DECISION ANALYSIS AND PORTFOLIO MANAGEMENT IN THE BIOPHARMA INDUSTRY

A PRACTITIONER'S GUIDE

Richard M. Bayney, Ph.D.
and Jose Orellana

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Phone: (954) 727-9333
Fax: (561) 892-0700
Web: www.jrosspub.com

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FOREWORD

Organizations that invest heavily in research and development (R&D) face a fundamental challenge. They must decide which ideas deserve scarce resources today in order to create value tomorrow. R&D portfolios unfold over long time horizons, operate under deep uncertainty, and require organizations to balance incremental improvements with transformational bets. Managing these investments well is not simply an operational concern. It is one of the most consequential strategic responsibilities any innovation-driven organization faces.

Over the past decade, the complexity of these decisions has increased significantly. Technology cycles move faster, development costs continue to rise, and leaders must weigh scientific promise against commercial opportunity while navigating uncertain regulatory, technical, and competitive landscapes. In this environment, the ability to manage innovation as a portfolio rather than as a collection of individual projects becomes essential.

In my work with strategic portfolio management teams across industries, including pharmaceuticals, manufacturing, chemicals, and high technology, I see these challenges play out every day. Organizations are increasingly applying advanced analytics and artificial intelligence to improve how they evaluate initiatives, identify emerging risks, and allocate resources across complex portfolios of work. These technologies can surface patterns, quantify uncertainty, and accelerate insight. Yet their value ultimately depends on the decision frameworks within which they operate. Without disciplined portfolio thinking, even the most sophisticated analytics do not translate into sound investment judgment.

Few people understand this discipline better than Dr. Richard Bayney. His career spans the full arc of R&D decision analysis and portfolio management. Trained as a molecular biologist, he began on the scientific front lines of drug discovery before moving into leadership roles across the pharmaceutical industry at Merck, Bayer, Bristol Myers Squibb, and Johnson & Johnson, where I first met him as a pragmatic and innovation-seeking leader. At Johnson & Johnson, he ultimately led portfolio management and decision analysis for all pharmaceutical R&D, helping guide investment decisions across complex, global development pipelines. In the years since, he has become a respected advisor, educator, and author, helping organizations around the world strengthen how they evaluate and govern innovation investments. This book reflects the perspective of someone who has spent decades navigating the practical realities of R&D decision making.

The chapters that follow guide the reader through a foundational methodology required to manage R&D portfolios effectively. Richard and his coauthor, Jose Orellana, begin by examining the structural realities of drug development, including the economics of the preclinical and clinical funnel and the necessary process of initiative attrition. They then introduce the principles of decision analysis and probabilistic thinking that allow leaders to evaluate opportunities under uncertainty.

Building on this foundation, the book presents a practical framework (**CREOPM**: asset **c**ategorization, **r**isk analysis, integrated **e**valuation, portfolio **o**ptimization, project **p**rioritization, **m**anagement best practices) for portfolio construction and governance that integrates strategic alignment, value assessment, and resource allocation. The result is a disciplined approach to managing innovation investments that brings greater transparency, rigor, and strategic clarity to some of the most difficult decisions organizations must make.

What further distinguishes this book from many treatments of portfolio management is the depth of its quantitative and decision analytic foundation. The authors introduce readers to the probabilistic and analytical tools required to evaluate R&D investments rigorously. Concepts such as probability of technical success, expected value modeling, scenario analysis, and risk-adjusted valuation are complemented by linear programming and stochastic optimization techniques that help organizations allocate constrained resources across portfolios of uncertain value. These methods translate scientific and technical risk into structured decision frameworks that allow leadership teams to compare opportunities across development stages, therapeutic areas, and time horizons while explicitly accounting for uncertainty.

At a time when scientific progress is accelerating and the stakes of innovation have never been higher, organizations must become better at deciding where to place their bets and be willing to take a long view on building lasting value. The work of Richard and Jose offers both the conceptual grounding and the practical guidance needed to meet that challenge. Leaders responsible for innovation, strategy, and portfolio governance will find in these pages a thoughtful, practical guide to making better R&D decisions about the future in a continuously challenging and competitive biopharma environment.

—Dr. Richard Sonnenblick, Chief Data Scientist, Planview

PREFACE

THE CURRENT STATE OF PORTFOLIO MANAGEMENT IN BIOPHARMACEUTICAL R&D

Across the biopharma sector, organizations continue to experience sustained pressure to restructure operating models, rebalance investment priorities, and improve capital efficiency in the face of escalating research and development (R&D) costs, increasing regulatory complexity, and persistently high attrition rates. Within this context, a commonly invoked internal mantra has emerged: *To be successful, we must do more with less.* While superficially compelling, this statement lacks the precision required to guide high-stakes, long-horizon investment decisions that define pharmaceutical R&D portfolios. From an executive perspective, the ambiguity embedded in this phrase is nontrivial. Notably absent is any explicit temporal framing without which the statement fails to provide the directional clarity required for scientific teams, portfolio managers, and senior leaders to align decisions across drug discovery, development, and commercialization.

In our experience, organizations that do not explicitly articulate their strategic and financial objectives—together with the metrics by which progress will be assessed over defined time frames—struggle to implement coherent portfolio management practices. A more precise articulation, albeit less succinct, would read:

> *To achieve sustained success—defined by measurable improvements in our primary financial and strategic performance indicators—over a defined multi-year horizon, we must maximize the value generated by our R&D investment portfolio, subject to finite financial, scientific, and organizational resources.*

Such clarity establishes the intellectual and operational foundation upon which disciplined portfolio management must rest. Without it, portfolio decisions become episodic, reactive, and susceptible to bias, rather than systematic and value maximizing.

FROM VALUE CREATION TO VALUE MAXIMIZATION IN R&D PORTFOLIOS

Value creation has become a ubiquitous concept in corporate and academic discourse. Yet, in practice, it is often invoked without reference to *optimality*. Assuming value is appropriately defined, the

rational objective of portfolio management is not merely to create value, but to create *maximum* value given resource constraints under conditions of uncertainty.

In biopharma R&D, skepticism is sometimes expressed regarding the quantification of value, particularly in early discovery or high-uncertainty development stages. While it is true that not all dimensions of value can be perfectly monetized, all R&D investments ultimately exist to deliver benefit—whether to patients, healthcare systems, or society at large. At a minimum, such benefit can be expressed in terms of expected utility, clinical impact, or probabilistic economic outcomes. Framed in this way, *value maximization* may be more intuitively understood as *benefit maximization*.

RESTRUCTURING, COST PRESSURE, AND THE PORTFOLIO QUESTION

Over multiple decades, we have observed highly successful biopharma companies deliver transformative therapies, only to subsequently reconfigure their business models in response to market, pricing, or competitive pressures. These transitions are often accompanied by broad restructuring initiatives, cost containment programs, and workforce reductions. Yet a fundamental question frequently remains unanswered:

> *Given constrained resources, is the organization demonstrably maximizing the value it is capable of creating through its R&D portfolio?*

If portfolio-level value maximization were more explicitly assessed and transparently demonstrated, the rationale for many investment decisions—and disinvestments—would be clearer.

LIMITATIONS OF CURRENT R&D PORTFOLIO MANAGEMENT PRACTICE

While most biopharma organizations practice some form of R&D portfolio management, the rigor, transparency, and analytical maturity of these practices vary considerably. Furthermore, despite their natural complementarity, decision analysis is seldom integrated with portfolio management in the governance of biopharma R&D portfolios.

The two disciplines evolved to address different decision contexts: decision analysis emerged from operations research and applied statistics to support individual high-stakes decisions under uncertainty, while portfolio management developed largely as a managerial and financial control function focused on collections of projects competing for scarce resources. This divergence has led many organizations to apply decision analysis narrowly at the asset or milestone level, while reserving portfolio management for budgeting, prioritization, and governance cycles—without formally integrating the two.

Organizational structure further reinforces this separation. Decision analysis expertise in biopharma companies is often embedded within specialized quantitative groups (e.g., modeling, biostatistics, or advanced analytics), whereas portfolio decisions are typically owned by senior governance committees with heterogeneous analytical sophistication.

Methodological misalignment also plays a role. Portfolio management practices in R&D have historically relied largely on deterministic scoring models, ranking schemes, and stage-gate heuristics that are perceived as transparent and easy to communicate. In contrast, decision analysis explicitly

embraces probability distributions, conditional dependencies, and nonlinear value functions—features that are essential for scientific realism.

Consequently, several recurring portfolio management deficiencies are evident:

- **Disassociation (or nonexistence) of decision analysis from portfolio management:** Many portfolio management decisions rest on fragile foundations, as the underlying data used to inform them often lack clear traceability, methodological rigor, and analytical defensibility.
- **Weak decision lineage:** It is often difficult to reconstruct why a given asset entered or progressed through the portfolio, what assumptions underpinned its approval, and how those assumptions have evolved over time.
- **Inadequate treatment of uncertainty:** Although risk is widely acknowledged, its quantification frequently lacks methodological rigor, traceability, and defensibility—particularly in early-stage programs.
- **Overreliance on point estimates:** Faced with uncertainty, organizations often default to single-point valuations to simplify decision making.
- **Conflation of prioritization with selection:** Asset ranking is frequently treated as synonymous with portfolio construction, even though prioritization alone is suboptimal to portfolio-level optimization.
- **Persistent execution underperformance:** Despite decades of focus on scope, schedule, and cost control, many R&D programs continue to experience delays, budget overruns, and scope erosion—indicating that broader portfolio-level drivers remain insufficiently addressed.

PURPOSE AND MOTIVATION OF THIS BOOK

This book is grounded in the conviction that decision analysis and portfolio management must be recognized and practiced as a continuous, enterprise-level discipline—not as a periodic budgeting or governance exercise. Absent such discipline, even commercially successful organizations leave substantial value unrealized. Worse, they may compensate through repeated restructuring cycles that erode institutional knowledge and destabilize scientific organizations. Embedding prescriptive decision analysis and portfolio management into the organizational fabric is therefore essential for long-term competitiveness in biopharma R&D.

Without this clarity, portfolio management becomes untethered from strategy and incapable of guiding meaningful trade-offs. Strategic planning is therefore a necessary precondition for effective R&D portfolio management.

THE EFFICIENT FRONTIER APPLIED TO R&D INVESTMENT PORTFOLIOS

Unlike financial portfolio management, which benefits from decades of theoretical and empirical development, portfolio management in R&D has struggled to achieve comparable disciplinary rigor. Central to financial portfolio theory is the *efficient frontier*, first articulated by Markowitz, which defines the set of portfolios that maximize expected return for a given level of risk.

This concept is directly applicable to R&D portfolios. For any given level of aggregate technical and financial risk, there exists a combination of R&D programs that maximizes expected portfolio value. Portfolios that lie below this frontier are, by definition, suboptimal—regardless of how attractive individual assets may appear in isolation.

THE CREOPM™ FRAMEWORK FOR R&D PORTFOLIO MANAGEMENT

To operationalize these principles, we introduce **CREOPM™**, a pragmatic framework for enterprise project portfolio management (EPPM) in R&D. The framework integrates six core components:

1. **Project categorization**
2. **Risk analysis**
3. **Integrated evaluation**
4. **Portfolio optimization**
5. **Project prioritization**
6. **Best practices in portfolio management**

CREOPM™ is intentionally modular and maturity-sensitive. While not presented as a universal prescription, its foundational principles—strategic clarity, analytical rigor, disciplined governance, and leadership accountability—are essential for any organization seeking to improve R&D portfolio performance systematically.

TARGET AUDIENCE AND BENEFICIARIES

This volume is designed to serve a diverse set of stakeholders engaged in the management, optimization, and strategic oversight of portfolios—whether of products, services, or organizational capabilities—within complex biopharma environments. The readership is expected to include the following categories:

1. **Portfolio management practitioners:** Professionals directly responsible for the execution and governance of project portfolios. For newcomers, this text provides a rigorous foundation in principles, methodologies, and analytical tools for robust project portfolio management (PPM). For experienced practitioners, it offers frameworks and case-based insights to elevate capability maturity and enhance decision rigor.
2. **Financial and resource managers:** Financial stewards who require transparency, defensibility, and traceability of project investment estimates, resource allocations, and expenditure patterns.
3. **Executive decision makers:** Senior leaders—including chief executive officers, chief financial officers, chief information officers, and heads of R&D—who may not be quantitative specialists but seek to evaluate the efficacy of their organization's PPM capabilities.
4. **Strategists and advisors:** Professionals charged with aligning organizational strategy with portfolio execution. The content provides actionable frameworks for integrating strategic objectives, R&D roadmaps, and business plans.
5. **Entrepreneurs and innovators:** Founders and business leaders navigating the complexities of both established and emerging markets. Those investing in novel technologies or platform-based innovations will find guidance on disciplined portfolio evaluation and risk-informed decision making.
6. **Graduate-level students and academics:** Master's-level students (e.g., MBA, EMBA, EMTM) with a serious interest in PPM and decision analysis. The book provides a bridge between the theoretical foundations of operations research/management science and the practical realities of organizational decision making in high-stakes R&D environments.

7. **Educators and thought leaders:** Instructors seeking to integrate quantitative rigor with organizational and strategic perspectives in portfolio management. The material offers a structured approach for teaching the intersection of analytical methods and executive decision making, emphasizing practical applicability in real-world contexts.
8. **Skeptics and pragmatists:** Individuals who question whether structured PPM frameworks add value beyond experiential judgment and intuitive decision making. The text addresses these perspectives by providing empirically grounded methodologies, illustrating how disciplined, evidence-based portfolio management complements, rather than replaces, managerial judgment.

