. Governments may seek lower prices, while, to compensate and sustain investment incentives, firms may seek longer or more predictable exclusivity periods. Recent U.S. negotiations between the administration and industry illustrate this bargaining logic, although the underlying trade-off is universal and intertemporal. A reduction in net prices lowers cash flows in every future year, whereas a reduction in exclusivity shortens the horizon over which any cash flows can be earned. To illustrate this joint trade-off, we use iso-value (isolines) maps that plot combinations of production years and the fraction of cash flow preserved that generate the same initial project value, F0. Points on the same contour therefore have the same F0, while moving left (fewer years) or down (lower cash-flow fraction) reduces value.

Figure 8 is constructed by evaluating the model over a two dimensional grid of (production years, cash-flow fraction) pairs and then plotting iso-value contours of the resulting mean F_0. The shape of the isolines reveals pronounced convexity in both arguments of the value function. Project value increases rapidly with additional years of exclusivity and deteriorates sharply once the protection period falls below approximately

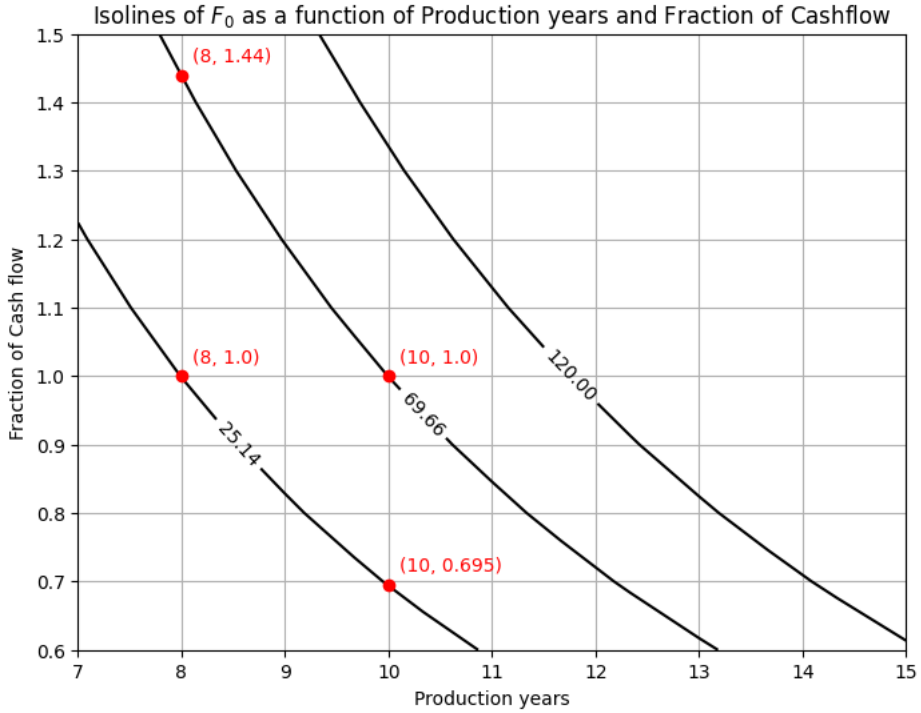
nine years. Similarly, modest reductions in cash flows have relatively contained effects, but larger reductions push the project quickly toward the zero-value boundary. The isolines located in the lower-left region highlight the fragility of incremental innovation projects when both pricing pressure and shortened exclusivity interact.

Figure 8: Iso-value (isoline) maps of the project value F_0 as a function of two regulatory parameters simultaneously.



At the base case ($K = 160$, $C_0 = 20$), holding all else constant, reducing exclusivity from 10 to 8 years leads to a valuation loss of approximately 64%, similar to a 30% cash-flow contraction if the 10 production period is kept (see figure 9). Conversely, offsetting the value loss associated with a two-year reduction in exclusivity would require an increase in cash flows of roughly 44%. Symmetrically, extending exclusivity by two years generates a value gain of about 75%, equivalent to an increase in cash flows of 34%. These equivalence examples confirm the strong convexity of project value with respect to regulatory parameters and are consistent with the earlier sensitivity analysis: the marginal value of the final years of exclusivity is very high, and regulatory interventions that compress the protected sales window can erode as much value as significant price controls

Figure 9: Specific equivalences of the project value F_0 as a function of two regulatory parameters simultaneously.



