HEALTH ECONOMIA

Life Sciences - Investors Series

Stacking the Odds: Probability of Success as the Foundation of Drug Development Portfolio Strategy

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Executive Summary

Probability of Success as the Foundation of Drug Development Portfolio Strategy

Why the 7.9% industry average is not a life sentence, and how to escape it

Across all therapeutic areas and modalities, only approximately 1 in 13 drug candidates entering Phase I clinical development will receive regulatory approval. That 7.9% aggregate figure — drawn from a decade of global clinical programmes and consistent across multiple independent analyses spanning twenty years — tends to land with a certain thud in boardrooms and investor decks alike.

The aggregate is a blunt instrument. Drug development success is not monolithic. Three distinct categories of risk sit behind any programme's probability of success, and clearly identifying these three categories is key to high-quality strategic decisions.

Biology Risk:

does the candidate molecule engage its target meaningfully, translate preclinical efficacy into human benefit, and maintain an acceptable safety profile in the intended patient population? This is the purest scientific question — and the one most directly captured by published phase transition success rates.

Methodology Risk:

is the development programme structured to demonstrate what the drug actually does? This encompasses indication selection, patient population definition, endpoint choice, study design, and the breadth and quality of the clinical evidence package. A drug with genuine biological activity can fail if the trial is conducted in the wrong population, or with endpoints that are unable to detect the efficacy signal or support regulators' and payers' assessments. The precision of endpoint specification illustrates this risk in practice: a patient-reported outcome measuring to change from the last visit — rather than from baseline — dilutes sensitivity to change, rendering a biologically active compound indistinguishable from placebo in regulatory review.

Execution Risk:

can the organisation actually deliver the plan? Operational excellence — CMC development, clinical supply, CRO selection, site activation, patient enrolment, data management, safety signal management, and regulatory interactions — separates programmes that advance on schedule from those that drift, dilute their evidence base, and consume capital without generating decisions.

In practice, the three risks rarely surface separately in published success rate data. Regulators may state the grounds for a rejection, but sponsors are — understandably — somewhat more circumspect about the precise design choices that contributed to a failure. This paper focuses principally on biology risk and on the portfolio strategy decisions that follow from understanding it. Methodology and execution risk — the other two members of this rather consequential trio — will each be the subject of dedicated Health Economia analyses. We shall report back.

The biology risk dimension of PoS, properly understood and disaggregated, varies by a factor of six across therapeutic areas, can be improved materially through evidence-based design choices, and — when combined with cost and revenue projections — becomes the most powerful single input in a drug development portfolio model.

PoS is not fate. It is architecture.

The 7.9% Problem

Across more than a decade of systematic, programme-level data, a single figure emerges with striking consistency: 7.9% — the likelihood that a molecule entering Phase I will eventually secure FDA regulatory approval *(BIO & Informa Pharma Intelligence, 2021)*. **One might be tempted to treat this as an occupational hazard of the industry — the price of scientific ambition** — and simply move on. That would be a mistake.

This figure does not stand alone. Hay et al. *(2014, Nature Biotechnology)*, analysing 4,451 phase transitions from 2003 to 2011, reported an overall Phase I → approval likelihood of **10.4%** — higher than today's figure, but already low enough to demand strategic attention. Thomas et al. (2016, BIO/ Biomedtracker), covering 2006–2015, found **9.6%**. The three analyses together — 10.4% (2003–2011), 9.6% (2006–2015), 7.9% (2011–2020) — chart a structural decline over two decades, using the same phase-transition methodology applied to the same Biomedtracker database.

This is not a statistical artefact of a single report period; it is a trend. It is driven in part by the growing share of CNS and oncology programmes in the development pipeline — both below-average PoS therapeutic areas — and by progressively higher regulatory evidentiary standards, particularly for chronic disease indications.

Consider what sits behind the current 7.9%. Phase I to Phase II transition sits at a respectable 52.0%; just over half of first-in-human programmes demonstrate sufficient tolerability to advance. The real attrition happens in Phase II, where only 28.9% of programmes proceed to Phase III. This is where the early scientific promise of a compound meets biological reality, and reality frequently wins. Of those that reach Phase III, 57.8% advance to regulatory submission; and 90.6% of submitted programmes ultimately receive approval.
Multiply those four rates sequentially: 0.520 × 0.289 × 0.578 × 0.906 = 7.9%. The mathematics are unforgiving; each gate compounds the loss.