ORGANIZATION OF THE BOOK

The book is structured into two sections containing a total of 10 chapters:

- **Section I: Decision Analysis and Portfolio Management in the Biopharma Industry**
  - **Chapter 1: Drug Research and Development Within an Evolving Industry—** This chapter argues that despite rising drug approvals and technological advances, biopharma R&D productivity remains constrained by persistent clinical attrition, high capitalized costs, and reliance on averages that obscure portfolio-level risk, making disciplined, probabilistic portfolio management essential for value creation.
  - **Chapter 2: Scenario Analysis and Strategic Planning—**This chapter positions scenario analysis as a decision-support discipline that helps biopharma leaders navigate deep uncertainty by clarifying causal logic, surfacing critical uncertainties, and stress-testing strategic robustness rather than forecasting outcomes.
  - **Chapter 3: Decision Analysis and Portfolio Management—**This chapter positions decision analysis as a rigorous, quantitative discipline for improving decision quality in biopharma R&D by explicitly framing uncertainty, trade-offs, and risk preferences, and by distinguishing sound decisions from stochastic outcomes.
- **Section II: CREOPM™—A Holistic Portfolio Management Framework**
  - **Chapter 4: Project Categorization—**This chapter explains project categorization as a core portfolio management discipline that enables consistent evaluation and governance by classifying initiatives into mutually exclusive categories based on obligation, risk, and strategic intent.
  - **Chapter 5: Risk Analysis—**This chapter presents a rigorous, probabilistic framework for quantifying and managing risk and uncertainty in biopharma R&D, distinguishing controllable operational risks from intrinsic scientific risks and extending analysis from projects to programs and portfolios.
  - **Chapter 6: Integrated Evaluation—**This chapter establishes a rigorous, decision-tree-based framework for valuing biopharma R&D investments using probabilistic financial metrics such as expected net present value, economic internal rate of return, and utility-adjusted value, explicitly modeling sequential risk resolution, timing, and interdependencies across projects and indications.
  - **Chapter 7: Portfolio Optimization—**This chapter presents portfolio optimization as a rigorous, quantitative framework for selecting the combination of biopharma R&D investments that maximizes value, balances risk, and satisfies strategic and resource constraints by identifying efficient-frontier portfolios.

- **Chapter 8: Project Prioritization—**This chapter describes project prioritization as a structured approach for ranking biopharma initiatives using financial metrics and multi-objective frameworks such as multiple objective decision analysis to integrate value, risk, cost, and strategic fit under resource constraints.
- **Chapter 9: Best Practices in Portfolio Management—**This chapter presents a comprehensive framework for achieving mature, value-driven EPPM in biopharma, emphasizing capability development across strategy, process, people, and technology domains.
- **Chapter 10: Epilogue—**This chapter summarizes CREOPM™ as a structured, enterprise-level framework that integrates categorization, risk analysis, evaluation, optimization, prioritization, and management to maximize value in complex biopharma R&D portfolios.

ACKNOWLEDGMENTS

The inherent complexity and sustained effort required to write a book are far from trivial, particularly when coauthors are working across different time zones while balancing professional responsibilities and family commitments. Under such conditions, successful collaboration depends critically on a shared mindset, aligned values, and a common passion for the subject matter. Fortunately, these elements were present from the very beginning of this project.

From the outset, we were fortunate to work with an exceptional editor, Stephen Buda of J. Ross Publishing, whose thoughtful refinement and steady guidance were instrumental in shepherding this manuscript from its earliest drafts through to final production. His contributions significantly improved both the clarity and coherence of the work.

From Richard Bayney:
To my wonderful wife, Pauls, who has been the bedrock of my existence and my constant companion through every chapter of life since Ma passed on—your strength, patience, and unwavering love have sustained me in ways words cannot adequately capture. You have stood beside me at every step of the journey, offering clarity in moments of uncertainty and warmth in times of challenge. To my precious children, Ma and Zico, whose presence has brought immeasurable joy, laughter, and purpose into my life—though I try, I can never fully express how profoundly fortunate I am to have you both. You are my greatest source of inspiration and my enduring reminder of what truly matters. And to my precious and loving granddaughters, Lexi and Savi—your boundless joy, infectious laughter, and unguarded curiosity have been a constant source of light in my life. Through you, I have learned anew the virtues of patience, presence, and gentle countenance that help define the true gift of grandparenthood.

I have been immensely fortunate to have formed friendships that have grown into bonds of lifelong brotherhood—Terry Banarsee, Robin Naraine, Martin White, and Subinay Ganguly, along with Rajendra Tiwari and Ruthven Thompson, who were both taken far too soon. Each of you enriched my life in ways that time cannot diminish, through shared experiences, loyalty, and unwavering support. Thank you all for welcoming me into your lives, for the memories we created together, and for the enduring imprint you have left on my heart.

As always, to my wonderful grandmother, Ma, who possessed a wisdom and humanity that surpassed that of anyone I have ever known. Her boundless and unconditional love, quiet strength, and deeply rooted values shaped the person I have become. I thank her every day for her sacrifices and her guidance, and for instilling in me a moral compass that has guided me throughout my life. Until we meet again, Ma.

From Jose Orellana:
To my wife, Sonia, and my daughters, Sonia Elizabeth and Emilia. I can't think of a better team to have in my corner or better people with whom to share our adventures around the world.

And to my parents, Hildegar and Jose, who made the difficult decision many years ago to let me pursue studies in a faraway place. That decision made me the person I am today, and I thank you for that.

I am honored to join Richard as a coauthor, and I thank him for his mentorship. I would also like to thank Lumivero for their support and for continuing to innovate and develop software in the risk analysis space.

ABOUT THE AUTHORS

RICHARD BAYNEY

Richard Bayney is the president and founder of Project & Portfolio Value Creation (PPVC), a specialized consulting boutique that delivers an integrated suite of services spanning executive education, decision-support analytics, asset valuation, and R&D portfolio strategy. PPVC's work is grounded in rigorous applications of decision analysis, risk analysis, and portfolio management, and is applied across multiple innovation-driven sectors, including biopharmaceuticals, medical devices and diagnostics, consumer care, and agriculture. Through this work, Richard advises organizations on aligning scientific uncertainty, regulatory risk, and capital allocation with long-term strategic and commercial objectives.

In parallel with his consulting practice, Richard has an extensive academic and professional speaking background. He has served as a lecturer at the University of Pennsylvania, where he taught graduate and executive courses in decision modeling and project portfolio management. He is also a frequently invited speaker at industry forums, where he addresses topics such as decision and risk analysis, portfolio optimization, and strategic planning in drug development.

Richard brings more than four decades of industry and consulting experience to his work. He is a 23-year veteran of the biopharma industry, having held roles at Merck, Bayer, Bristol-Myers Squibb, and Johnson & Johnson. In addition, he has spent 18 years in management consulting, working primarily with clients in the United States and Europe. Over the course of his career, he has built and led functions in strategic planning, decision analysis, and portfolio management, and has hands-on operational experience, including two years as an international project manager for a marketed cardiovascular therapy.

Earlier in his career, Richard spent a decade as a molecular biologist, conducting research on gene expression in drug detoxification systems and in the pathophysiology of Alzheimer's disease. He has an M.Sc. and Ph.D. from the University of London, an MBA from Columbia University, and professional certification as a Project Management Professional (PMP) from the Project Management Institute.

JOSE ORELLANA

Jose Orellana is a senior business consultant and quantitative solutions engineer at Lumivero with over 25 years of experience applying numerical modeling to high-stakes decision making. As a globally recognized expert in the DecisionTools Suite (@RISK, PrecisionTree, Evolver) and XLSTAT, Jose has advised organizations worldwide on navigating the inherent uncertainties of complex R&D cycles.

While his foundational expertise was forged in the demanding engineering environments of Schlumberger and P&G, his work now focuses on the *last mile* of decision analysis—the critical bridge between raw data and executive strategy. Leveraging a mastery of Python, machine learning, and traditional Monte Carlo simulation, Jose provides a robust framework for modeling the binary outcomes and long-tail risks characteristic of the pharmaceutical and life sciences sectors.

Jose holds a B.S. in Electrical Engineering from Cornell University, where he graduated Magna Cum Laude and was inducted into the Tau Beta Pi and Eta Kappa Nu honor societies. His interdisciplinary approach is further bolstered by a Data Analytics Certification from UC Berkeley and a Diploma of Management from the Australian Institute of Management. He currently resides in Perth, Western Australia, with his wife and two teenage daughters.

This book has free material available for download from the Web Added Value™ resource center at *www.jrosspub.com*

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Downloads for *Decision Analysis and Portfolio Management in the Biopharma Industry* include figures and tables that were too large or complex to fit inside the printed book and a bonus chapter on attrition in drug development.

Section I

Decision Analysis and Portfolio Management in the Biopharma Industry

1

DRUG RESEARCH AND DEVELOPMENT WITHIN AN EVOLVING INDUSTRY

Some of the figures and tables in this chapter are too large or complex to properly format in printed form. Figures and tables marked with a "WAV" label can be downloaded from the Web Added Value Download Resource Center at www.jrosspub.com/wav for proper viewing.

1.1 THE RESEARCH AND DEVELOPMENT FUNNEL—THE IMPACT OF RISK, COST, AND TIME TO PRODUCTIVITY

Since the early 2000s, the biopharmaceutical industry (biopharma) has experienced sustained structural disruption, fundamentally reshaping operating models across leading organizations. A primary driver has been the widespread erosion of intellectual property protection for blockbuster products, undermining many companies' ability to sustain the double-digit revenue growth that characterized the late twentieth century.

This challenge has been compounded by persistent difficulty in replenishing late-stage and commercial portfolios fast enough to offset generic and biosimilar competition. Although global approvals of new molecular entities (NMEs) have increased—averaging ~51 per year from 2015 through 2019 and rising to ~76 annually from 2020 through 2024—the distribution of innovation remains highly concentrated. Of the 634 NMEs approved globally between 2015 and 2024, oncology (34.4%) and neurology (12.1%) accounted for nearly half of all launches (IQVIA 2025). In 2024 alone, emerging biopharma companies (EBPs), defined by research and development (R&D) spend below $200M and revenues under $500M, originated ~85% of the 48 NMEs approved in the U.S. market. That same year, small-molecule (new chemical entity) and biologic (new biologic entity) modalities contributed roughly equally, highlighting continued platform diversification (IQVIA 2025).

Despite major advances in discovery technologies—such as high-throughput screening, combinatorial chemistry, and genomics-enabled target identification—overall R&D conversion efficiency has improved only marginally. While discovery throughput has expanded dramatically, downstream clinical and regulatory attrition rates have remained largely unchanged. In response, the industry has increasingly externalized discovery and development through outsourcing and offshoring, while reducing internal R&D headcount. In parallel, mergers and acquisitions have become a dominant strategy to augment pipelines, diversify risk, and capture operational synergies, often followed by further workforce rationalization.

Although these measures may enhance near-term efficiency, their ability to deliver durable improvements in long-term R&D productivity is uncertain. As a result, sustainable value creation is

increasingly viewed as dependent less on organizational scale and more on disciplined, data-driven portfolio management in an environment characterized by high technical failure rates and substantial commercial uncertainty. Effective portfolio governance requires decision frameworks that integrate strategic intent with probabilistic assessments of risk, value, and timing—addressing not only which assets to advance, but also when and why capital should be allocated.

A biopharma portfolio typically comprises two components: an R&D portfolio (*pipeline*) spanning research, clinical development, and regulatory submission, and a portfolio of marketed products (*base business*) generating current revenues. By convention, the pipeline is burdened primarily by technical and regulatory risk, while the commercial portfolio faces market uncertainty driven by competition and pricing pressure but minimal technical risk. Many organizations—particularly EBPs—may have robust pipelines without any marketed products. Managing the interaction between these portfolio components has therefore become a critical determinant of long-term resilience and shareholder value.

Industry attrition statistics underscore the magnitude of this challenge. Based on historical success rates, approximately 23–36 drug candidates of chemical or biological origin are required to achieve FDA approval of a single product (see Figure 1.1). Of these, roughly 12–18 advance to preclinical development, 8–14 enter clinical development, and only one or two reach the registrational phase, ultimately yielding one approved product. This funnel structure necessitates robust portfolio decision-making processes to maximize the value of constrained capital and human resources.

Drug *discovery*, typically spanning two to four years (Rang 2006), includes three core activities. *Target selection and validation* focus on identifying and confirming disease-relevant, druggable molecular targets using genomic, proteomic, computational, and translational approaches. *Lead identification* centers on developing and deploying biochemical, biophysical, and cell-based assays to screen

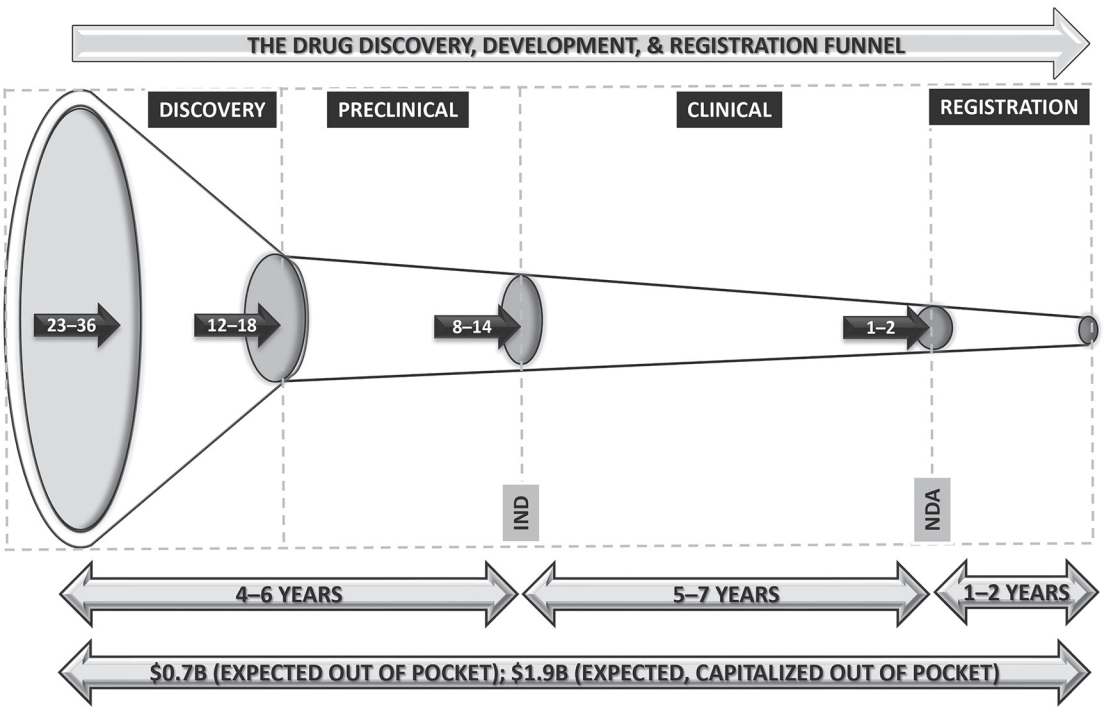


Figure 1.1 The drug discovery, development, and registration funnel.

chemical or biologic libraries, triaging hits based on potency, selectivity, and preliminary pharmacokinetics (PK); adsorption, distribution, metabolism, and excretion characteristics (ADME), and prioritizing lead series through structure–activity relationships (SAR). *Lead optimization* involves iterative refinement of selected leads through medicinal chemistry or modality-specific engineering, supported by in vitro and in vivo pharmacology, PK/PD (pharmacodynamic) characterization, developability assessments, and translational biomarker identification to enable candidate selection and readiness for Good Laboratory Practice (GLP) toxicology and first-in-human (FIH) studies.

