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Beyond the Odds: The Rare Disease Winning Formula

Part 1 of 3 in our Rare Disease White Paper Series

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About Arya Consulting Partners

Arya Consulting Partners is a full-service boutique consulting firm that partners with biopharma companies to navigate complexity and support growth. We combine deep therapeutic expertise, real-world insights, and end-to-end commercialization capabilities with a people-first approach. Our mission is simple: deliver strategies that create measurable results and lasting impact for our clients, our people, and the communities we serve.

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Introduction

One of the biggest unmet needs in healthcare is the development of therapies for rare diseases, conditions with a prevalence of less than **200,000 patients** in the United States.

There are more than 7,000 rare diseases that affect 25-30 million patients in the U.S. and over 400 million patients worldwide (Han, 2022; Schieppati, 2008). In the U.S. alone, almost 900 therapies with orphan drug designation have been approved across roughly 400 different rare diseases. Yet, only about 5% of rare diseases in the United States currently have an FDA approved therapy, leaving most patients without effective treatments or a disease-specific standard of care (Han, 2022). The economic burden of rare diseases is ~10x higher than non-rare diseases on a per patient per year (PPPY) basis and a rare disease lacking treatment is associated with a 22.1% increase in PPPY costs due to indirect and mortality-related costs (Andreu, 2022). In total, this represents an extremely high disease burden not only on patients and caregivers, but also on society at large.

Unlike crowded therapeutic areas such as cardiovascular disease or diabetes, rare diseases typically lack multiple approved therapies, and pipeline competition is often minimal. For small and mid-cap biotechnology companies, this represents a strategic opportunity to operate in less competitive markets while delivering transformative therapies for patients with few or no alternatives. However, this opportunity was not always obvious. Early skepticism about the commercial potential of orphan drugs was widespread. Investors were reluctant to back programs with such small patient pools, fearing that development costs could never be recouped (Miller, 2017). The pharmaceutical industry prioritized mass-market conditions like cardiovascular disease, metabolic disorders, and oncology, where the addressable population justified significant resource investment. Payers worried that even if therapies for rare diseases were approved, the very high per-patient costs would be unsustainable for health systems and insurers (Nuijten, 2020).

The turning point came through a combination of three factors that demonstrated the viability of rare disease development:

01 Policy Incentives

02 Scientific Breakthroughs

03 Early Commercial Successes

The Orphan Drug Act of 1983 (Fig. 1) and a select few additional policies introduced and extended market exclusivity, R&D tax credits, and fee waivers that lowered financial barriers to development (Roberts, 2023). The emergence of landmark therapeutic modalities like enzyme replacement therapies (ERTs), monoclonal antibodies, gene therapies, and cell-based CAR-T therapies proved that even ultra-rare conditions could be treated effectively (Han, 2022). Finally, early commercial blockbusters validated the business model: therapies such as Ceredase and Cerezyme for Gaucher disease and Soliris for paroxysmal nocturnal hemoglobinuria (PNH) not only transformed patient outcomes but also achieved multi-billion-dollar revenues despite serving very small patient populations (Han, 2022).

The alignment of supportive policy, scientific viability, and commercial validation overturned early skepticism and set the stage for the rare disease sector to become one of the most dynamic growth areas in the biopharmaceutical industry. Over the course of this three-part white paper series, we intend to argue that, especially for small and mid-cap biotechnology and biopharmaceutical companies, focusing on rare diseases represents an attractive, sustainable corporate strategy. Furthermore, this space marks one of the most promising areas for business development and licensing (BD&L) activity, linking innovative small biopharmaceuticals with the scale and resources of large-cap ($10-50B) and mega-cap (>50B) pharmaceutical companies.

Unlocking Rare Disease Potential White Paper Series: Overview of Upcoming White Papers

Part II **Topic:** The Global Pricing and Access Landscape of Rare Disease

A deep dive into the complex world of pricing strategies, payer dynamics, and access challenges. We discuss sustainability concerns and how companies can balance innovation and affordability to navigate reimbursement hurdles.