The isolines therefore provide a visual summary of the regulatory risk surface, showing how combinations of exclusivity erosion and pricing constraints can push incremental innovation projects below their economic break-even thresholds. These patterns reinforce the conclusion that regulatory design affects not only expected returns but also the feasibility frontier of R&D investment.

8. Conclusion and study limitations

This paper develops a project level ROV framework to quantify how regulatory uncertainty affects pharmaceutical R&D value. We introduce two policy shocks that represent common regulatory levers: a reduction in effective exclusivity (time-based regulation) and a reduction in net cash flows through price negotiation or controls (price-based regulation). The model is solved by least squares Monte Carlo and calibrated to an incremental CNS program.

Three results stand out. First, project value at initiation is highly right-skewed. The mean value is positive, while the median is negative, indicating that expected returns are driven by a thin upper tail of high-upside outcomes. Second, regulatory risk reduces value even at moderate probabilities, and it does so mainly by compressing this upper tail rather than by increasing the downside, because the shocks operate through post-approval cash flows. In our calibration, a 10% probability of a two-year exclusivity loss lowers mean value by

6.5%, while a 30% probability of a 25% cash-flow cut lowers mean value by 16.1% and increases optimal abandonment.

Third, the sensitivity and isoline analyses show strong nonlinearities that matter for policy design. Value is convex in effective exclusivity length, with the final years of protection carrying the highest marginal value. The iso-value isoline maps make the intertemporal trade-off between price and years transparent by identifying value-equivalent policy packages. In our calibration, reducing exclusivity from 10 to 8 years produces a value loss comparable to roughly a 30% cash-flow contraction, and offsetting a two-year exclusivity loss would require an increase of about 42% in cash flows. These equivalences illustrate that shortening the protected sales window can be as consequential as large price cuts, and that combining both levers can push projects quickly below the zero-value boundary.

These results link regulatory design to investment incentives. Using an elasticity of 1.54 between revenues and R&D spending (Philipson & Durie 2021), the probability-weighted valuation losses imply about a 10% to 24.8% reduction in R&D effort over time. This estimate is consistent with the empirical pattern that tighter pricing regimes are associated with lower R&D intensity. It also clarifies the mechanism. Policy risk reduces the expected upside that finances portfolios. It tightens the feasibility frontier for projects near break-even.

Our contribution is twofold. First, it offers a transparent and tractable model that connects financial valuation and policy analysis, enabling regulators and firms to assess the economic impact of policy uncertainty on innovation incentives. This paper advances the literature toward a simulation-based understanding of policy risk. Second, it extends existing research by quantifying how regulatory risk alters the expected value of incremental projects, which account for a big part of drug approvals but are rarely modeled explicitly. The framework can be readily adapted to alternative policy regimes, parameter settings, or radical innovation cases.

Several limitations should be acknowledged. First, we do not incorporate post-approval R&D expenditures, which can be substantial. Wong et al. (2019) document that a high proportion of approved drugs undergo extensive Phase IV trials to assess long-term safety and effectiveness. These post-marketing studies increase overall drug costs and reduce profitability over time. Wouters et al. (2020) and Higgins et al. (2021) estimate that post-approval R&D can represent a significant share of total development spending, altering project attractiveness. Furthermore, preclinical expenditures were excluded from the analysis, even though the literature indicates that these early investments can account for up to 40% of total development costs.

Second, the model abstracts from dynamic cash flow revisions based on clinical-trial outcomes. As noted by Bhatt (2025), exceptionally strong Phase II or Phase III results

often lead to upward adjustments in commercial forecasts, which could be captured, in future research, through adaptive valuation mechanisms. In addition, cash flows are modeled to grow at a constant rate during the production phase. Alternative specifications, such as faster uptake following launch and a mature phase with slower growth after four to five years, could be accommodated within the same framework.