Preclinical development typically spans 18–24 months and includes following Good Manufacturing Practices in the manufacture of drug substance and product, dose-ranging and tolerability studies, formulation and stability characterization, safety pharmacology, genotoxicity and repeat-dose toxicology, and establishment of validated analytical methods. These activities culminate in the preparation of the Investigational New Drug (IND) dossier and investigator's brochure from the Institutional Review Board, including Chemistry, Manufacturing, and Controls, for regulatory submission.

Following IND authorization, clinical development proceeds sequentially over ~5–8 years. Phase I studies assess safety, tolerability, and human PK/PD. Phase II trials refine dose–response relationships, establish proof-of-mechanism (PoM) or proof-of-concept (PoC), and select optimized dosing regimens. Phase III trials provide statistically powered confirmatory evidence of safety and efficacy to support regulatory approval, while Phase IV encompasses post-marketing commitments and pharmacovigilance. Upon completion, a New Drug Application is submitted, typically requiring 1–1.5 years for FDA review. Across the full discovery-to-approval continuum, the risk-adjusted, capitalized cost of a successful FDA approval is estimated at ~$1.7B–$3.4B, inclusive of the cost of failed projects (Paul et al. 2010; DiMasi et al. 2016; Sertkaya et al. 2024).

Throughout this process, portfolio decisions must be made under conditions of extreme technical risk and commercial uncertainty. While project management emphasizes executing individual programs efficiently, portfolio management focuses on selecting the right projects—those that maximize strategic and financial value under constrained resources. This challenge raises critical questions regarding asset entrance, progression, delay, and termination, along with portfolio selection:

- **Asset prioritization and development speed:** Which assets should be actively advanced, and at what development cadence, given capital constraints, probability of technical success, and anticipated value inflection points?
- **Decision readiness and evidentiary standards:** What minimum data packages, decision criteria, and analytical rigor are required to support informed progression, delay, hold, and terminate decisions at each stage of asset maturation?
- **Inter-asset and portfolio interdependencies:** What scientific, operational, or commercial linkages exist across assets—such that outcomes or decisions for one program materially influence the technical and/or commercial viability of others—and how should these dependencies be explicitly modeled and governed?
- **Stage-gate progression discipline:** Should attainment of predefined timelines or milestones automatically trigger advancement to the next development phase, or should progression remain contingent on reassessment of risk-adjusted value, strategic alignment, and opportunity cost?
- **Resource intensity and risk-based funding:** Which programs warrant full resource commitment, which should receive constrained or staged investment, and which should be pursued under *at-risk* funding models to preserve option value while limiting downside exposure?
- **Capital reallocation and opportunity cost management:** At what point should investment in an asset—regardless of prior sunk costs—be discontinued or redeployed toward higher-value internal programs or externally sourced opportunities?

- **Strategic resource allocation across portfolios:** How should financial, human, and operational resources be optimally distributed across projects, programs, and sub-portfolios (e.g., therapeutic area (TA) portfolios) to achieve enterprise-level strategic and financial objectives?
- **Enterprise value maximization in complex organizations:** In multi-TA or multi-business-unit (BU) organizations, how can resources be allocated to maximize aggregate enterprise value while maintaining sufficient autonomy to foster innovation, scientific differentiation, and sustainable growth within individual TAs or BUs?

The purpose of this book is to provide structured guidance and practical answers to these foundational portfolio management questions.

1.1.1 Drivers of Productivity in Biopharma

Over the past three decades, a small handful of biopharma companies—most notably Eli Lilly—have dissected the components of R&D productivity. As early as 2010, Paul et al. published a seminal article aimed at examining ways to improve R&D productivity, in which a *pharmaceutical value equation* was defined as follows:

$$P \propto \frac{WIP \times p(TS) \times V}{CT \times C}$$

where P = productivity, WIP = phase-specific work in process, p(TS) = probability of technical success, V = value, CT = cycle time, and C = cost. This expression reflects the productivity of a pipeline in terms of securing a single product from a specific phase of research or development.

We have proposed modest modifications to this value equation in two forms which are referred to as the *non-risk-adjusted productivity index* (PI) and the *expected* (*or risk-adjusted*) *productivity index* (ePI) that reflect the productivity of a pipeline across all phases of research and development. Accordingly, PI is defined as:

$$PI \propto \frac{\sum_{i=0}^{n} Mean\ CVGS_i}{\sum_{i=0}^{n} Mean\ Cost_i}$$

where $CVGS_i$ = present value of commercial cash flows (i.e., from the point of product launch) given technical and regulatory success and $Cost_i$ = present value of cost cash (out)flows from a specific phase until launch.

Similarly, ePI can be expressed as:

$$ePI \propto \frac{\sum_{i=0}^{n} Mean\ eCVGS_i}{\sum_{i=0}^{n} Mean\ eCost_i}$$

where $eCVGS_i$ = risk-adjusted, present value of commercial cash flows given technical and regulatory success and $eCost_i$ = present value of risk-adjusted cost cash (out)flows from a specific phase until launch. In this way, cycle time (CT) is accounted for in the calculation of the present value of cost cash (out)flows, whether risk-adjusted or not.

Using some of the data from Paul et al. (2010) and Sertkaya et al. (2024), we have adjusted cost per phase in 2010 and 2018 dollars to 2025 dollars using an annual inflation rate of 2.62% and have

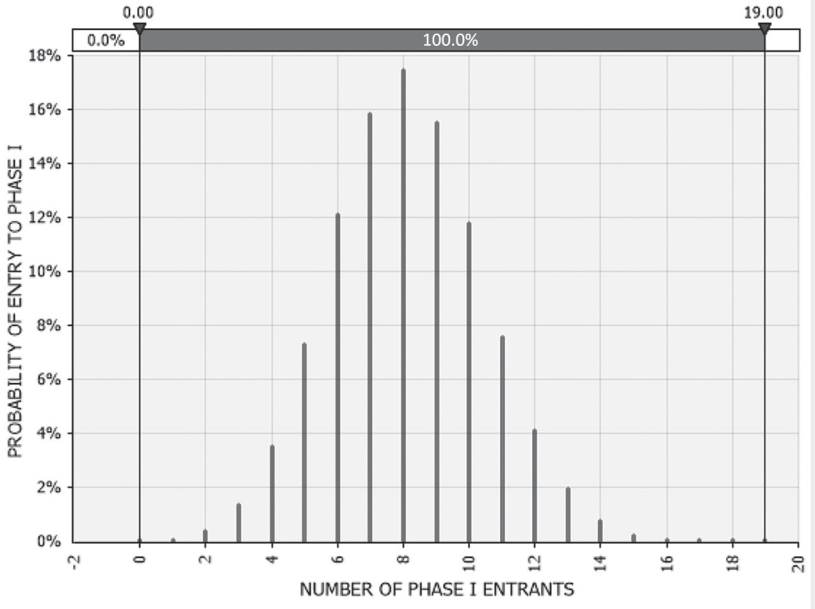
Table 1.1 R&D pipeline throughput attrition model incorporating risk, cost, and cycle time to generate a single new product launch (Modified from Paul et al. 2010 and Sertkaya et al. 2024).

	TARGET-TO-HIT	HIT-TO-LEAD	LEAD OPTIMIZATION	PRECLINICAL	PHASE I	PHASE IIa	PHASE IIb	PHASE III	SUBMISSION TO LAUNCH	LAUNCH
p (Phase Success)	80%	75%	85%	69%	60%	48%	75%	66%	88%	
OUT-OF-POCKET COST IN 2025 $ (M)	1.5	3.7	14.7	7.4	8.5	10.1	15.1	107.0	3.1	171.1
CAPITALIZED OUT-OF-POCKET COST IN 2025 $ (M)	6.1	13.9	48.7	21.4	20.8	21.0	27.1	146.3	3.3	308.5
EXPECTED OUT-OF-POCKET COST IN 2025 $ (M)	33.3	66.7	200.3	85.1	67.8	48.3	34.7	184.2	3.5	723.9
EXPECTED CAPITALIZED OUT-OF-POCKET COST IN 2025 $ (M)	139.1	251.0	661.8	246.9	165.4	100.3	62.2	252.0	3.8	1,882.3
CYCLE TIME (Years)	1.0	1.0	1.5	1.0	2.3	0.8	2.0	3.2	1.4	14.2
PTRS	4.4%	5.5%	7.4%	8.7%	12.5%	20.9%	43.6%	58.1%	88.0%	88.0%
AVERAGE # PROJECTS REQUIRED FOR 1 NEW PRODUCT LAUNCH	22.7	18.1	13.6	11.6	8.0	4.8	2.3	1.7	1.1	1
% TOTAL EXPECTED OUT-OF-POCKET COST PER NEW PRODUCT LAUNCH	4.6%	9.2%	27.7%	11.8%	9.4%	6.7%	4.8%	25.4%	0.5%	

created an R&D pipeline throughput attrition model (see Table 1.1) which allows for an analysis of the cost of generating a commercial product on three metrics as defined by Sertkaya et al. (2024):

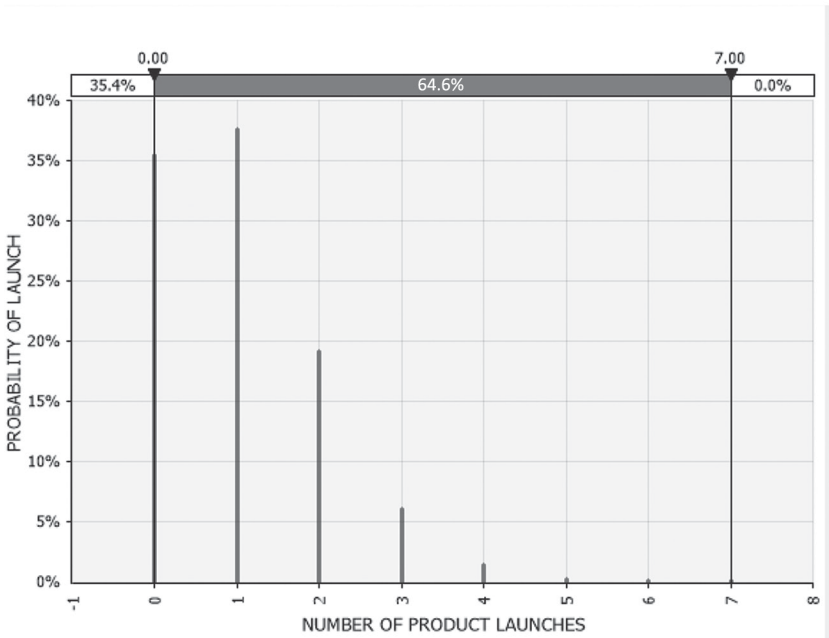
1. **Direct out-of-pocket (OOP) cost:** This represents the cash outlay required to bring a single product to approval, excluding any investments associated with failed projects.
2. **Risk-adjusted or expected OOP cost:** This extends the OOP estimate by accounting for the cost of failures due to attrition at any phase of R&D and registration. As such, this metric distributes the cost burden of attrition across a full portfolio of R&D investments.
3. **Expected capitalized OOP cost:** This elaborates the expected OOP estimate by incorporating the time value of money. It factors in phase-specific timelines, overall program duration, and the opportunity cost of capital accumulated throughout the R&D and registration process.

Given the phase-specific risks shown in Table 1.1, approximately 23 entities are required at the *target-to-hit* stage to generate, on average, a new product launch. As entities are terminated during the research phases, nearly 12 survive to enter preclinical, of which almost 8 advance to the first phase of clinical development. On average, from eight NMEs that enter Phase I, one new product is generated. Because this is a discrete, deterministic analysis, we do not know the likelihood that exactly eight preclinical molecules will enter Phase I, nor do we know that one, less than one, or more than one new product will emerge from these 23 target-to-hit or eight Phase I entities. This is solved by conducting a simulation analysis of the NMEs entering and exiting each phase—the launch results of which are shown in Figures 1.2A and 1.2B. The range of possible entrants from target-to-hit to Phase I is 0–19, with a mean and mode of eight (see Figure 1.2A). Similarly, while the mean and modal number of launches is one, the range of possible launches is 0–7, of which one launch has the highest probability of occurrence at 38% (see Figure 1.2B). It is noteworthy that the second-highest likely outcome is zero launches with a probability of 35%, meaning the probability of securing at least one product launch from 23 target-to-hit NMEs is 65%. This probabilistic analysis demonstrates that while calculations of averages are useful, they should be treated with caution as there are distributions of outcomes associated with each calculated mean.



Statistics	SUM SIM
Cell	23P%@35.2%!D25
Minimum	0
Maximum	19
Mean	8.094
90% CI	± 0.0119
Mode	8
Median	8
Std Dev	2.288
Skewness	0.1321
Kurtosis	2.9384
Values	100000
Errors	0
Filtered	0
Left X	0.00
Left P	0.0%
Right X	19.00
Right P	100.0%
Dif. X	19
Dif. P	100.0%

Figure 1.2A Distribution of Phase I entrants from 23 target-to-hit entrants.



Statistics	SUM SIM
Cell	23P%@4.4%!D25
Minimum	0
Maximum	7
Mean	1.0143
90% CI	± 0.00512
Mode	1
Median	1
Std Dev	0.9837
Skewness	0.9200
Kurtosis	3.7400
Values	100000
Errors	0
Filtered	0
Left X	0.00
Left P	35.4%
Right X	7.00
Right P	100.0%
Dif. X	7
Dif. P	64.6%

Figure 1.2B Distribution of product launches from 23 target-to-hit entrants.