Part III **Topic:** BD&L Trends and Investment Outcomes in Rare Disease

A thorough look at BD&L strategy in the rare disease space. With insights from industry experts and analysis of rare disease deals, understand how strategic partnerships can accelerate development, reduce risk, and drive greater valuations.

Global Policy Incentives as a Catalyst for Rare Disease Development

The rise of rare disease drugs can be directly linked to a host of policies that reshaped the economic incentives of clinical development. The U.S. Orphan Drug Act (ODA) of 1983 provided a suite of incentives including seven years of market exclusivity, tax credits for clinical research, and waivers for certain FDA submission fees. These measures reduced the financial risks for companies pursuing therapies for small patient populations, making projects that once seemed impossible more feasible (Roberts, 2023).

US Policies that have encouraged an expansion of development for rare diseases

Policy / Legislation	Year	Incentives
Orphan Drug Act	1983	• 7 years of market exclusivity • Tax credits for clinical testing • Waiver of FDA application fees • Grant funding for rare disease trials
Orphan Products Grants Program	1983	• Provides grants to academic and small-company sponsors for rare disease clinical trials • De-risked early-stage development
Accelerated Approval Pathway	1992	• Allows approval based on surrogate or intermediate clinical endpoints • Enables earlier patient access while confirmatory trials continue
Biologics Price Competition and Innovation Act	2010	• 12 years of exclusivity for innovator biologics • Streamlined biosimilar approval pathway • Encourages biologic innovation, including rare diseases
Food and Drug Administration Safety and Innovation Act	2012	• Created Breakthrough Therapy & Rare Pediatric Disease PRV programs • Expanded Accelerated Approval • Strengthened patient-focused development
Rare Pediatric Disease Priority Review Voucher (PRV) program	2012	• Provides transferable vouchers for expedited FDA review of another drug thereby • Strong financial incentive for pediatric rare disease R&D • The program was sunset in 2024 after Congress failed to extend the program
21st Century Cures Act	2016	• Introduced Regenerative Medicine Advanced Therapy (RMAT) designation • Encouraged real-world evidence & patient input • Streamlined rare disease trial design
RACE for Children Act	2017	• Requires evaluation of adult oncology drugs in pediatric cancers with shared molecular targets • Speeds pediatric rare cancer drug access
Rare Disease Endpoint Advancement (RDEA) Pilot Program	2023	• Part of PDUFA VII updates • FDA–sponsor collaboration to develop novel endpoints • Facilitates more feasible rare disease trials
Rare Disease Evidence Principles	2025	• Receive clearer guidance on acceptable evidence for ultra-rare disease clinical trials • Approvals may rely on single adequate and well-controlled trial plus confirmatory evidence (e.g., biomarkers, mechanism, natural history comparisons) • Increases regulatory flexibility in small populations driven by known genetic defects • Applications can be submitted before pivotal trials have initiated to ensure early engagement with regulators on evidence strategies
Give Kids a Chance Act	2025* (initially proposed in 2021)	• Has not been enacted* • Expands pediatric study requirements for drugs targeting relevant molecular mechanisms • Builds on RACE for Children Act incentives • Would reinstate PRV program

Table 1 – Key U.S. policies that have shaped the rare disease innovation landscape. Over the past four decades, federal legislation has steadily expanded incentives – financial, regulatory, and scientific – to reduce development barriers and stimulate investment in orphan drugs. Together, these initiatives have transformed rare diseases from an overlooked niche into one of the fastest-growing areas in biopharma innovation.

In addition to core orphan incentives, supplementary regulatory accelerators have been particularly influential (see table 1 for expanded list of policies). The FDA's Accelerated Approval pathway, established in 1992 and expanded for oncology and rare diseases, allows drugs to be approved with surrogate endpoints that are "reasonably likely" to predict clinical benefit. While controversial, particularly when confirmatory trials lag, it has provided patients with earlier access to breakthrough therapies (Richey, 2009). The ODA has also enabled the development of novel biologic classes (e.g., enzyme replacement therapies) in rare indications, proving the commercial viability of high-cost biologics. Financial incentives were further cemented by the 2010 Biologics Price Competition and Innovation Act, which created 12 years of exclusivity and accelerated the development for novel therapeutics. The Rare Pediatric Disease Priority Review Voucher (PRV) program, introduced in 2012, grants companies tradable vouchers for expedited FDA review of another product, often valued at over $100 million on the secondary market (Mease, 2024). Although congress failed to reauthorize the program in 2024, causing the FDA to sunset the PRV program, congress is currently working on new legislation, the Give Kids a Chance Act, to reinstate the PRV voucher. Finally, expanded access programs, real-world data collection and long-term natural history studies, and the rise of decentralized trials, especially during and after the COVID-19 pandemic, have played a growing role in supporting regulatory submissions, particularly when traditional randomized trials are not financially feasible (Polak, 2020).