Third, in the price-control scenario (Event II), we assume a constant level of cash flow risk. However, as Golec and Vernon (2010) document, pharmaceutical firms operating under stricter price regulation exhibit lower average returns and reduced volatility, consistent with compressed profit opportunities. Incorporating these feedback effects could refine future analyses.

9. References

117th Congress. (2021). *H.R. 5376: Inflation Reduction Act of 2022.* Congress.gov. Retrieved October 11, 2025, from https://www.congress.gov/bill/117th-congress/house-bill/5376

Adams, C. P., & Brantner, V. V. (2006). Estimating the cost of new drug development: Is it really $802 million? *Health Affairs, 25*(2), 420–428. https://doi.org/10.1377/hlthaff.25.2.420

Agha, L., Kim, S., & Li, D. (2022). Insurance design and pharmaceutical innovation. *American Economic Review: Insights, 4*(2), 191–208. https://doi.org/10.1257/aeri.20210063

Allianz Trade. (2025). *What to watch: Quarterly country and sector risk update, term premia and investment promises as trade war currency.* Retrieved October 13, 2025, from https://www.allianz-trade.com/en_global/news-insights/economic-insights/what-to-watch-9-october-2025.html

Arcidiacono, P., Ellickson, P. B., Landry, P., & Ridley, D. B. (2013). Pharmaceutical followers. *International Journal of Industrial Organization, 31*(5), 538–553. https://doi.org/10.1016/j.ijindorg.2013.10.005

Barnes, M., & Raghavan, I. (2025). *Health care woes.* LSEG. Retrieved October 11, 2025, from https://www.lseg.com/en/insights/ftse-russell/health-care-woes

Bhatt, J. (2025). *Tariffs, pricing, and regs: Navigating exponential complexity.* Deloitte. Retrieved October 10, 2025, from https://www.deloitte.com/us/en/Industries/life-sciences-health-care/blogs/health-care/tariffs-pricing-and-regs-navigating-exponential-complexity.html

Blenkinsop, P. (2025). EU, Japan trust they have secured limits to US drug tariffs. *Reuters.* Retrieved October 11, 2025, from https://www.reuters.com/business/healthcare-pharmaceuticals/eu-japan-express-confidence-in-capped-us-tariffs-drugs-2025-09-26/

Bokhari, F. A., & Fournier, G. M. (2013). Entry in the ADHD drugs market: Welfare impact of generics and me-too's. *The Journal of Industrial Economics, 61*(2), 339–392. https://doi.org/10.1111/joie.12017

Bose, N., & Wingrove, P. (2025, September 30). Pfizer does deal with Trump on prescription drug prices. *Reuters.* (Updated October 1, 2025)

Caggese, A. (2019). Financing constraints, radical versus incremental innovation, and aggregate productivity. *American Economic Journal: Macroeconomics*, *11*(2), 275-309. DOI: 10.1257/mac.20160298.

Canestaro, W. J., Patterson, J. A., & Campbell, J. D. (2025). Inflation Reduction Act impact on pharmaceutical investment: Insights from investor interviews. *Health Affairs Scholar, 3*(9), Article qxaf156. https://doi.org/10.1093/haschl/qxaf156

Carnegie, T. C., John, S. A., Shaikh, H., Khan, A. S., Callander, G., & Shenoy, S. (2025, October 7). *A pivotal week for pharmaceutical policy: Trump administration advances tariff and drug pricing initiatives.* Mintz. Retrieved October 11, 2025, from https://www.mintz.com/insights-center/viewpoints/2146/2025-10-07-pivotal-week-pharmaceutical-policy-trump-administration

Cassimon, D., Engelen, P. J., Thomassen, L., & Van Wouwe, M. (2004). The valuation of a NDA using a 6-fold compound option. *Research Policy, 33*(1), 41–51. https://doi.org/10.1016/S0048-7333(03)00089-1

Cassimon, D., De Backer, M., Engelen, P. J., Van Wouwe, M., & Yordanov, V. (2011). Incorporating technical risk in compound real option models to value a pharmaceutical R&D licensing opportunity. *Research Policy, 40*, 1200–1216. https://doi.org/10.1016/j.respol.2011.05.020