Transition	N	Success rate	Cumulative PoS from Phase I
Phase I → Phase II	4'414	52.0%	52.0%
Phase II → Phase II	4'933	28.9%	15.0%
Phase III → NDA / BLA	1'928	57.8%	8.7%
NDA/BLA → Approval	1'453	90.6%	**7.9%**

Primary source: BIO & Informa Pharma Intelligence (2021), Figure 1. Based on 12,728 phase transitions across 9,704 development programmes, 2011–2020. Consistent with Hay et al. (2014, n=4,451, 2003–2011: 10.4% overall LOA) and Thomas et al. (2016, 2006–2015: 9.6% overall LOA), confirming the declining trend across all three independent study periods.

One feature of the regulatory transition is worth noting: the 90.6% NDA/BLA approval rate reflects eventual success, including re-submissions following Complete Response Letters. It is not a first-cycle approval rate; it reflects the determination of sponsors who have already committed to Phase III and are disinclined to abandon programmes at the final hurdle.

All Therapeutic Areas Are Not Alike

Therapeutic area	LOA: BIO 2021	LOA: Hay et al. 2014	Trend
Haematology	23.9%	~26%	Stable; consistently highest TA
Metabolic / Endocrine	15.5%	~15%	Stable
Infectious diseases	13.2%	~19%	Declining; reflects post-antibiotic era
Ophthalmology	11.9%	~12%	Stable
Autoimmune	10.7%	~11%	Stable
All indications	**7.9%**	**~10%**	**Declining trend**
Psychiatry	7.3%	-	Separated in BIO 2021
Neurology	5.9%	~6% (CNS combined)	Stable
Oncology	5.3%	~5%	Stable; large n drives aggregate down
Cardiovascular	4.8%	~4%	Stable; consistently among lowest

Primary source: BIO & Informa Pharma Intelligence (2021), Figure 5b, n=12,728. Cross-check: Hay et al. (2014), Nature Biotechnology, 32(1), 40–51, n=4,451; Hay 2014 TA-level figures are approximate due to different category definitions. Schuhmacher et al. (2025), Drug Discovery Today, 30(5), 104326, provides a complementary company-level perspective confirming the TA hierarchy.

The aggregate 7.9% conceals strikingly different odds across therapeutic areas — differences large enough to materially alter the investment calculus, and differences that have remained structurally consistent across successive independent analyses.

The stability of the TA ranking across two independent datasets, spanning different time periods and different study populations, substantially increases the analytical confidence in these figures. The relative ordering — haematology and metabolic at the top, CNS and cardiovascular at the bottom — is a structural feature of drug development biology and regulatory expectations, not a property of any single study's methodology.

The **haematology advantage is partly structural**: many haematology programmes target molecularly defined patient populations with well-validated surrogate endpoints, and the clinical readout is often unambiguous. Infectious disease similarly benefits from clear, binary efficacy outcomes and, in some settings, from pathogen biology that is better characterised than the underlying mechanisms of many chronic diseases. The decline from approximately 19% to 13.2% between the two study periods partly reflects the contraction of the antibacterial pipeline and the changing composition of infectious disease programmes over that interval.

Neurology and Psychiatry present a different picture, and it is worth being precise about why. The relatively lower PoS in these indications is not a reflection of insufficient effort or inadequate investment — these areas have attracted enormous scientific and financial resources over decades. Rather, **it reflects the extraordinary biological complexity of central nervous system diseases**. The human brain remains, in many respects, the most challenging organ system in drug development: target validation is difficult, patient heterogeneity is substantial, biomarkers of target engagement and disease modification are still emerging, and the blood-brain barrier imposes formidable pharmacokinetic constraints on essentially all modalities.

The challenge is perhaps most starkly illustrated in Alzheimer's disease. Cummings et al. *(2014, Alzheimer's Research & Therapy)*, analysing 413 Alzheimer's disease clinical trials conducted between 2002 and 2012, found a failure rate of 99.6% — meaning that of all programmes entering clinical development in that decade, fewer than one

in 200 ultimately reached registration. This is not a reflection of poor drug development practice; **it reflects the depth of the scientific problem**, particularly the delayed clinical manifestation of pathology, the heterogeneity of the patient population, and the long-standing absence of validated surrogate endpoints for disease modification.

There are, however, meaningful pockets of progress. Recent approvals in Alzheimer's disease for anti-amyloid antibodies, in spinal muscular atrophy for gene and antisense oligonucleotide therapies, and in Duchenne muscular dystrophy share a common thread: highly targeted mechanisms with validated biomarkers of biological activity and carefully defined patient populations. The lesson, relevant across all therapeutic areas, is that CNS programmes with well-characterised mechanisms and patient stratification strategies can succeed — they require more rigorous biological validation ahead of Phase II than programmes in better-understood disease areas, but the path exists.