Global Rare Disease Policies

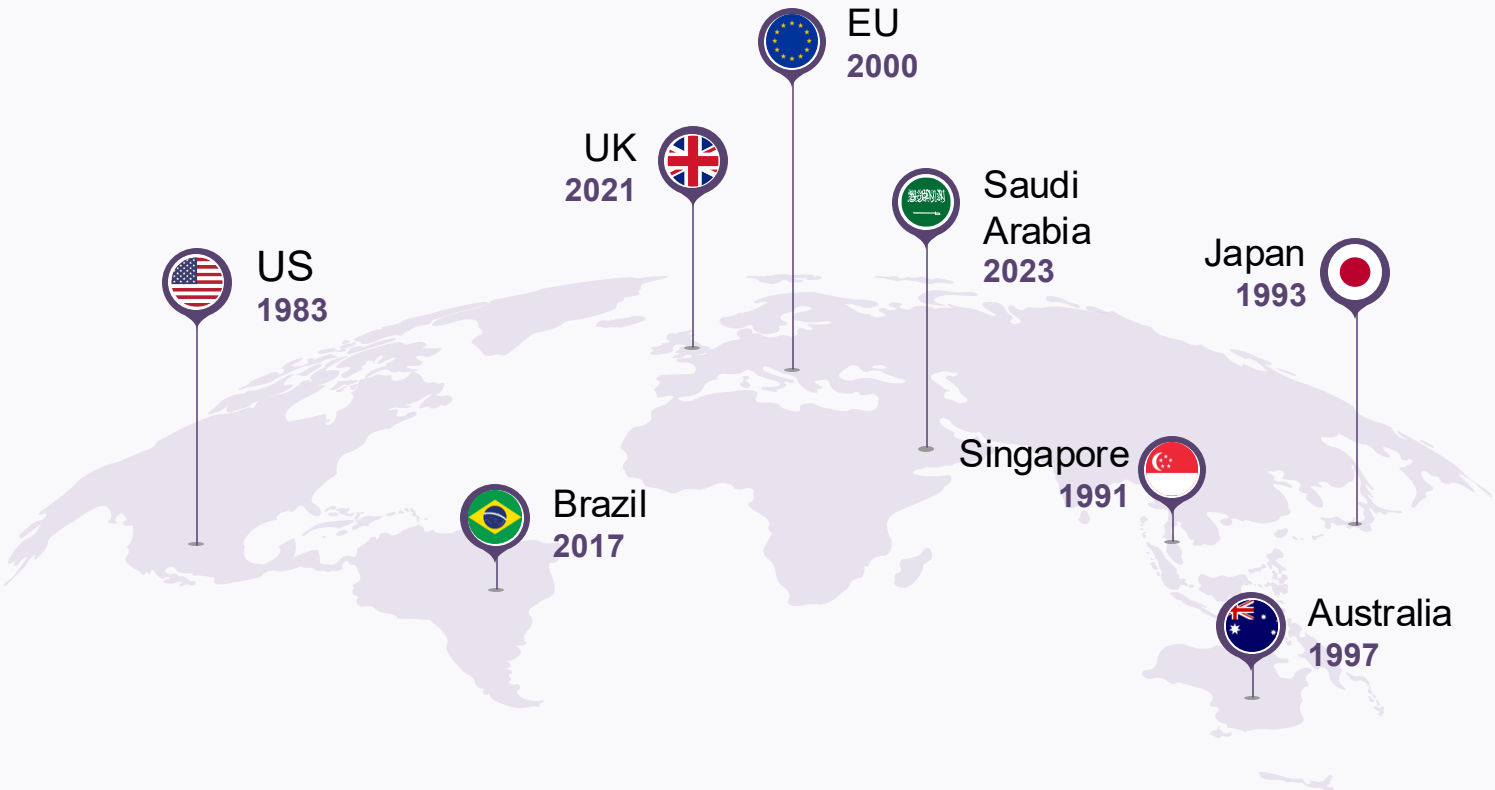


Figure 1 – The Rise of Global Rare Disease Policy: Taking inspiration from the U.S. Orphan Drug Act, 50 countries globally have created some form of orphan drug legislation.