Chorniy, A., Bailey, J., Civan, A., & Maloney, M. (2021). Regulatory review time and pharmaceutical research and development. *Health Economics, 30*(1), 113–128. https://doi.org/10.1002/hec.4180

Ciarametaro, M., & Buelt, L. (2022). *Assessing the effects of biopharmaceutical price regulation on innovation.* National Pharmaceutical Council. Retrieved October 14, 2025, from https://www.npcnow.org/sites/default/files/2022-07/Assessing_the_Effects_of_Biopharma_Price_Regs_on_Innovation_Final.pdf

D'Amico, G., & Villani, G. (2021). Valuation of R&D compound option using a Markov chain approach. *Annals of Finance, 17*, 379–404. https://doi.org/10.1007/s10436-021-00389-1

Dao, H., & Ledley, F. D. (2025). Sustaining pharmaceutical innovation after the Inflation Reduction Act: Trends in R&D spending, equity investment, and business development. *Drug Discovery Today*, Article 104394. https://doi.org/10.1016/j.drudis.2025.104394

DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics, 47*, 20–33. https://doi.org/10.1016/j.jhealeco.2016.01.012

Dubois, P., De Mouzon, O., Scott Morton, F., & Seabright, P. (2015). Market size and pharmaceutical innovation. *The RAND Journal of Economics, 46*(4), 844–871. https://doi.org/10.1111/1756-2171.12113

Eger, T., & Mahlich, J. (2014). Pharmaceutical regulation in Europe and its impact on corporate R&D. *Health Economics Review, 4*, Article 23. https://doi.org/10.1186/s13561-014-0023-5

European Federation of Pharmaceutical Industries and Associations. (2025). *The pharmaceutical industry in figures.* Retrieved October 8, 2025, from https://www.efpia.eu/publications/downloads/efpia/the-pharmaceutical-industry-in-figures

Executive Office of the President. (2025a). *Executive Order 14273 of April 15, 2025: Lowering drug prices by once again putting Americans first. Federal Register* (Published April 18, 2025)

Executive Office of the President. (2025b). *Executive Order 14297 of May 12, 2025: Delivering most-favored-nation prescription drug pricing to American patients. Federal Register* (Published May 15, 2025)

Frankel, A. P., Krieger, J. L., Li, D., & Papanikolaou, D. (2023). *Evaluation and learning in R&D investment* (NBER Working Paper No. 31290). National Bureau of Economic Research

Frech, H. E., Pauly, M. V., Comanor, W. S., & Martinez, J. R. (2023). *Pharmaceutical pricing and R&D as a global public good* (NBER Working Paper No. 31272). National Bureau of Economic Research

Gassmann, O., Schuhmacher, A., von Zedtwitz, M., & Reepmeyer, G. (2018). *Leading pharmaceutical innovation: How to win the life science race.* Springer

Goldman, D., & Lakdawalla, D. (2018). *The global burden of medical innovation* (Schaeffer Center White Paper Series). Retrieved October 1, 2025, from https://schaeffer.usc.edu/research/global-burden-of-medical-innovation/

Golec, J., & Vernon, J. A. (2009). Financial risk of the biotech industry versus the pharmaceutical industry. *Applied Health Economics and Health Policy, 7*(3), 155–165. https://doi.org/10.1007/BF03256149

Golec, J., Hegde, S., & Vernon, J. A. (2010). Pharmaceutical R&D spending and threats of price regulation. *Journal of Financial and Quantitative Analysis, 45*(1), 239–264

Golec, J., & Vernon, J. A. (2010). Financial effects of pharmaceutical price regulation on R&D spending by EU versus US firms. *Pharmacoeconomics*, *28*(8), 615-628. https://doi.org/10.2165/11535580-000000000-00000

Green, J. R., & Scotchmer, S. (1995). On the division of profit in sequential innovation. *The RAND Journal of Economics, 26*, 20–33. https://doi.org/10.2307/2556033

Hartmann, M., & Hassan, A. (2006). Application of real options analysis for pharmaceutical R&D project valuation—Empirical results from a survey. *Research Policy, 35*(3), 343–354. https://doi.org/10.1016/j.respol.2005.12.005