In building our pipeline throughput model (data shown in Table 1.1), we have done the following:

- **Risk—**Used phase-specific *p*(Success) data for the four stages of research from Paul et al. (2010) and for the four stages of clinical development and registration from Sertkaya et al. (2024). Additionally, while keeping the *p*(Success) of Phase II at 0.36 (Sertkaya et al. 2024), we have disaggregated this phase into Phase IIa and Phase IIb and assigned a lower *p*(Success) for Phase IIa (0.48) than for Phase IIb (0.75).
- **Cost—**Taken phase-specific OOP cost in 2010 dollars for the four stages of research from Paul et al. (2010) and for the four stages of clinical development and registration in 2018 dollars from Sertkaya et al. (2024) and adjusted for inflation to 2025 dollars. The Phase II OOP cost from Sertkaya et al. (2024) has been disaggregated into Phase IIa and Phase IIb with Phase IIb being more expensive ($15.1M) than Phase IIa ($10.1M).
- **Cycle time—**Modified phase-specific cycle time for the four stages of research from Paul et al. (2010) and applied cycle time for the four stages of clinical development and registration from Sertkaya et al. (2024). The Phase II cycle time from Sertkaya et al. (2024) has been disaggregated into Phase IIa and Phase IIb with Phase IIb taking longer (2.0 years) than Phase IIa (0.8 years).
- **Inflation and cost of capital—**Utilized 2.62% annually and 11.0%, respectively.

Beginning with the target-to-hit phase, and without accounting for the cost of failures or opportunity cost of capital, the OOP cost to bring an NME product through the pipeline to launch is $171M. When opportunity cost is considered, this amount rises to $309M (see Table 1.1). When the cost of failures, but not the opportunity cost of capital, is taken into consideration, the expected OOP cost of securing a single NME product launch is $724M. On an expected capitalized basis, i.e., when both the cost of failures and opportunity cost of capital are accounted for, the OOP cost of successfully navigating every phase of research, clinical development, and registration to bring a single NME product to market is $1.882B (see Table 1.1). This estimate is lower than that of Paul et al. ($2.621B in 2025 dollars; based on self-reported data by members of the Pharmaceutical Benchmarking Forum) and higher than the average estimate of Sertkaya et al. ($1.053B in 2025 dollars; based on publicly available data).

While including the post-approval phase (Phase IV), but without accounting for costs and durations associated with target-to-hit, hit-to-lead, and lead optimization phases, Sertkaya et al. (2024), using publicly available databases, have reported phase-specific costs by TA as shown in Table 1.2.

In the study of Sertkaya et al. (2024), aggregate, OOP costs for non-clinical, clinical, regulatory, and Phase IV phases range from a low of $72.5M ($52.7M–$83.7M) for the genitourinary TA to a high of $297.2M ($82.8M–$515.9M) for pain and anesthesia. When accounting for the cost of failures due to the probability of successfully transitioning from one phase to another, the corresponding costs are $244.0M ($152.4M–$345.8M) for genitourinary and $887.9M ($325.3M–$1,476.9M) for pain and anesthesia TAs. Finally, on a capitalized basis, the analogous costs are $394.9M ($228.9M–$626.7M) for genitourinary and $1,756.2M ($648.5M–$3,171.5M) for pain and anesthesia (see Table 1.2). While it is clear that the cost of drug development remains idiosyncratic to a TA and, more important, to a specific disease, in our opinion, it is incumbent on analysts to utilize a transparent, financially defensible methodology based on after-tax cash flows from which to assess the impact of revenues and costs on R&D productivity. Further, as Sertkaya et al. (2024) have shown, the use of average costs to compute the cost of drug discovery and development by any metric can be quite misleading unless adequate attention is paid to the intended TA(s) of origin.

When investigated by TA, Sertkaya et al. (2024) have shown that from non-clinical research, mean aggregate drug development cycle time to launch ranges from 121 months (genitourinary) to

Table 1.2 Phase-specific costs across TAs measured by OOP, expected OOP, and expected capitalized OOP costs (reproduced with permission: Sertkaya et al. 2024).

THERAPEUTIC AREA	PTRS FROM NON-CLINICAL %, (95% CI)	OOP $M	EXPECTED OOP $M	EXPECTED CAPITALIZED OOP $M
ANTI-INFECTIVE	15.5 (10.9-21.7)	109.4 (65.3-186.7)	251.0 (166.7-360.3)	378.7 (244.6-556.1)
CARDIOVASCULAR	7.1 (3.6-15.3)	153.5 (73.7-593.3)	519.3 (273.9-2,168.1)	890.3 (445.0-3,807.9)
CENTRAL NERVOUS SYSTEM	6.7 (4.0-12.9)	113.0 (84.9-132.0)	463.7 (302.5-714.3)	894.6 (526.1-1,550.3)
DERMATOLOGY	8.5 (8.5-8.5)	143.8 (60.0 - 253.0)	419.1 (221.5-688.9)	683.1 (349.5-1,252.2)
ENDOCRINE	11.1 (6.2-17.7)	181.2 (139.2-226.8)	492.0 (359.4-728.4)	780.0 (541.0-1,243.2)
GASTROINTESTINAL	8.2 (6.4-10.3)	216.7 (101.4-363.6)	591.1 (285.2-898.3)	963.5 (451.5-1,564.5)
GENITOURINARY SYSTEM	11.8 (7.8-16.3)	72.5 (52.7-83.7)	244.0 (152.4-345.8)	394.9 (228.9-626.7)
HEMATOLOGY	17.8 (17.8-17.8)	152.9 (82.5-230.7)	381.9 (214.3-578.0)	720.4 (348.2-1,295.1)
ONCOLOGY	4.1 (2.2-8.6)	84.7 (65.5-121.6)	595.5 (344.3-1,041.0)	1,209.2 (624.6-2,388.7)
RESPIRATORY SYSTEM	8.6 (5.3-11.7)	167.8 (94.0-332.2)	409.3 (246.3-685.5)	686.4 (399.5-1,164.1)
OPHTHALMOLOGY	13.9 (11.6-16.2)	256.2 (101.2-381.8)	787.6 (333.4-1,179.7)	1,191.6 (496.3-1,910.8)
PAIN & ANESTHESIA	8.5 (8.5-8.5)	297.2 (82.8-515.9)	887.9 (325.3-1,476.9)	1,756.2 (648.5-3,171.5)
IMMUNOMODULATION	11.9 (7.5-18.0)	119.3 (74.0-180.1)	363.7 (201.7-586.2)	605.8 (306.1-1,041.9)
ALL	8.5 (3.9-16.1)	172.7 (132.5-197.9)	515.8 (327.0-773.2)	879.3 (416.9-1,307.3)

171 months (oncology). If Phase IV is included, between 29.9 and 45.7 months need to be added for these two TAs (see Figure 1.3). While oncology boasts the shortest cycle time necessary for FDA registration (9.6 months), it takes the longest in Phase I (31.9 months) among all TAs, marginally longer than that of the central nervous system in Phase II (40.3 months), and second only to hematology in Phase III (57.7 months). If modeled on the basis of the average of all 13 TAs, eight TAs would have shorter durations, while five TAs would show longer cycle times than the average.

As it is with phase-specific costs, it is tempting to draw conclusions with respect to which TAs show shorter or longer cycle times in drug development. However, it is more important to recognize that over the past three decades, the lines of distinction between clinical development phases have become intentionally blurred. What was previously deemed a Phase I study to investigate safety and tolerability in humans has, in many cases, morphed into a longer, riskier study to investigate early efficacy using either a single ascending drug dose or multiple ascending doses. Understandably, this type of trial lends itself to a longer cycle time with higher cost and higher risk. The same is true of Phase II, which is a combination of Phase IIa to demonstrate that the drug conveys physiologic benefit in accordance with its hypothesized target(s) and Phase IIb, which is geared toward finding the optimal dose (and regimen) necessary to conduct registrational trials in Phase III. The authors therefore remain cautious about drawing inferences and conclusions from data sets, no matter how large they may be.

While phase-specific cost and cycle time affect the denominator of the R&D productivity equation, phase-specific risk remains a keenly debated topic as a critical numerator. Paul et al. (2010) have shown, quite elegantly, the key areas for improving R&D productivity in which clinical risk dominates all other parameters. We have used our model to conduct a similar sensitivity analysis, which shows that risk—defined as 1-p(Success)—and, in particular, clinical risk, remains the most important determinant of R&D productivity.

The mean OOP expenditure required to advance an NME from discovery to market authorization is approximately $171M, with late-stage clinical development representing the primary cost driver. Phase III clinical development alone accounts for roughly $107M of this total. Sensitivity

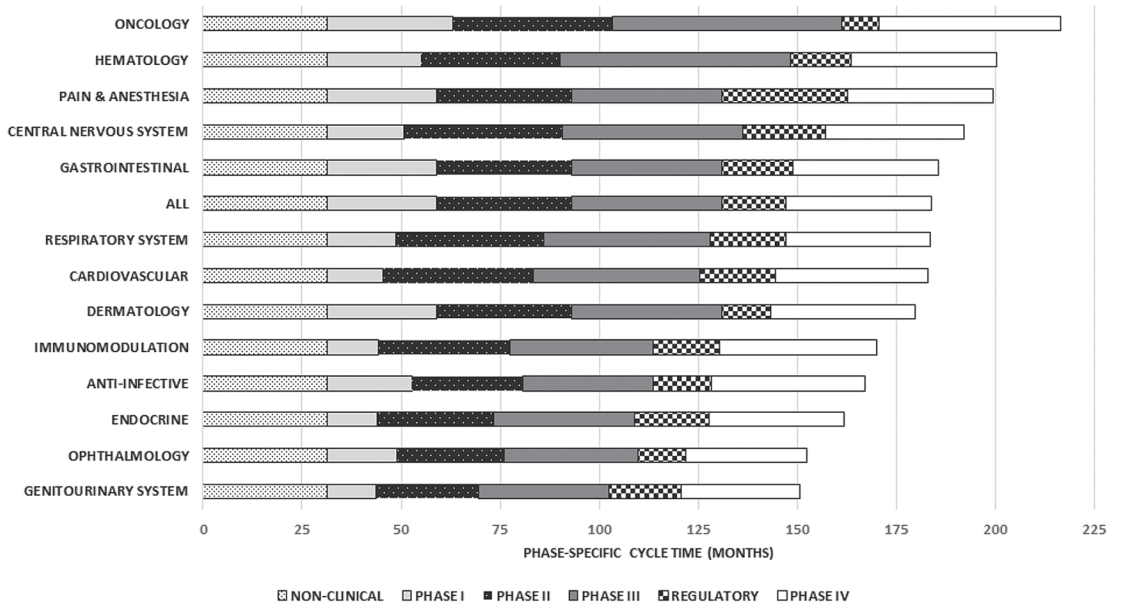


Figure 1.3 Phase-specific cycle times across TAs (Sertkaya et al. 2024).

analysis demonstrates that a ±25% variation in Phase III base cost produces a corresponding range in total OOP expenditure from approximately $144M to $198M. In contrast, equivalent proportional changes applied to OOP costs in other development phases exert only modest effects on aggregate mean OOP cost, underscoring the disproportionate influence of Phase III spending (see Figure 1.4).

When costs are evaluated on an expected-value basis that incorporates phase-specific probabilities of technical and regulatory success, the average OOP investment required to achieve a single marketed NME increases substantially to approximately $724M. Under this framework, the expected OOP cost is highly sensitive to changes in success probabilities across most development stages, with the largest contributions arising from Phases IIa and III. For example, adjusting the probability of success in Phase IIa from its base value of 48% by ±15 percentage points results in an expected OOP cost range spanning approximately $605M to $952M (see WAV Figure 1.5). A comparable perturbation applied to the Phase III success probability (base value 66%) yields a range from roughly $591M to $936M. Among phase-specific OOP expenditures, lead optimization—despite its relatively modest absolute cost ($14.7M)—emerges as the most influential cost variable on expected OOP outcomes, producing a swing of nearly $100M when varied by ±25%.

Capitalized OOP cost, which accounts for development duration and the time value of money, exhibits a distinct sensitivity profile. Within this framework, Phase III direct costs again dominate all other phase-specific cost inputs. A ±25% change in Phase III OOP expenditure results in a capitalized cost range of approximately $272M to $345M per successfully launched NME. Among cycle-time assumptions, Phase III duration (base value 3.2 years) exerts the greatest leverage on capitalized cost; varying this parameter by ±25% drives capitalized OOP cost between approximately $290M and $329M. As expected, the assumed cost of capital is a critical determinant of capitalized investment. A one percentage point decrease in the cost of capital reduces capitalized OOP cost to approximately $292M, while a one percentage point increase raises it to roughly $327M.

When all key inputs—including phase-specific probabilities of success, OOP costs, development cycle times, and cost of capital—are simultaneously subjected to sensitivity analysis, the resulting

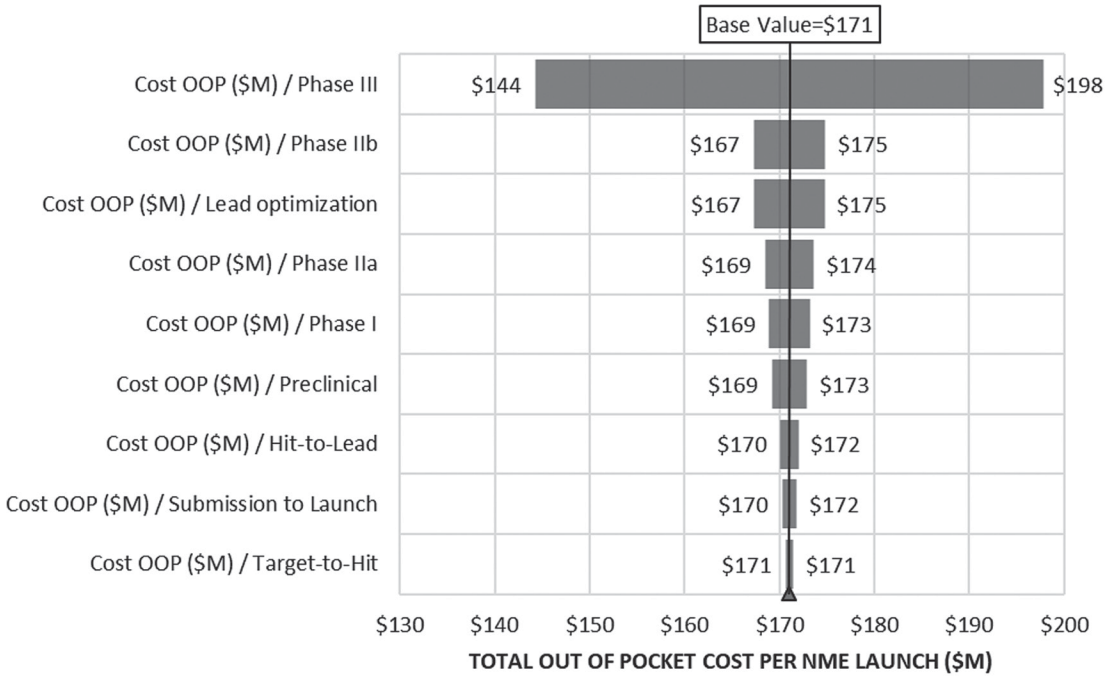


Figure 1.4 Impact of phase-specific cost variables to OOP cost per NME launch.

variability in expected capitalized OOP cost is substantial (see Figure 1.6). The probability of success in Phase IIa emerges as the single most influential parameter. Increasing this probability from its base value of 48% to 63% lowers expected capitalized OOP cost to approximately $1.51 billion, whereas reducing it to 33% increases expected cost to roughly $2.59 billion. The probability of success in Phase III represents the second most impactful variable, shifting expected capitalized OOP cost from approximately $1.53 billion to $2.44 billion when varied by ±15 percentage points from its base value of 66%.