U.S. policy success quickly inspired global adoption of orphan drug frameworks. Japan introduced orphan drug incentives in 1993, and more recently, China enacted an orphan drug policy framework in 2019 (Costa, 2025). Today, more than 50 countries have some form of orphan drug legislation, creating a largely harmonized global policy environment that encourages innovation across markets.
The European Medicines Agency (EMA) implemented its orphan drug regulation in 2000, granting the following. Moreover, in 2007, the FDA and EMA reduced regulatory burdens by agreeing to utilize a universal orphan drug application (Hall, 2014).

- Ten years of market exclusivity
- Protocol assistance
- Fee reductions for qualifying products

Together, these policies represent a deliberate recalibration of regulatory and financial systems to support development in areas of high unmet need. Without them, many landmark therapy classes targeting single gene mutation disorders (e.g., enzyme replacement therapies, gene therapies, and even monoclonal antibodies) may have remained scientifically interesting but not commercially viable.

Clinical Developments: Scientific Breakthroughs and the Evolution of Rare Disease Therapeutics

The rare disease field illustrates how policy incentives and scientific breakthroughs reinforced each other in a self-sustaining cycle. The ODA lowered financial barriers, enabling small biotechs and academic groups to explore ultra-rare conditions that had been commercially unthinkable (Roberts, 2023). Over the past four decades, orphan drug designations have multiplied, therapeutic focus has broadened, and novel molecule classes have reshaped treatment possibilities. At the same time, development costs, trial design innovations, and evolving evidentiary standards have influenced both the pace and character of rare disease innovation. Together, these trends highlight how the field has matured from small molecule repurposing to sophisticated gene and cell therapy platforms.