Henderson, R. M., & Clark, K. B. (1990). Architectural innovation: The reconfiguration of existing product technologies and the failure of established firms. *Administrative Science Quarterly, 35*(1), 9–30. https://doi.org/10.2307/2393549

Hemphill, C. S., & Sampat, B. N. (2012). Evergreening, patent challenges, and effective market life in pharmaceuticals. *Journal of Health Economics, 31*(2), 327–339. https://doi.org/10.1016/j.jhealeco.2012.01.004

Higgins, M. J., Yan, X., & Chatterjee, C. (2021). Unpacking the effects of adverse regulatory events: Evidence from pharmaceutical relabeling. *Research Policy, 50*(1), 104126. https://doi.org/10.1016/j.respol.2020.104126

Hoe, S., & Diltz, J. D. (2012). A real options approach to valuing and negotiating licensing agreements. *The Quarterly Review of Economics and Finance, 52*, 322–332. https://doi.org/10.1016/j.qref.2012.04.005

IQVIA. (2025). *Global trends in R&D 2025.* Retrieved October 21, 2025, from https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-trends-in-r-and-d-2025

Ji, Y., & Rogers, P. (2024). *The long-run impacts of regulated price cuts: Evidence from Medicare* (NBER Working Paper No. 33083). National Bureau of Economic Research

Johnson, H. (2020). The moderating effects of dynamic capability on radical innovation and incremental innovation teams in the global pharmaceutical biotechnology industry. *Journal of Innovation Management, 8*(1), 51–83. https://doi.org/10.24840/2183-0606_008.001_0006

Kellogg, D., & Charnes, J. M. (2000). Real-options valuation for a biotechnology company. *Financial Analysts Journal, 56*(3), 76–84. https://doi.org/10.2469/faj.v56.n3.2362

Krieger, J., Li, D., & Papanikolaou, D. (2022a). Missing novelty in drug development. *The Review of Financial Studies, 35*(2), 636–679. https://doi.org/10.1093/rfs/hhab024

Krieger, J. L., Li, X., & Thakor, R. T. (2022b). Find and replace: R&D investment following the erosion of existing products. *Management Science, 68*(9), 6552–6571. https://doi.org/10.1287/mnsc.2021.4243

Lazard. (2025). *The geopolitics of biotech.* Retrieved September 29, 2025, from https://www.lazard.com/research-insights/the-geopolitics-of-biotech

Light, D. W. (2007). Misleading Congress about drug development. *Journal of Health Politics, Policy and Law, 32*(5). https://doi.org/10.1215/03616878-2007-036

Lo, A. W., & Thakor, R. T. (2022). Financing biomedical innovation. *Annual Review of Financial Economics, 14*(1), 231–270. https://doi.org/10.1146/annurev-financial-031721-081537

Lo, A. W., & Thakor, R. T. (2023). Financial intermediation and the funding of biomedical innovation: A review. *Journal of Financial Intermediation, 54*, 101028. https://doi.org/10.1016/j.jfi.2023.101028

Longstaff, F. A., & Schwartz, E. S. (2001). Valuing American options by simulation: A simple least-squares approach. *The Review of Financial Studies, 14*(1), 113–147. https://doi.org/10.1093/rfs/14.1.113

Merton, R. C. (1973). An intertemporal capital asset pricing model. *Econometrica: Journal of the Econometric Society*, 867-887. https://www.jstor.org/stable/1913811

Mestre-Ferrandiz, J., Sussex, J., & Towse, A. (2012). *The R&D cost of a new medicine* (Report No. 000135). Office of Health Economics

Michielssens, S. (2025). *Pharma tariffs: A complex puzzle.* Candriam. Retrieved October 11, 2025, from https://www.candriam.com/en-ca/professional/insight-overview/topics/equities/pharma-tariffs-a-complex-puzzle/

Mulcahy, A. W., Whaley, C. M., Gizaw, M., Schwam, D., Edenfield, N., & Becerra-Ornelas, A. U. (2021). *International prescription drug price comparisons: Current empirical estimates and comparisons with previous studies* (RR-2956-ASPEC). RAND Corporation