What matters for portfolio strategy is that a developer choosing haematology with a validated biomarker is operating in a fundamentally different probability space from one pursuing CNS with an insufficiently characterised mechanism and a heterogeneous patient population. Both represent legitimate and important scientific endeavours; only one is likely to survive a rigorous expected value analysis at a capital-constrained organisation.

Phase III: The Expensive Way to Fail

If there is one finding that should reshape how development teams and investors alike think about portfolio risk, it is this: **Phase III accounts for approximately 68% of the total direct out-of-pocket cost of a drug development programme** — roughly USD 90 million of a USD 132 million total per programme (*Sertkaya et al., 2024, JAMA Network Open)*. This single phase consumes more capital than all preceding development stages combined.

The implications extend well beyond the immediate programme budget. On the one hand, if a programme reaches Phase III, the probability of eventually securing approval is reasonable: approximately 52% (Phase III → NDA × NDA → approval). On the other hand, entering Phase III with an inadequate proof-of-concept or a poorly defined patient population is — quite literally — the most expensive mistake a development organisation can make. Phase II failure is painful; Phase III failure carries consequences that ripple through the entire organisation.

A failed Phase III does not simply consume the USD 90 million invested in that trial. It also eliminates the opportunity cost of that capital — all other programmes, partnerships, or strategic options foregone in its favour. More significantly, **late-stage failure destroys value in a way that early failure does not**: a programme that reaches Phase III has been communicated to investors, partners, and the market as a high-probability near-term revenue contributor. Its failure therefore removes not just sunk costs but anticipated future revenues from the company's valuation — revenues that the market had already, at least in part, discounted into the share price or the investor model. The financial and reputational impact of a late Phase III failure is categorically different from, and substantially larger than, an equivalent write-off at Phase II.

This creates a **clear strategic imperative**: the most valuable investment in a drug development programme is not in Phase III execution efficiency. It is in the rigour of the Phase II decision to proceed. Every dollar spent on high-quality biomarker validation, appropriate dose selection, and a Phase II trial genuinely powered to inform a go/no-go decision is a dollar that either averts USD 90 million in futile Phase III expenditure — and protects the company's forward-looking value — or commits it with justified scientific confidence.

The industry has not always honoured this logic. The persistence of underpowered, biomarker-naive Phase II designs — driven by preclinical optimism and the institutional pressure to show progress — accounts for a substantial proportion of the Phase II → Phase III transition failures visible in the aggregate data. The compounding effect on aggregate PoS is significant.

What Actually Moves PoS: The Validated Levers

Biomarker-driven patient selection

is the most powerful single lever in the published data. The BIO 2021 analysis, drawing on 12,728 phase transitions, identifies trials employing patient preselection biomarkers as achieving a two-fold higher likelihood of approval from Phase I: 15.9% versus 7.6% for programmes without such biomarkers. **The Phase II transition rate in biomarker-selected programmes reaches 46.3%, versus 28.3% for those without.**

Hay et al. (2014) reached the same conclusion from an independent dataset, identifying validated patient selection as the strongest single determinant of Phase II success. The mechanism is straightforward: biomarker enrichment concentrates the study population in those most likely to respond, producing a larger treatment effect in a smaller, faster, and less expensive trial — and reducing the probability of a false-negative Phase II result that would otherwise terminate a genuinely active drug.

Computational and AI-assisted drug development

where represents an emerging lever whose full impact on published PoS statistics is not yet visible in the data — the compounds selected and designed using these approaches have not yet matured through the pipeline in sufficient numbers to move the aggregate figures.

However, the directional evidence is encouraging. Machine learning approaches applied to compound libraries have demonstrated improved predictive accuracy for ADME properties, off-target toxicity, and target engagement likelihood (Vamathevan et al., 2019, *Nature Reviews Drug Discovery*). The BIO 2021 report itself employed machine learning across more than 200 drug, trial, indication, and sponsor attributes to identify the top predictive factors for clinical success. The impact should become increasingly visible in Phase I and Phase II transition statistics over the coming decade, as the pipeline of AI-selected candidates matures.

Rare and orphan disease targeting

offers a structurally different and highly favourable risk profile. The BIO 2021 data show an LOA from Phase I of **17.0%** for rare disease programmes (excluding oncology rare indications), compared to **5.9%** for chronic high-prevalence disease programmes — nearly a three-fold advantage.