Notably, the cost of capital exerts greater influence on expected capitalized OOP cost than any individual phase-specific cost or cycle-time variable. A reduction in the cost of capital from 11% to 10% lowers the expected capitalized OOP cost to approximately $1.72B, while an increase to 12% raises it to approximately $2.06B. Among direct cost inputs, lead optimization remains the most sensitive driver, whereas Phase III duration dominates among cycle-time parameters in shaping the overall capitalized investment required to bring an NME to market.

Across all TAs, Sertkaya et al. (2024) report no differentiation in attrition rates in the non-clinical phase of research. In Phase I, the probability of success ranges from a low of 60% (dermatology and pain and anesthesia) to a high of 86% (ophthalmology) (see Table 1.3).

In Phase II, where attrition rates are at their highest, a probability of success of greater than 50% is observed in only two TAs (hematology and ophthalmology), with a low of 27% reported for oncology and diseases of the respiratory system. Approximately one-third of all projects in five TAs—cardiovascular, central nervous system, dermatology, gastrointestinal, and pain and anesthesia—succeed in Phase II. This phase of clinical development is often referred to as the *valley of clinical death* and will be discussed in detail in this chapter.

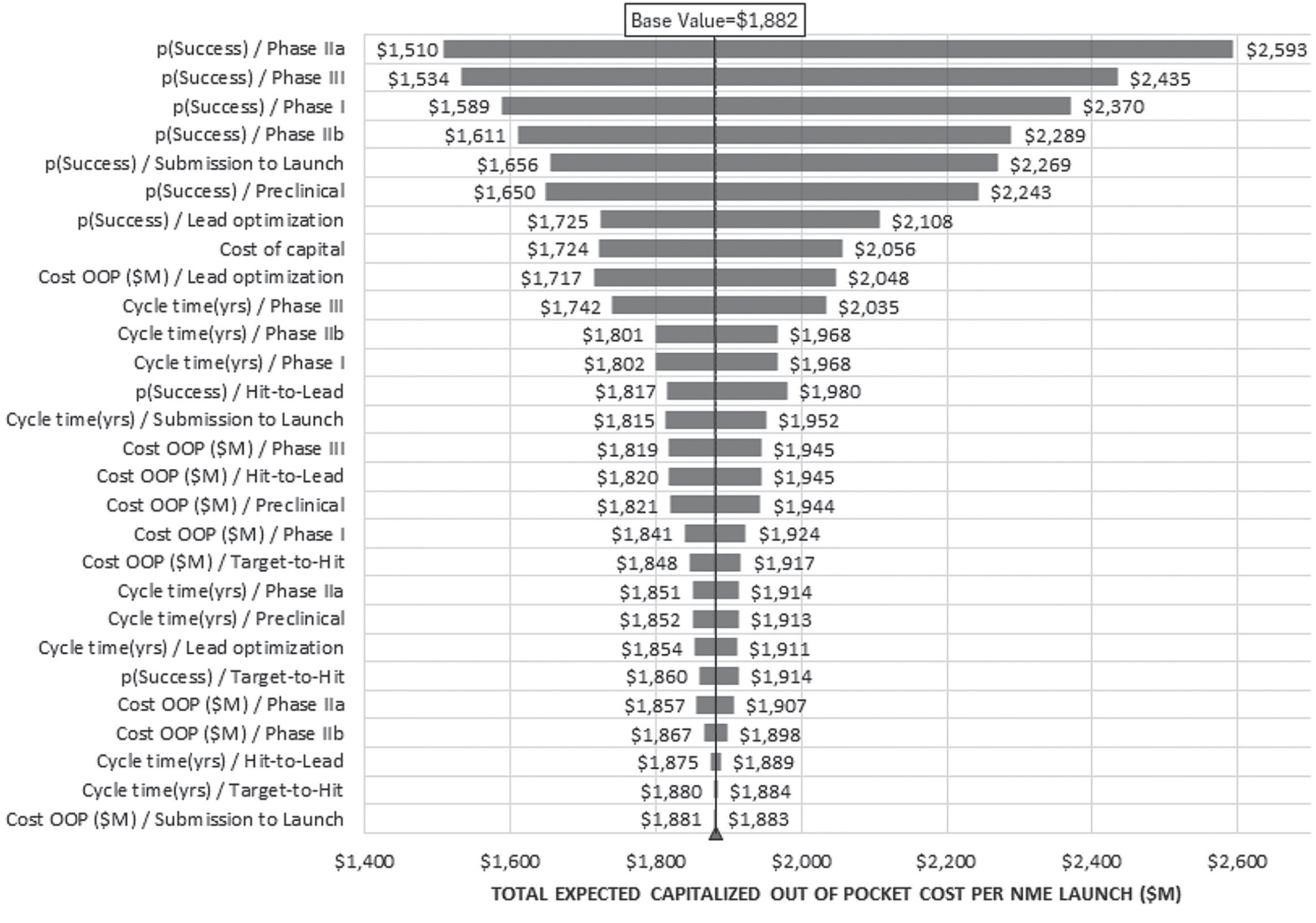


Figure 1.6 Impact of phase-specific risk, cost, and cycle time, and cost of capital variables to expected capitalized OOP cost per NME launch.

Table 1.3 Phase-specific probabilities of success across TAs (Sertkaya et al. 2024).

THERAPEUTIC AREA	NON-CLINICAL	PHASE I	PHASE II	PHASE III	REGULATORY
ANTI-INFECTIVE	68.0%	65.9%	49.6%	74.1%	94.4%
CARDIOVASCULAR	68.0%	65.0%	37.1%	57.6%	75.5%
CENTRAL NERVOUS SYSTEM	68.0%	61.5%	33.1%	55.9%	87.0%
DERMATOLOGY	68.0%	60.2%	35.9%	65.5%	88.3%
ENDOCRINE	68.0%	68.0%	46.3%	63.9%	81.3%
GASTROINTESTINAL	68.0%	71.6%	35.3%	55.3%	86.2%
GENITOURINARY SYSTEM	68.0%	62.9%	44.9%	71.4%	85.7%
HEMATOLOGY	68.0%	73.3%	56.6%	75.0%	84.0%
ONCOLOGY	68.0%	61.5%	26.8%	42.7%	85.5%
RESPIRATORY SYSTEM	68.0%	68.5%	27.4%	75.6%	89.5%
OPHTHALMOLOGY	68.0%	86.0%	52.7%	58.3%	77.5%
PAIN & ANESTHESIA	68.0%	60.2%	35.9%	65.5%	88.3%
IMMUNOMODULATION	68.0%	69.9%	40.1%	65.4%	95.3%
ALL	68.0%	60.2%	35.9%	65.5%	88.3%

In Phase III, roughly three-fourths of all projects are successful in three TAs (anti-infectives, hematology, and diseases of the respiratory system) while less than half succeed in oncology. In the United States, with the exception of cardiovascular and ophthalmology, registration is achieved successfully more than 80% of the time in all TAs, with the highest probabilities of registrational success reported in anti-infectives and immunomodulation.

At what cost is phase-specific risk resolved within and between TAs? An examination of phase-specific risk resolution across selected TAs reveals substantial heterogeneity in both the timing and cost at which technical uncertainty is reduced. Using average cross-TA data (Sertkaya et al. 2024), projects entering non-clinical development exhibit a cumulative probability of technical and regulatory success (PTRS) to launch of approximately 8.5%. Completion of non-clinical development—at an average cost of $11.8M—increases cumulative PTRS to 12.5%, corresponding to the resolution of roughly four percentage points of risk (see Table 1.4 and Figure 1.7).

Assuming uninterrupted progression through development to regulatory approval, Phase I resolves an additional 8.3 percentage points of risk at an average cost of $7.1M. Phase II accounts for the largest single increment of risk resolution—approximately 37 percentage points—at a cost of $21.0M, while Phase III resolves an additional 30.5 percentage points at a substantially higher cost of $89.3M. Registration contributes the final 11.7 percentage points of risk resolution at a comparatively modest cost of $2.6M.

Across the four TAs analyzed, oncology exhibits the lowest average launch cost ($69.9M) but retains disproportionate technical risk into late-stage development. Fewer than 10% of oncology programs entering Phase II ultimately achieve launch, compared with materially higher rates in central nervous system (16.1%), anti-infective (34.7%), and hematology (35.7%). As a result, oncology programs entering Phase III succeed at a markedly lower rate (36.5%), reflecting substantial unresolved risk carried forward from earlier phases. Parenthetically, hematology has the highest launch cost burden at $121.8M.

Table 1.4 The cost of phase-specific risk resolution (I) (Sertkaya et al. 2024).

AVERAGE	*p*(SUCCESS)	COST ($M)	AVERAGE CUM *p*(SUCCESS)	AVERAGE CUM COST ($M)
NON-CLINICAL	68.0%	11.8	8.5%	11.8
PHASE I	60.2%	7.1	12.5%	18.9
PHASE II	35.9%	21.0	20.8%	39.9
PHASE III	65.5%	89.3	57.8%	129.2
REGISTRATION	88.3%	2.6	88.3%	131.8

ONCOLOGY	*p*(SUCCESS)	COST ($M)	ONCOLOGY CUM *p*(SUCCESS)	ONCOLOGY CUM COST ($M)
NON-CLINICAL	68.0%	7.0	4.1%	7.0
PHASE I	61.5%	8.1	6.0%	15.1
PHASE II	26.8%	14.5	9.8%	29.6
PHASE III	42.7%	37.7	36.5%	67.3
REGISTRATION	85.5%	2.6	85.5%	69.9

CENTRAL NERVOUS SYSTEM	*p*(SUCCESS)	COST ($M)	CENTRAL NERVOUS SYSTEM CUM *p*(SUCCESS)	CENTRAL NERVOUS SYSTEM CUM COST ($M)
NON-CLINICAL	68.0%	8.7	6.7%	8.7
PHASE I	61.5%	6.8	9.9%	15.5
PHASE II	33.1%	16.1	16.1%	31.6
PHASE III	55.9%	59.4	48.6%	91.0
REGISTRATION	87.0%	2.6	87.0%	93.6

ANTI-INFECTIVE	*p*(SUCCESS)	COST ($M)	ANTI-INFECTIVE CUM *p*(SUCCESS)	ANTI-INFECTIVE CUM COST ($M)
NON-CLINICAL	68.0%	9.4	15.5%	9.4
PHASE I	65.9%	2.8	22.9%	12.2
PHASE II	49.6%	22.3	34.7%	34.5
PHASE III	74.1%	41.6	70.0%	76.1
REGISTRATION	94.4%	2.6	94.4%	78.7

HEMATOLOGY	*p*(SUCCESS)	COST ($M)	HEMATOLOGY CUM *p*(SUCCESS)	HEMATOLOGY CUM COST ($M)
NON-CLINICAL	68.0%	17.9	17.8%	17.9
PHASE I	73.3%	17.3	26.1%	35.2
PHASE II	56.6%	22.1	35.7%	57.3
PHASE III	75.0%	61.9	63.0%	119.2
REGISTRATION	84.0%	2.6	84.0%	121.8

In contrast, anti-infective and central nervous system programs achieve their largest reductions in risk between Phase II and Phase III—resolving approximately 35.3 and 32.5 percentage points, respectively—at costs of $22.3M and $16.1M. Hematology and central nervous system are the most capital-intensive TAs for late-stage risk resolution—requiring approximately $61.9M and $59.4M, respectively—during Phase III to resolve 21.0 and 38.4 percentage points of remaining risk.

Beginning from the non-clinical phase of research, the aggregate probability of technical and regulatory success to a successful registrational drug is highest for hematology (17.8%), anti-infective (15.6%), and ophthalmology (13.9%) and is lowest across oncology (4.1%), central nervous system (6.7%), and cardiovascular (7.1%) (see Figure 1.8).

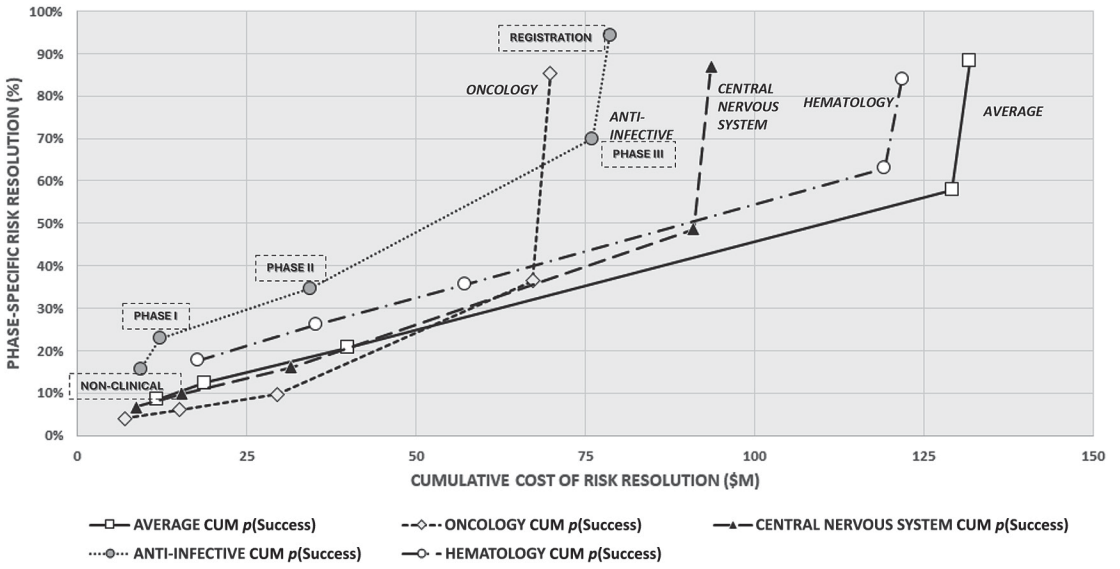


Figure 1.7 The cost of phase-specific risk resolution (II) (Sertkaya et al. 2024).