Office of the United States Trade Representative. (2025, December). *U.S. government announces agreement in principle with the United Kingdom on pharmaceutical pricing.* https://ustr.gov/about/policy-offices/press-office/press-releases/2025/december/us-government-announces-agreement-principle-united-kingdom-pharmaceutical-pricing

Okuyama, R. (2017). Importance of tacit knowledge in incremental innovation: Implications from drug discovery cases. *Journal of Strategy and Management*, *10*(1), 118-130. https://doi.org/10.1108/JSMA-02-2016-0016

Okuyama, R. (2024). Increased contribution of small companies to late-entry drugs: A changing trend in FDA-approved drugs during the 2020s. *Drug Discovery Today, 29*(2), 103866. https://doi.org/10.1016/j.drudis.2023.103866

Philipson, T. J., & Durie, T. (2021). *The evidence base on the impact of price controls on medical innovation* (Becker Friedman Institute of Economics Working Paper No. 2021-108). Becker Friedman Institute of Economics

Philipson, T. J., Ling, Y., & Chang, R. (2023). *The impact of price setting at 9 years on small molecule innovation under the Inflation Reduction Act.* POLICY

Pindyck, R. S. (1993). Investments of uncertain cost. *Journal of Financial Economics, 34*(1), 53–76. https://doi.org/10.1016/0304-405X(93)90040-I

Rogers, M. J., Gupta, A., & Maranas, C. D. (2002). Real options based analysis of optimal pharmaceutical research and development portfolios. *Industrial & Engineering Chemistry Research, 41*(25), 6607–6620

Rogers, P. (2023). *Regulating the innovators: Approval costs and innovation in medical technologies.* Cato Institute

Schlander, M., Hernandez-Villafuerte, K., Cheng, C. Y., Mestre-Ferrandiz, J., & Baumann, M. (2021). How much does it cost to research and develop a new drug? A systematic review and assessment. *PharmacoEconomics, 39*(11), 1243–1269. https://doi.org/10.1007/s40273-021-01065-y

Schuhmacher, A., Gassmann, O., & Hinder, M. (2016). Changing R&D models in research-based pharmaceutical companies. *Journal of Translational Medicine, 14*(1), 105. https://doi.org/10.1186/s12967-016-0838-4

Schuhmacher, A., Wilisch, L., Kuss, M., Kandelbauer, A., Hinder, M., & Gassmann, O. (2021). R&D efficiency of leading pharmaceutical companies—A 20-year analysis. *Drug Discovery Today, 26*(8), 1784–1789. https://doi.org/10.1016/j.drudis.2021.05.005

Schulthess, D. G., O'Loughlin, G., Askeland, M., Gassull, D., & Bowen, H. P. (2025). The Inflation Reduction Act's impact upon early-stage venture capital investments. *Therapeutic Innovation & Regulatory Science*, 1–12. https://doi.org/10.1007/s43441-025-00773-3

Schwartz, E. S. (2004). Patents and R&D as real options. *Economic Notes, 33*(1), 23–54. https://doi.org/10.1111/j.0391-5026.2004.00124.x

Scotchmer, S. (1991). Standing on the shoulders of giants: Cumulative research and the patent law. *Journal of Economic Perspectives, 5*(1), 29–41. https://doi.org/10.1257/jep.5.1.29

Sertkaya, A., Beleche, T., Jessup, A., & Sommers, B. D. (2024). Costs of drug development and research and development intensity in the US, 2000–2018. *JAMA Network Open, 7*(6), e2415445. https://doi.org/10.1001/jamanetworkopen.2024.15445

Shaikh, M., Del Giudice, P., & Kourouklis, D. (2021). Revisiting the relationship between price regulation and pharmaceutical R&D investment. *Applied Health Economics and Health Policy, 19*(2), 217–229. https://doi.org/10.1007/s40258-020-00601-9

Sood, N., De Vries, H., Gutierrez, I., Lakdawalla, D. N., & Goldman, D. P. (2008). The Effect Of Regulation On Pharmaceutical Revenues: Experience In Nineteen Countries: If the United States implemented price controls and negotiations similar to those in other developed countries, US revenues would fall by as much as 20.3 percent. *Health Affairs*, *27*(Suppl1), w125-w137. https://doi.org/10.1377/hlthaff.28.1.w125