The mechanisms are multiple: smaller Phase III populations, regulatory acceptance of surrogate endpoints, a substantially higher Phase I transition rate (67.4% vs 46.0%), and the availability of Accelerated Approval, Priority Review, and Breakthrough Therapy Designation pathways. Approximately 35% of orphan drug approvals use Phase II as the pivotal study, bypassing Phase III entirely (Jayasundara et al., 2019, *Orphanet Journal of Rare Diseases*), eliminating the largest single cost item in a development programme. The financial incentives — fee waivers, tax credits on qualifying clinical trial costs, extended market exclusivity — further improve the economic profile of an already PoS-advantaged strategy.

Regulatory pathway selection

operates as a PoS multiplier at the programme level. Breakthrough Therapy Designation is associated with approximately two to three years' reduction in total development time (BIO, 2021). Fewer years in development mean fewer opportunities for a programme to fail for non-scientific reasons: funding shortfalls, competitive landscape shifts, and patent lifecycle pressure are all duration-dependent risks.

Adaptive trial design

where appropriately applied, offers meaningful Phase III efficiency gains without requiring changes to the biology or the indication. FDA and EMA guidance endorses seamless Phase II/III, dose-finding adaptations, and group sequential designs as mechanisms to reduce patient numbers and programme duration. Published analyses estimate a 20–40% reduction in Phase III patient numbers and six to 18 months' shortening of Phase III duration in well-suited indications (IQVIA, 2024).

Building a PoS-Optimised Portfolio: From Statistics to Strategy

The strategic implication is frequently counterintuitive. A programme with a 17% PoS in a rare disease with USD 400 million peak revenue potential will typically generate a higher rNPV than a programme with a 5% PoS chasing a USD 2 billion addressable market — while requiring substantially less capital to reach a definitive decision point. The higher-PoS asset is not merely safer; in expected value terms, it is often more valuable.

For the purposes of this comparison, it is worth noting that we do not account for differences in execution speed — which is a function of the organisation's operational maturity, the number of studies required, and the practical challenges of patient enrolment in each indication. These factors are real and can materially influence realised value, but they are specific to each programme and organisation, and go beyond the scope of a cross-sectional PoS analysis.

The standard framework for drug development programme valuation is risk-adjusted net present value (rNPV): the expected commercial outcome of a programme, discounted by its probability of success at each milestone.

In practice: rNPV ≈ PoS × NPV(success) – cost of failure. PoS is the multiplier. Everything else is arithmetic.

Converging on a portfolio strategy that layers biomarker-driven patient selection, rare or orphan indication focus, and adaptive Phase II/III design is therefore not primarily a risk-reduction exercise. It is an active value-maximisation strategy. The combination:

- reduces Phase III sample size and cost through biomarker enrichment;
- enables Phase II as a potentially pivotal study in orphan settings, eliminating or substantially reducing the largest single cost item in a development programme;
- shortens total programme duration through priority regulatory designations; and
- simultaneously improves Phase II-to-III and Phase III-to-submission transition probabilities.

For capital-constrained organisations — which describes most of the biotech sector, most of the time — this is not an aspirational consideration. It is the architecture of survivability.

One further dimension deserves mention.

A development organisation building a common technological platform — a shared antibody scaffold, a validated vector system, a common formulation platform — can amortise chemistry, manufacturing and controls (CMC) knowledge across multiple assets, reducing per-programme manufacturing costs from the second asset onward by 30–50% of CMC Phase I/II costs relative to a standalone first-in-class programme (Schuhmacher et al., 2025, Drug Discovery Today).

Platform technology is, in effect, a PoS multiplier for programmes two, three, and four: the organisation that invested in and validated the platform through programme one enters subsequent programmes with a durable structural knowledge advantage.

Conclusion
PoS Is Architecture, Not Destiny

The 7.9% aggregate success rate is not an immutable law of nature. It is the arithmetic average of a heterogeneous collection of programmes — some well-designed, some not; some biomarker-validated, many biomarker-naive; some pursuing well-characterised biology, others advancing on preclinical enthusiasm and institutional momentum. The fact that this figure has been declining for two decades — from 10.4% to 9.6% to 7.9% across successive independent analyses — makes the case for more deliberate portfolio construction more urgent, not less.

The gap between the industry average and what is achievable through **disciplined portfolio construction** is large and well-documented. Programmes that combine rare or orphan indication focus, validated patient stratification biomarkers, and adaptive trial designs operate in a materially different probability space from the aggregate. They cost less, take less time, and generate more definitive decision points at each stage.

For investors evaluating drug development companies, **PoS — and the quality of thinking behind it — is the most revealing variable in the model.** A management team that can articulate, with evidence, the specific drivers of its programme's probability of success is demonstrating something more important than a forecast: it is demonstrating how it makes decisions under uncertainty. That is worth examining carefully before any term sheet is signed.

The data are available. The strategic logic is established. The remaining question is whether portfolio construction decisions are made accordingly.

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