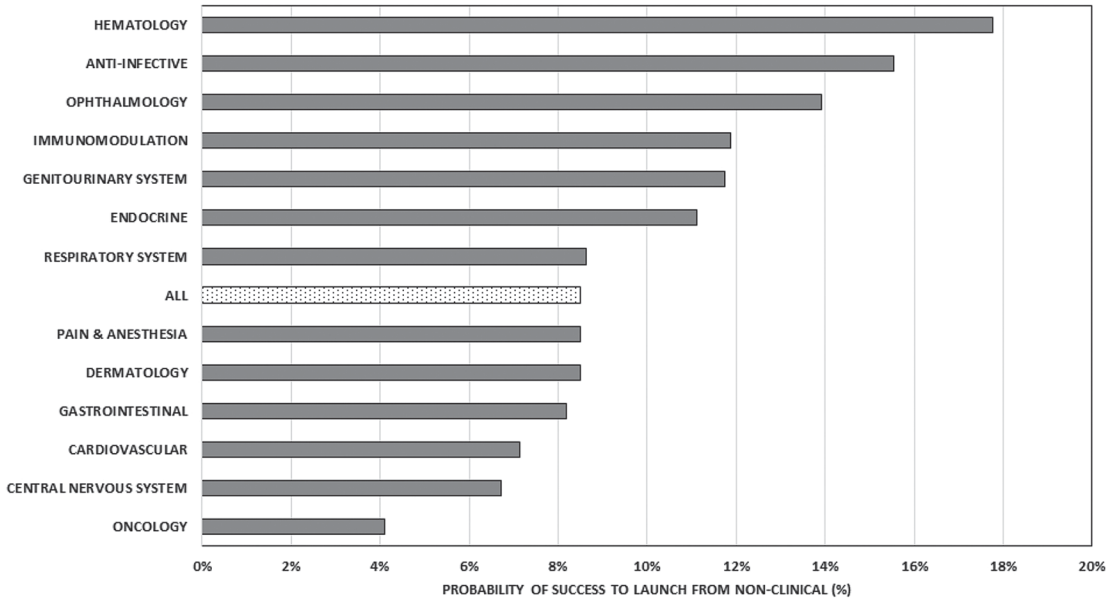


Figure 1.8 Probability of success to launch from non-clinical across all TAs (Sertkaya et al. 2024).

1.2 THE VALLEY OF CLINICAL DEATH

As shown in Table 1.3, clinical probability of success accounts for the highest levels of attrition in R&D productivity. In particular, Phase II, often described as the *valley of clinical death*, continues to be a graveyard for the majority of NMEs. On average, across all TAs, the likelihood of emerging successfully from Phase II is 35.9% with a range of 26.8% (oncology) and 56.6% (hematology) after

$39.9M in OOP cost (range = $29.6M in oncology and $57.3M in hematology) has been spent from the beginning of non-clinical (see Table 1.4) (Sertkaya et al. 2024). It is clear that reducing attrition in Phase II remains the strongest lever for improving R&D productivity and, consequently, to better manage the cost of generating new drug products from novel molecular entities.

From a study of a decade's worth of drug attrition across several TAs (1991–2000), Kola and Landis (2004) have shown that while drug failure due to PK and bioavailability had been reduced dramatically over this period, efficacy, safety, and toxicology remained the major drivers of drug failure. This study points to the broad distinction between largely controllable risks (e.g., bioavailability due to alternative formulations and drug delivery systems) and largely uncontrollable risks (e.g., efficacy due to poor target validation and druggability). In an effort to reduce Phase II (and Phase III) attrition, Eli Lilly has pointed to two key approaches: (a) better target selection—specifically target validation and druggability—and (b) achievement of earlier clinical PoC via the use of biomarkers and surrogate endpoints (Paul et al. 2010). While target selection is a function of earlier target identification, it represents a critical step in the protracted commitment of resources to downstream drug development. The same can be stated of clinical PoC, which sets the stage for the final and most expensive phase of drug development—Phase III. It is here that the biopharma industry continues to struggle with decision making based on imperfect clinical data and information as it attempts to minimize both Type I (false positive) and Type II (false negative) errors.

In response to rising development costs and persistent late-stage attrition, Eli Lilly introduced an alternative clinical development paradigm in the early 2000s aimed at accelerating early human data generation to support earlier investment decisions. Launched in 2002, this model—internally known as *Chorus*—was designed to prioritize early demonstration of human PoC, ideally during Phase I, rather than following a conventional, sequential escalation of clinical investment. By front-loading critical data acquisition, Chorus sought to accelerate go/no-go decisions and limit capital exposure to high-risk assets (Paul et al. 2010; Owens et al. 2015).

The Chorus framework embodied a *quick-win or fast-failure* philosophy, explicitly seeking to maximize changes—positive or negative—in a program's probability of technical success over the shortest feasible timeframe and at minimal cost. This approach later became known as *lean-to-proof-of-concept* (L2POC). Assets selected for L2POC typically had below-average baseline probabilities of success due to uncertainties in target biology, translational relevance, or clinical feasibility, but were considered suitable for early risk reduction through well-defined biomarkers or clinically interpretable endpoints (Owens et al. 2015).

Under this model, the primary objective prior to Phase II was not demonstration of efficacy, but resolution of key mechanistic and translational uncertainties. Chorus programs focused on establishing whether adequate target engagement could be achieved in humans within acceptable safety margins, whether a clinically viable dosing regimen could be defined, and whether PK and PD variability could be sufficiently controlled. Collectively, these criteria defined achievement of PoM, which served as the threshold for committing additional resources to later-stage development (Owens et al. 2015).

Retrospective evaluation of the Chorus model demonstrated a reduction in the number of candidates advancing into Phase II, but a marked improvement in the quality of those that did. Phase II success rates increased from approximately 34% under traditional development to nearly 50% under Chorus. Importantly, early PoC was achieved at substantially lower cost—approximately $6M (2010 dollars) versus ~$22M using conventional approaches (Paul et al. 2010).

Across a ten-year comparison (2002–2012), Eli Lilly reported that cumulative probabilities of technical and regulatory success remained constant at roughly 6% under both paradigms, while total development costs were consistently lower for Chorus programs. Inflation-adjusted OOP, capitalized,

and risk-adjusted capitalized costs were all meaningfully reduced, demonstrating that early, disciplined risk resolution can materially improve capital efficiency without compromising overall success rates (Owens et al. 2015).

Notably, concerns that lean development might significantly extend timelines were not supported by the data. Aggregate development cycle time under Chorus was only approximately six months longer than under traditional development, indicating that improved early-stage decision quality and capital efficiency can be achieved without materially delaying market entry.

It is noteworthy that Owens et al. (2015) have assumed that 50% of Phase II risk is resolved at PoC in the Chorus model. This is a debatable assumption, as we believe there is a far greater risk in achieving a successful PoC (equivalent to Phase IIa) than in conducting a successful dose-finding study (equivalent to Phase IIb). Unfortunately, to our knowledge, there are no published reports of differences between Phase IIa and Phase IIb probability-of-success estimates. To this extent, we have conducted sensitivity analyses of the impact of phase-specific, non-clinical (target-to-hit to preclinical) and clinical (Phase I to Phase III) risks on the expected capitalized cost of bringing one NME successfully to market. A synopsis of the results is as follows:

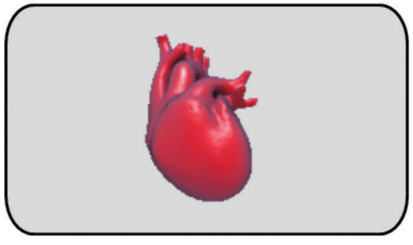
- When varied by ±15 percentage points, the *p*(Success) of preclinical is the most dominant risk variable in research to total expected capitalized OOP cost. At its base value of 69%, expected capitalized OOP cost is $1.882B; when the base value increases by 2.5%, 5.0%, 7.5%, 10.0%, 12.5%, and 15.0%, the corresponding expected capitalized OOP costs are $1.837B, $1.795B, $1.755B, $1.718B, $1.683B, and $1.650B. Conversely, when the base value is lowered by 2.5%, 5.0%, 7.5%, 10.0%, 12.5%, and 15.0%, the corresponding expected capitalized OOP costs are $1.931B, $1.984B, $2.041B, $2.102B, $2.170B, and $2.243B (see WAV Figure 1.9A).
- Sensitivity analysis indicates that *p*(Success) of Phase IIa is the single most influential driver of total expected capitalized OOP cost in clinical development. Within a ±15 percentage point variation range, changes in this parameter produce the largest swing in capitalized spend relative to all other clinical risk inputs (see WAV Figure 1.9B). At the reference assumption of a 48% Phase IIa *p*(Success), the modeled expected capitalized OOP cost is $1.882B. Incremental improvements in Phase IIa success probability materially alter expected cost. Specifically, increasing *p*(Success) by 2.5, 5.0, 7.5, 10.0, 12.5, and 15.0 percentage points reduces expected capitalized OOP cost to $1.805B, $1.735B, $1.671B, $1.613B, $1.559B, and $1.510B, respectively. Conversely, deterioration in Phase IIa performance assumptions results in rapid cost escalation. Reductions of 2.5, 5.0, 7.5, 10.0, 12.5, and 15.0 percentage points from the base case increase expected capitalized OOP cost to $1.968B, $2.064B, $2.172B, $2.294B, $2.433B, and $2.593B, respectively.

Collectively, these results underscore Phase IIa success probability as the dominant economic risk lever in clinical development, with relatively modest changes in early PoC performance translating into several hundred million dollars of downstream capital efficiency impact.

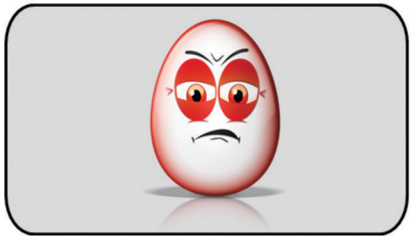
In 2014, Pfizer conducted a review of 44 NMEs that had reached a decision point in Phase II over the 2005–2009 period and found that only one-third of these programs had achieved a positive clinical PoC (Morgan et al. 2012). While the primary reason for such high attrition was insufficient (or a lack of) clinical efficacy, a more granular analysis led to the conclusion that three fundamental elements—referred to by Pfizer as the *three pillars of survival*—needed to be demonstrated in order to achieve Phase II success (see Figure 1.10):

1. **Pillar 1—Target-site exposure:** Achieving and maintaining adequate drug concentrations at the site of pharmacologic action for a sufficient duration to enable the intended mechanism of action. This includes ensuring appropriate systemic and tissue exposure profiles,

- **EXPOSURE AT THE TARGET SITE OF ACTION OVER A DESIRED PERIOD OF TIME**
  - Establishing that unbound drug concentrations at the site of action exceed the potency threshold for the necessary duration provides strong assurance that pharmacologically relevant exposure is achieved
  - Potential contribution of active metabolites to overall target-site exposure or pharmacologic effect



- **BINDING TO THE PHARMACOLOGICAL TARGET AS EXPECTED FOR ITS MODE OF ACTION**
  - In vivo PK/PD studies that directly quantify target occupancy offer the most definitive evidence that the molecule is binding to its intended target at the required level
  - Evaluation of binding kinetics, including association/dissociation rates and their translation across in vitro systems, animal models, and potentially human-derived assays, further supports confidence in sustained target engagement



- **EXPRESSION OF PHARMACOLOGICAL ACTIVITY COMMENSURATE WITH THE DEMONSTRATED TARGET EXPOSURE AND TARGET BINDING**
  - PK/PD analyses incorporating mechanism-relevant biomarkers at the site of action provide the strongest demonstration that target exposure and engagement are producing the expected biological effect. Such biomarkers serve as direct readouts of primary pharmacology and confirm that the degree of target modulation is sufficient to support progression through clinical development

Figure 1.10 Pfizer's three pillars of survival for improving Phase II success (Morgan et al. 2012).

informed by PK parameters such as maximum concentration, area under the curve, and target-site penetration.
2. **Pillar 2—Target engagement:** Demonstrating that the molecule interacts with its intended biological target at levels consistent with the required degree of modulation. Evidence may include occupancy assays, binding kinetics, and affinity measurements.
3. **Pillar 3—Pharmacologic response:** Verifying that target exposure and target engagement translate into measurable PD activity consistent with the proposed mechanism. This encompasses, for example, downstream biomarker modulation and pathway activation/inhibition that confirm the drug is exerting its expected therapeutic effect.

Evaluation of programs stratified by performance against three development pillars (pharmacology confidence, exposure confidence, and translational evidence) reveals a strong concordance between early evidence of quality and late-stage success:

1. Of 14 programs meeting all three pillars with high confidence in both pharmacology and exposure, 12 achieved a positive PoC, with eight advancing to Phase III.
2. From 12 assets that satisfied the criteria of Pillars 1 and 2 by exhibiting low pharmacology confidence but high exposure confidence, there was substantially lower progression, with only two Phase III initiations.
3. Of six programs meeting the hurdles of Pillars 2 and 3 by demonstrating high confidence in pharmacology but low exposure confidence, all failed to progress to Phase III.
4. All 12 assets failing to meet the full definitions of the three pillars by showing both low pharmacology confidence and low exposure confidence uniformly failed to advance to Phase III.