Stengel, K., Cole, M., & Brantley, K. (2020). *Impact of H.R.3 as passed by the House on federal spending and drug manufacturer revenue.* Avalere. Retrieved October 12, 2025, from https://avalere.com/insights/impact-of-h-r3-scenarios-on-federal-spending-and-drug-manufacturer-revenues

The White House. (2025a, November 6). *Fact sheet: President Donald J. Trump announces major developments in bringing most-favored-nation pricing to American patients.*

The White House. (2025b, December 19). *Fact sheet: President Donald J. Trump announces largest developments to date in bringing most-favored-nation pricing to American patients.*

U.S. Department of Commerce, Bureau of Industry and Security. (2025, April 16). *Notice of request for public comments on Section 232 national security investigation of imports of pharmaceuticals and pharmaceutical ingredients. Federal Register*

U.S. Food and Drug Administration. (2022). *Summary of NDA approvals & receipts, 1938 to the present.* Retrieved October 21, 2025, from https://www.fda.gov/about-fda/histories-fda-regulated-products/summary-nda-approvals-receipts-1938-present

U.S. Food and Drug Administration. (2024). *Report on the state of pharmaceutical quality.* Retrieved October 21, 2025, from https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/report-state-pharmaceutical-quality

Vernon, J. A. (2005). Examining the link between price regulation and pharmaceutical R&D investment. *Health Economics, 14*(1), 1–16. https://doi.org/10.1002/hec.897

Willigers, B. J., & Hansen, T. L. (2008). Project valuation in the pharmaceutical industry: A comparison of least-squares Monte Carlo real option valuation and conventional approaches. *R&D Management, 38*(5), 520–537. https://doi.org/10.1111/j.1467-9310.2008.00530.x

Wong, C. H., Siah, K. W., & Lo, A. W. (2019). Estimation of clinical trial success rates and related parameters. *Biostatistics, 20*(2), 273–286. https://doi.org/10.1093/biostatistics/kxx069

Wouters, O. J., McKee, M., & Luyten, J. (2020). Estimated research and development investment needed to bring a new medicine to market, 2009–2018. *JAMA, 323*(9), 844–853. https://doi.org/10.1001/jama.2020.1166

Wouters, O. J., & Kesselheim, A. S. (2024). Quantifying research and development expenditures in the drug industry. *JAMA Network Open, 7*(6), e2415407. https://doi.org/10.1001/jamanetworkopen.2024.15407

Yin, N. (2023). Pharmaceuticals, incremental innovation and market exclusivity. *International Journal of Industrial Organization, 87*, 102922. https://doi.org/10.1016/j.ijindorg.2023.102922

Zheng, H., Patterson, J. A., & Campbell, J. D. (2025). Early impact of the Inflation Reduction Act on small molecule vs biologic post-approval oncology trials. *Health Affairs Scholar, 3*(8), Article qxaf152. https://doi.org/10.1093/haschl/qxaf152

Appendix A. Glossary of Acronyms

API — Active Pharmaceutical Ingredient.
CDER — Center for Drug Evaluation and Research (U.S. FDA).
CNS — Central Nervous System.
EFPIA — European Federation of Pharmaceutical Industries and Associations.
EMA — European Medicines Agency.
FDA — U.S. Food and Drug Administration.
IRA — Inflation Reduction Act (U.S., 2022).
IQVIA — IQVIA Institute for Human Data Science.
LSM — Least Squares Monte Carlo.
MFN — Most Favored Nation (pricing clause).
NBE — New Biological Entity.
NDA — New Drug Application.
NME — New Molecular Entity.
NMPA — National Medical Products Administration (China).
NPV — Net Present Value.
OECD — Organization for Economic Co-operation and Development.
PMDA — Pharmaceuticals and Medical Devices Agency (Japan).
POS — Probability of Success.
R&D — Research and Development.
ROV — Real Options Valuation.
SME — Small and Medium-sized Enterprise.
TRIPS — Agreement on Trade-Related Aspects of Intellectual Property Rights (World Trade Organization).
USD — United States Dollar.
U.S. — United States.