Further evidence of Pfizer's success in positive step changes in Phase II clinical success has been documented by Wu et al. (2020) and Fernando et al. (2022). Beginning in Phase I and from a low of 4% PTRS to launch in 2016, Pfizer's cumulative success rate rose to 21% in 2020 when compared to industry averages of 8% and 11% over the same time points. This dramatic rise in overall success rate is due to higher success rates in Phase I, Phase II, and combined Phase III and regulatory, the most pronounced contributors being observed in Phase II and combined Phase III and regulatory where (a) Phase II probability of success rose from 15% in 2016 to 52% in 2020 (compared to an industry average of 29% and 34% over the same time points) and (b) Phase III and regulatory probability of success increased from 67% in 2016 to 85% in 2020 (compared to an industry average of approximately 70% over the same years) (Fernando et al. 2022). Interestingly, over the 2010–2020 period, Pfizer adopted a drug development paradigm akin to Eli Lilly's Chorus in which they have labeled Signs of Clinical Activity (SOCA) that incorporates both PoM and Early Signal of Efficacy (ESOE). It is believed that adherence to the SOCA program led to the rapid and successful development with BioNTech of the COMIRNATY vaccine for COVID-19, which achieved regulatory approval for adult usage in the United States, the United Kingdom, and the European Union in eight months (Fernando et al. 2022). Further, the company attributes its decade-long success in improving R&D productivity to three key elements: (1) enhanced scientific depth within prioritized therapeutic areas**,** (2) expansion of therapeutic modalities to broaden target accessibility, and (3) implementation of quantitative, evidence-based frameworks for portfolio decision making.

In a vein similar to that performed by Eli Lilly and Pfizer, AstraZeneca (in 2011) began its own investigations of its small-molecule pipeline of 142 projects that had been active between preclinical and Phase II over the 2005–2010 period across all TAs with a specific focus on data and subsequent decisions made, as well as root causes of project attrition (Cook et al. 2014). During this period, the prevailing industry paradigm emphasized throughput-driven R&D—often characterized as a *multiple-shots-on-goal* strategy. While this approach increased the number of assets entering

development, it had the predictable effect of diverting resources away from rigorous interrogation of disease pathophysiology and therapeutic rationale. Over time, this bias toward volume eroded both the scientific integrity and long-term durability of R&D portfolios. In an environment optimized for advancement velocity, Ringel et al. (2013) posited that progress-oriented decision making tended to displace hypothesis-driven, truth-seeking behaviors that could have yielded deeper biological insight and more robust target validation.

Internal performance metrics at AstraZeneca illustrate the downstream consequences of this strategy. Preclinical transition success rates were broadly aligned with external benchmarks, at slightly above 60%. Phase I outcomes were comparatively strong, with a 59% success rate compared to the industry median of 48%. However, this apparent early-stage strength did not translate into mid-stage development performance. The median probability of success in Phase II was approximately half the industry benchmark of 29%, indicating a pronounced attrition inflection. These data suggest that increased Phase I throughput was achieved at the expense of asset quality, leaving programs insufficiently differentiated or mechanistically substantiated to demonstrate efficacy in Phase II.

This quality deficit manifested in poor late-stage productivity. Between 2005 and 2010, AstraZeneca's NME launch rate was reported at approximately 2%, materially below the industry median of 6% (Cook et al. 2014). Failure mode analysis further reinforced the conclusion that the core issue was not early safety, but inadequate biological and translational validation. Safety-related liabilities dominated terminations in preclinical development (82% of failures, largely due to compound-related organ toxicities) and in Phase I (62% of failures). In contrast, lack of efficacy was the principal driver of attrition in Phase IIa (57%) and Phase IIb (88%), underscoring weaknesses in target selection, mechanism validation, and clinical translation.

Comprehensive post hoc reviews of portfolio outcomes led AstraZeneca to redefine its progression framework around three foundational scientific criteria: (1) a robust understanding of disease biology, (2) a clearly established causal link between the target and the disease, and (3) a well-characterized and testable mechanism of action. Building on this reframed philosophy, and as detailed by Cook et al. (2014) and Morgan et al. (2018), the organization identified five critical technical determinants of project success termed the *5R framework* (see Figure 1.11), which collectively shifted decision making from volume-driven advancement to evidence-based value creation:

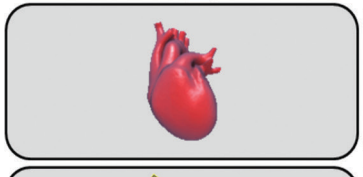
1. The strength and quality of target validation—the right target
2. Demonstration of target engagement—the right tissue
3. Adequate safety margins—the right safety
4. Patient stratification plans—the right patient
5. Medical value proposition—the right commercial potential

Cook et al. (2014) emphasize that the 5R framework was never intended to require unequivocal strength across all five dimensions in order for a program to advance. Rather, its primary value lies in systematically surfacing the most consequential sources of technical risk—those most likely to precipitate failure during preclinical or clinical development—so they can be explicitly tested, mitigated, or used as a basis for early termination decisions.

The impact of this approach on AstraZeneca's R&D productivity, particularly in navigating the so-called *valley of clinical death*, has been substantial. Analyses spanning two development eras, as reported by Morgan et al. (2018), demonstrate a marked inflection in end-to-end performance. Aggregate success from candidate nomination through Phase III completion increased from approximately 4% during the 2005–2010 period to 19% during the 2012–2016 period. This improvement coincided with a deliberate shift toward more stringent target rationale at the research stage and a fundamental rebalancing of portfolio scale and composition.

- **RIGHT TARGET**
  - Demonstration of strong mechanistic association between biological target and disease process
  - Clear potential for clinically meaningful differentiation in therapeutic activity relative to existing or emerging therapies
  - Availability or feasibility of developing predictive biomarkers to support target engagement

- **RIGHT PATIENT**
  - Evidence that the candidate achieves sufficient systemic and relevant tissue exposure
  - Establishment of validated PD biomarkers to quantify biological response
  - Comprehensive characterization of preclinical and clinical PK/PD relationships to inform dose and regimen selection
  - Assessment of metabolic pathways and interactions to predict and mitigate drug–drug interaction risks



- **RIGHT TISSUE**
  - Characterization of exposure margins that support a differentiated and favorable safety profile
  - Evaluation of secondary pharmacology liabilities, including off-target interactions
  - Assessment of reactive metabolite formation, genotoxicity potential, and interaction risks that could impact safety or efficacy
  - Understanding of target-related safety liabilities, including on-target toxicity mechanisms

- **RIGHT SAFETY**
  - Identification of patient subgroups most likely to exhibit an optimal therapeutic response based on mechanistic, biomarker, or genetic insights
  - Quantitative assessment of benefit–risk profiles across the intended indication and target population(s)

- **RIGHT COMMERCIAL POTENTIAL**
  - Clear articulation of a differentiated clinical and economic value proposition relative to anticipated future standards of care
  - Integration of market access considerations, including payer expectations and provider adoption barriers
  - Development of a precision-medicine strategy where appropriate, incorporating companion diagnostics, predictive biomarkers, and patient-selection tools

Figure 1.11 AstraZeneca's 5R framework for improving clinical success (Cook et al. 2014; Morgan et al. 2018).

Prior to adoption of the 5R framework, AstraZeneca advanced 287 small-molecule projects between 2005 and 2010. In contrast, only 76 such projects entered development from 2012 to 2016. Importantly, this contraction reflected not only a reduction in activity but a strategic elevation of quality thresholds. Backup programs were aggressively pruned, declining from roughly 28% of the portfolio to less than 7%. Simultaneously, the company reshaped its target class mix, increasing kinase-focused programs from 21% to 36% while reducing reliance on G protein-coupled receptor targets from 25% to 5%, and placing greater emphasis on assets with differentiated and novel mechanisms of action (Morgan et al. 2018).

These strategic shifts translated into measurable improvements in development efficiency. Before implementation of the framework, only 23% of discovery programs yielded leads of sufficient quality to progress into lead optimization, corresponding to an approximately 4:1 ratio of lead generation efforts to viable lead optimization candidates. Following adoption, this transition probability rose to 48%, effectively halving the number of projects required to produce a development-ready lead. In parallel, cycle times were substantially compressed: time from project initiation to lead optimization decreased from 26 to 19 months, Phase II duration was reduced from 31 to 14 months, and cost to PoC fell from approximately $100M to $69M—well below the industry benchmark of $119M.

The nature of project attrition also evolved. Across the two periods, terminations driven by strategic considerations (35%) or failure to identify viable leads (32%) declined sharply, while failures increasingly reflected explicit target validation outcomes, which accounted for 77% of closures in the later period. This shift underscores the centrality of target validation within the 5R construct and highlights its role as the dominant determinant of downstream success.

Comparative analyses against industry benchmarks further illustrate the magnitude of change. During 2005–2010, AstraZeneca underperformed the industry in preclinical (66% vs. 71%) and Phase II (15% vs. 22%) success rates, exceeded industry norms in Phase I (59% vs. 51%), and matched them in Phase III (60%). By contrast, in the 2012–2016 period, the company outperformed industry comparators across all development stages, with the most dramatic differential observed in Phase II (43% vs. 18%). As a result, AstraZeneca's cumulative probability of technical and regulatory success from preclinical development to launch increased from 4% to 19%, while the industry average remained flat at approximately 4% across both time periods.

Failure mode distributions also shifted in a manner consistent with earlier, more decisive risk resolution. In the earlier period, safety considerations dominated preclinical and Phase I failures (82% and 63%, respectively), while lack of efficacy was the primary driver in Phase II (64%). In the later period, safety remained the leading cause of preclinical attrition (50%), but efficacy emerged as an equally important factor in Phase I (38.5%) and became overwhelmingly dominant in Phase II (84%), reflecting more effective early elimination of safety liabilities and a sharper focus on biological and translational validity.

Both Cook et al. (2014) and Morgan et al. (2018) note that the effectiveness of the 5R framework was contingent on a broader cultural transformation. The expanded use of interim analyses further reinforced this discipline, enabling earlier and more confident determinations of futility or acceleration, and materially improving the quality of development decisions across the portfolio.

It is noteworthy that AstraZeneca has added a sixth dimension to the 5R framework—the *right* digital health technology solution in clinical trials aimed at improving patient and clinical trial site experience (Duran et al. 2023). Across three TAs, the positive impact of digital technology in clinical trials was demonstrated in cardiovascular (DAPA-MI study in myocardial infarction), inflammation (CRESCENDO study in COPD), and oncology (TROPION-PanTumor01 study in stomatitis that accompanies anticancer therapy).

Although the experiences of Eli Lilly, Pfizer, and AstraZeneca clearly illustrate how rigorous science can move the evidentiary burden for critical go/no-go decisions upstream in the R&D continuum, scientific excellence alone has not been sufficient to drive sustained productivity gains. Equally consequential has been the implementation of disciplined, fit-for-purpose decision frameworks that enable timely, consistent, and high-quality portfolio choices.

The true cost of suboptimal decision making in biopharma R&D is inherently difficult to quantify and is rarely disclosed. Nevertheless, a compelling case can be made that a substantial proportion of pipeline attrition is attributable not to unavoidable scientific uncertainty, but to opaque, inconsistent, or poorly governed decision processes. In the absence of structured mechanisms that enforce transparency, explicitly surface assumptions, and align evidence thresholds with development risk, organizations are prone to advance programs based on incomplete data, implicit biases, or organizational momentum. As a result, assets may progress further than warranted, accumulating avoidable cost and risk before ultimately failing.

1.3 THE STAGE-GATE REVIEW PROCESS

The stage-gate research (SGR) framework (Cooper et al. 2001) provides a structured governance mechanism for determining whether to commit capital and organizational resources to a molecular entity as it advances through the R&D continuum. At the initial decision point (Gate G0), leadership determines whether a scientific concept warrants formal investment and entry into discovery research (see Figure 1.12).

For a typical small-molecule NME, early development follows a largely sequential pathway encompassing target identification and validation, assay development, compound screening, hit-to-lead activities, and iterative lead optimization. Successful completion of these activities enables nomination of a development candidate eligible for advancement through Gate G1 and formal entry into preclinical development.

Upon clearance of Gate G1, the asset undergoes a defined package of nonclinical studies, including PK, PD, and toxicology assessments in relevant animal and cellular models. These data are evaluated at Gate G2 to determine readiness for FIH studies and transition into Phase I clinical development.

Phase I trials represent the initial component of early clinical development and are primarily designed to characterize safety, tolerability, and human PK, typically in healthy volunteers or, where appropriate, patient populations. Secondary objectives often include exploratory biomarkers and early PD signals. Assets that meet prespecified criteria may then advance into Phase IIa, which is commonly focused on PoC. As established across therapeutic areas, PoC represents the highest-risk inflection point in the clinical life cycle, given its emphasis on demonstrating clinically meaningful efficacy.

Although not always depicted formally in high-level process diagrams, a governance decision point almost invariably exists between Phase I and Phase IIa across most therapeutic areas. Successful demonstration of PoC enables consideration at Gate G3 for entry into Phase IIb, the initial stage of late clinical development. Phase IIb studies are typically dose-ranging in design, with the objective of defining the optimal therapeutic dose by balancing efficacy against safety and tolerability constraints. The selected dose regimen is subsequently carried forward into Phase III registrational trials, the second component of late clinical development.

If Phase IIb and Phase III studies collectively demonstrate statistically robust efficacy and an acceptable benefit–risk profile, the program may advance through Gate G4 to pursue regulatory

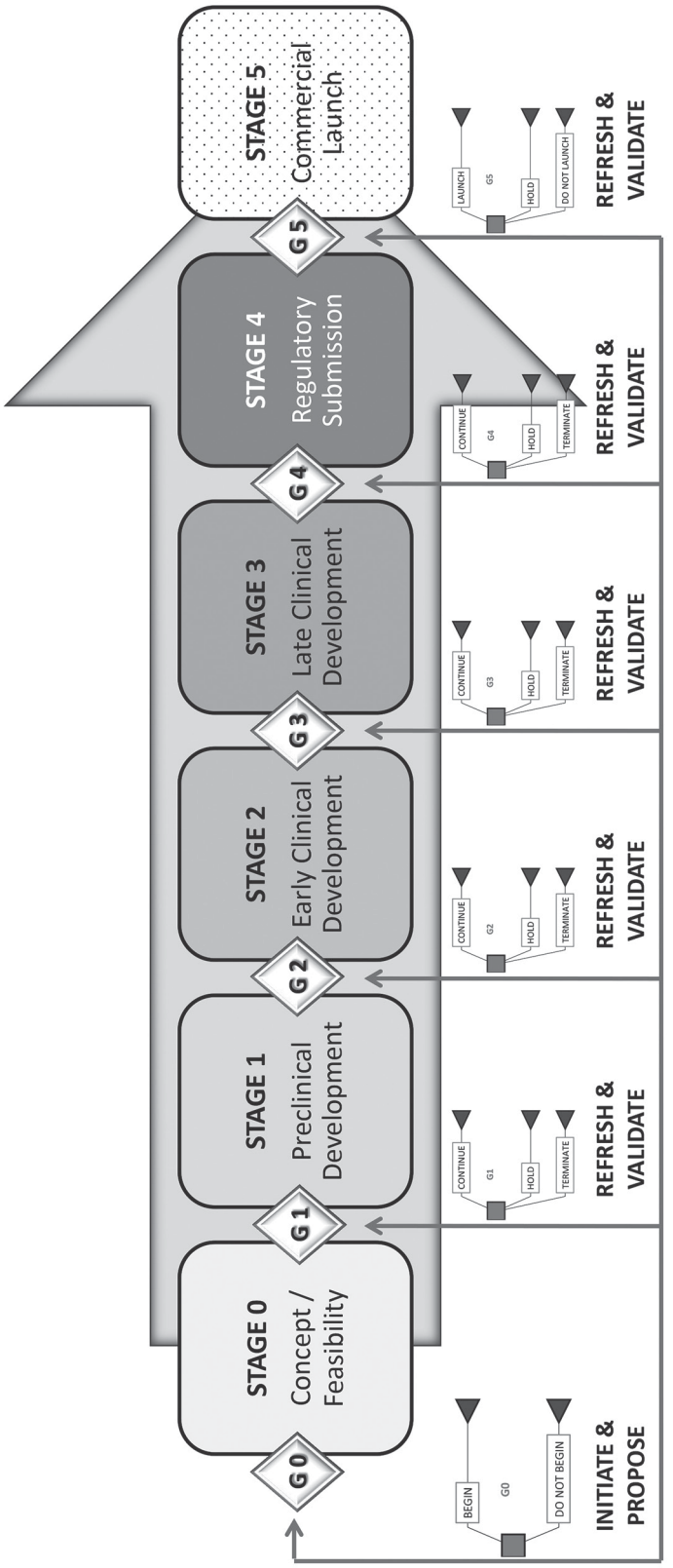


Figure 1.12 Stage-gate review process for drug research and development.

approval across one or more jurisdictions. Following regulatory authorization and label definition, a final decision is made at Gate G5 regarding commercial launch and life-cycle management strategy.

It should be emphasized that this linear representation of development is an abstraction. In practice, many NMEs progress through adaptive or hybrid trial designs (e.g., Phase I/IIa or Phase IIb/III), particularly in oncology and other high-unmet-need therapeutic areas, where regulatory flexibility and accelerated development paradigms are common.

Strategic and Governance Considerations

Prima facie, the stage-gate model appears conceptually rigorous and operationally tractable. However, effective implementation requires more than procedural compliance. The SGR framework, in isolation, does not resolve several foundational strategic and governance challenges that materially influence portfolio outcomes. Key questions that must be addressed as the process matures include:

- What scientific, clinical, and commercial evidence thresholds justify initial asset investment?
- Which quantitative and qualitative criteria should govern advancement, pause, or termination decisions at each gate?
- Should externally sourced assets (e.g., in-licensing or acquisitions) be evaluated and governed differently from internally discovered programs?
- How systematically are post hoc reviews conducted to enable organizational learning, improve project team execution, and refine future governance decisions?

Addressing these questions is essential to ensure that the stage-gate process functions not merely as a control mechanism, but as a value-optimizing system aligned with enterprise-level R&D strategy.

1.3.1 Rationale for Initiation of Investments

In industries with low capital intensity, short development cycles, and limited downside risk, initiating investment in new ideas is often routine and of modest strategic consequence. Biopharma operates under markedly different conditions: investments are large, timelines are long, and the probability of failure—particularly during early research and clinical translation—far exceeds the likelihood of commercial success. Under these constraints, the most consequential decision in a drug's life cycle is often not a late-stage funding commitment, but the initial allocation of resources to explore a scientific concept.

This reality elevates the importance of early-stage governance. Regardless of scientific novelty or internal advocacy, no idea should advance without a clearly articulated business case that links the concept to a defined strategic objective or unmet business need. Critically, the opportunity must be evaluated, not in isolation, but relative to the organization's broader portfolio of actionable alternatives. Only by understanding how a potential success would contribute to portfolio strategy and long-term financial objectives can leadership justify committing scarce resources. Accordingly, each investment proposal should be supported by explicit documentation of its business rationale, including prescriptive and measurable criteria that define continuation, pause, or termination thresholds. Absent such predefined decision rules, governance becomes vulnerable to subjectivity, organizational politics, and hierarchical influence. Complementing the business case, a credible project plan is required that transparently characterizes anticipated value, technical and regulatory risk, resource requirements, and the timeline to a potentially marketable product.

Despite uncertainty in future clinical outcomes and market dynamics, constructing a credible business case requires at least a preliminary understanding of the commercial environment over the product life cycle. Two fundamental drivers of value are the magnitude of unmet patient need and the willingness or ability of payers, healthcare systems, or patients to fund access. Perceived

product uniqueness is therefore closely linked to the degree to which a therapy alters disease burden. Disease-modifying interventions are typically valued more highly than purely symptomatic treatments, although exceptions exist—for example, symptom-focused therapies are valued in chronic conditions such as osteoarthritis, where disease-modifying options are limited.

In competitive markets, differentiation is a primary determinant of value. Experience in lipid-lowering demonstrates that being best in class, as with atorvastatin (Lipitor), can be more commercially advantageous than being first in class, as exemplified by lovastatin (Mevacor). Consequently, new therapeutic investments must align tightly with corporate strategy while supporting financial objectives. Organizations that allow individual assets to dictate strategy often struggle to achieve sustained success due to gaps in expertise, execution, or competitive positioning.

It is sometimes argued that assigning financial value to early research-stage assets is inappropriate, given limited data. While early estimates are inherently uncertain, the absence of a valuation framework leaves decision makers unable to compare opportunities with differing risk profiles, resource demands, and time horizons. We contend that all investment opportunities should be associated with a bounded range of commercial value estimates, spanning plausible scenarios from narrow indications to broader, multi-indication applications. As evidence accumulates, this range should be progressively refined and narrowed.

Although not all drivers of value can be precisely quantified, a defensible business case remains essential to sound investment governance in high-uncertainty, asymmetric-risk environments. Where conventional financial valuation is impractical, utility theory—integrating quantitative and qualitative attributes into a common unit of measure—offers a pragmatic and robust decision-support alternative.

1.3.2 Decision Criteria for Progression, Hold, and Termination

A broad range of financial evaluation methodologies—applied in nominal or risk-adjusted form—are used to support gated investment decisions across the drug development life cycle. Despite their widespread adoption, no single metric is universally accepted or without conceptual limitations. Net present value (NPV) and expected NPV (eNPV) remain the most commonly applied once assets enter clinical development, as they consolidate discounted future cash flows. However, both suffer from a key limitation: they lack an intrinsic benchmark for absolute attractiveness, as there is no consensus on what constitutes an acceptable NPV or eNPV across organizations, TAs, or development stages.

The same discounted cash-flow models can be used to derive return-based metrics, namely internal rate of return (IRR) and expected IRR (eIRR). Unlike value-based measures, rates of return can be evaluated directly against an organization's weighted average cost of capital, providing a more intuitive assessment of whether an investment is expected to create or destroy shareholder value after accounting for time and risk. For this reason, eIRR is particularly useful as a primary financial decision criterion for assets in clinical development, especially when comparing programs with differing capital requirements, timelines, and risk profiles.

At the portfolio level, we also strongly advocate the use of the PI and its risk-adjusted form, ePI, particularly under conditions of constrained resources. These metrics capture the efficiency with which capital is converted into expected value and are especially informative for evaluating marginal investments near portfolio capacity. While no industry standard defines a *healthy* PI or ePI by development phase, their practical value lies in revealing the characteristic concave efficiency curve observed in Pareto analyses. This curve should be interpreted as an efficiency frontier for individual investments ranked by reward-to-cost ratio, rather than as a classical efficient frontier of optimized

asset combinations. The application of PI and ePI to incremental portfolio optimization is discussed further in Chapter 6.

Because most biopharma organizations do not operate with explicit corporate targets for NPV, eNPV, PI, or ePI, alternative metrics are often needed to support gated decision making. Given that long-range planning is frequently anchored in sales growth objectives, we propose the non-risk-adjusted present value of cumulative sales (PV Sales) and the risk-adjusted present value of cumulative sales (PV eSales) as complementary portfolio-relevant measures. These metrics directly link individual asset investments to enterprise-level growth expectations. Once a program has met predefined clinical thresholds—such as acceptable safety margins, clinically meaningful efficacy, and viable dosing—its projected contribution to future portfolio sales growth should be a key determinant of strategic priority and continued funding.

While financial metrics can be applied with reasonable consistency during clinical development, their utility diminishes in earlier research stages, where commercial assumptions are highly speculative. Nevertheless, the absence of financial valuation does not obviate the need for disciplined progression frameworks. Instead, early-stage decisions should rely on predefined scientific criteria, including target exposure and occupancy, target engagement, downstream biological activity, and demonstrable physiological effect. When established in advance, these criteria provide a defensible basis for progression, pause, or termination.

In practice, the primary weakness in research decision making is not the lack of metrics but the failure to define explicit continuation and, critically, discontinuation thresholds. Without clear termination rules, organizations tend to perpetuate investments beyond the point where evidence supports further development, often driven by sunk-cost bias. This results in a systematic bias toward continuation, an excess of Type I errors (advancing programs that should be terminated), and heightened fear of Type II errors (terminating programs that might have succeeded). Over time, this imbalance erodes portfolio efficiency and diverts resources from higher-value opportunities aligned with the organization's strategic, scientific, and financial objectives.

1.3.3 The Attractiveness of External Assets

When comparing the strategic and economic merit of internally originated programs with externally sourced assets, organizations are often subject to asymmetric decision biases that can materially distort portfolio outcomes. Although these biases operate in opposing directions, both undermine objective capital allocation and risk-adjusted value creation.

Internal assets are typically evaluated with a high degree of scrutiny due to deep institutional knowledge of their discovery history, preclinical liabilities, translational uncertainties, and prior development challenges. While this transparency should be advantageous, it can foster overly conservative or pessimistic assessments of technical and regulatory viability. At the same time, internal programs may be driven by optimism bias that is fueled by organizational attachment, scientific advocacy, and the belief that shortcomings can be addressed in later stages. The result is a paradox in which internal assets are both rigorously critiqued at the technical level and implicitly assumed to succeed eventually, even when near- or mid-term evidence does not fully justify continued investment.

Externally sourced assets exhibit a complementary but equally problematic bias. Limited visibility into their full development history, failure modes, and unresolved risks can cause these programs to appear cleaner, more differentiated, or more advanced than internal comparators. Information asymmetry, selective disclosure, and reliance on sponsor narratives often produce an inflated perception of their risk/benefit profile, particularly during early diligence. This effect is frequently

reinforced by incentive structures within business development organizations, where successful acquisitions or partnerships are more visibly rewarded than decisions to out-license, divest, or deprioritize internally generated programs that are scientifically weak, strategically misaligned, or financially unattractive.

Collectively, these dynamics create a structural imbalance in how internal and external opportunities are framed, debated, and funded. To mitigate this, we advocate a unified, origin-agnostic decision framework in which all assets are evaluated against the same predefined thresholds, value drivers, and risk-adjusted metrics. These criteria should encompass scientific robustness, probability of technical and regulatory success, capital intensity, time-to-value inflection, strategic fit, and opportunity cost relative to competing portfolio alternatives.

Applied consistently and transparently, such a framework aligns gated investment decisions with evolving enterprise strategy, financial objectives, and resource constraints. It reinforces the principle that capital deployed toward external acquisitions is economically indistinguishable from capital invested in internal programs—both represent irreversible commitments of scarce resources. By enforcing equivalence in evaluation standards and decision rigor, leadership can increase confidence that portfolio resources are allocated to the highest-quality opportunities, thereby maximizing the likelihood of sustainable value creation across the development pipeline.

1.3.4 Learning from Footprints in the Sand

Leading biopharma organizations—including Eli Lilly, Pfizer, and AstraZeneca—have shown that rigorous retrospective analysis can be a powerful strategic tool when applied systematically. The purpose of these reviews is not simply to catalog past successes or failures, but to identify what has demonstrably improved over time, what has remained static or underperformed, and which decision behaviors, operating assumptions, or execution patterns should be deliberately replicated or avoided. When used effectively, retrospective analysis functions as an institutional learning mechanism that informs forward-looking capital allocation and risk governance.

At the project level, formal *lessons-learned* reviews are a standard component of professional project management and are routinely conducted at major milestones or program closure. These reviews examine timelines, costs, technical outcomes, and execution efficiency in detail. By contrast, comparable analytical rigor is far less commonly applied to portfolio- or enterprise-level decision making, particularly with respect to gated investment decisions that determine whether assets are initiated, advanced, paused, or terminated.

One explanation for this imbalance is discomfort with separating decision quality from eventual outcomes. In drug development, well-reasoned, data-driven decisions may still result in clinical or regulatory failure due to factors beyond managerial control, whereas poorly substantiated decisions may occasionally lead to success driven by chance or unforeseen biology. This outcome ambiguity can obscure causal relationships and discourage critical examination of the decision logic itself, independent of the result.

In the absence of clear executive accountability for both decision processes and downstream consequences, governance mechanisms—especially stage-gate reviews—can become diffuse. Programs may persist through multiple investment cycles without explicit reaffirmation of value, advancing by default rather than deliberate recommitment. Termination decisions are often deferred until negative data become unequivocal, by which point disproportionate capital, talent, and organizational focus have already been consumed, eroding portfolio efficiency.

Our experience suggests that executive committees are not inherently reluctant to make advancement or termination decisions; rather, the limiting factor is the lack of structured ownership, post

hoc evaluation, and feedback loops that link decision rationale to observed outcomes over time. Without these mechanisms, organizations miss the opportunity to refine decision frameworks, calibrate risk tolerance, and improve the consistency of portfolio-level judgments.

From a governance standpoint, embedding disciplined retrospective review of gated decisions—analogous to project-level lessons-learned processes—offers a significant opportunity to strengthen enterprise decision quality. By explicitly examining what decisions were made, why they were made, and on what assumptions and evidence, biopharma leaders can institutionalize learning, reduce systemic bias, and enhance the long-term productivity of their R&D portfolios.