Growth of Orphan Disease Development in the US

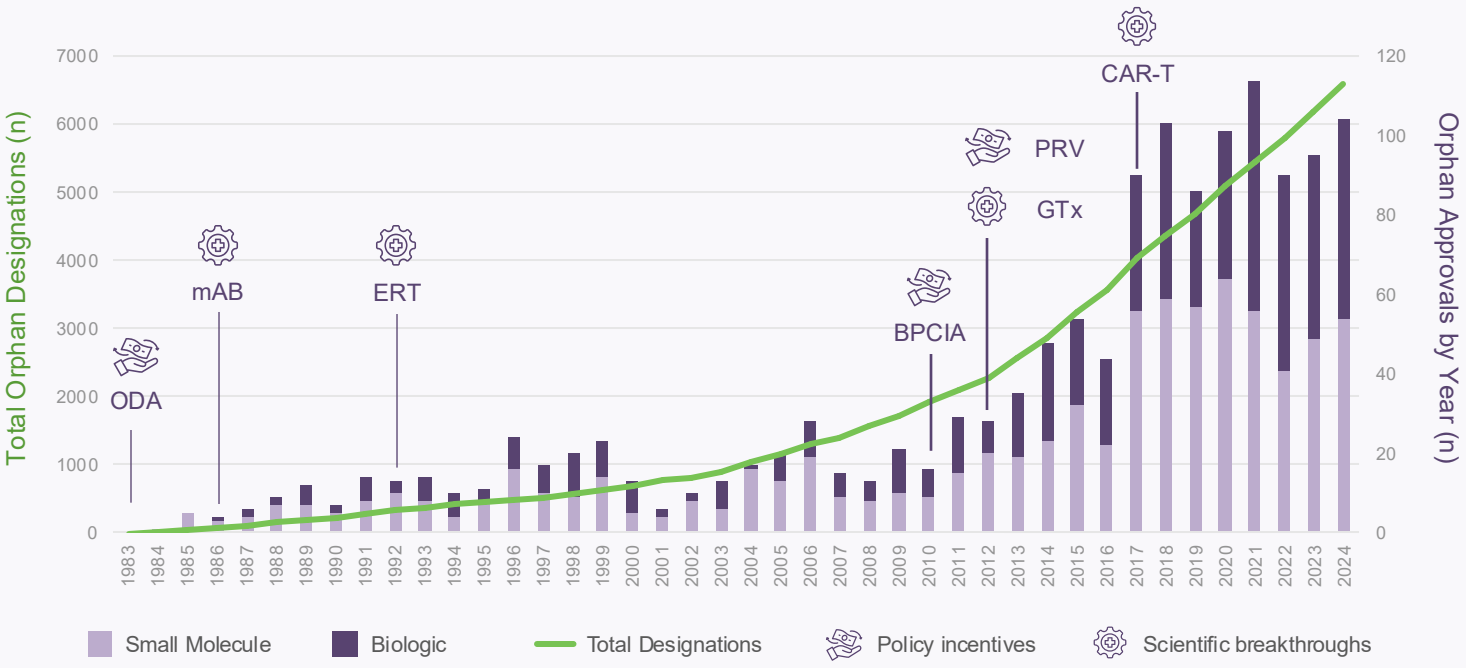


Figure 2 – Growth of Orphan Disease Development in the U.S. from the enactment of the Orphan Drug Act in 1983 until present also showing the enactment year of the Biologics Price Competition Innovation Act (BPCIA) and the establishment of the Rare Pediatric Disease Priority Review Voucher (PRV) program. During this time period, the first monoclonal antibody (mAB; Orthoclone OKT3), the first enzyme replacement therapy (ERT, Ceredase), the first gene therapy (GTx, Glybera), and the first chimeric antigen receptor T-cell (CAR-T, Kymriah) were all approved.

The scale of rare disease drug development is most clearly reflected in the dramatic growth of orphan designations. Since the passage of the U.S. Orphan Drug Act in 1983 until the end of 2024, more than 6,500 orphan designations have been granted (Fig. 2). The pace of designations has accelerated markedly, quadrupling from the 1990s to the 2010s. Notably pediatric-onset diseases accounted for 27% of designations in the 2010s (Miller, 2021). Not surprisingly, development of rare oncology indication therapies have consistently dominated these numbers, accounting for more than a third of all orphan designations over the past four decades (Miller, 2017). This growth underscores not only the success of incentives, but also the scientific advances that enabled programs once considered impossible.

The clinical development of novel molecule classes reflects a clear progression in step with broader scientific advancement

1980s-1990s

Most early designations were small molecules, often repurposed for rare cancers or metabolic disorders (Pushpakom, 2019).

1990s-2000s

Biologics surged in prominence, including ERTs for single gene knockout disorders and monoclonal antibodies for rare cancers (Miller, 2019). The sharp increase in biologics can be attributed to scientific advancement in the 1990s. In fact, the first ERTs, such as Ceredase (1991) and later Cerezyme (1994) for Gaucher disease, created a blueprint that has led to the approval of at least 15 therapies for various lysosomal storage disorders (Han, 2022). The monoclonal antibody Soliris (2007) for paroxysmal nocturnal hemoglobinuria (PNH) showed that ultra-rare therapies could still sustain blockbuster revenues.

2010s-2020s

Gene therapies, RNA-based therapies, and cell therapies defined a new era. From the pioneering but commercially limited Glybera (2012), to Zolgensma (2019) for spinal muscular atrophy and CAR-T therapies in hematologic cancers (Han, 2022), rare disease innovation pushed the boundaries of what was clinically and commercially viable. These modalities benefit from platform approaches where validated safety and efficacy data can be leveraged across indications, accelerating trial timelines and improving success rates (Jones, 2025).

Importantly, clinical trial design has adapted to the constraints of rare disease development as trials are smaller, more targeted, and often make use of surrogate endpoints, yet approval timelines are faster, and success probabilities higher compared to non-orphan drugs (Jayasundara, 2019). Moreover, contrary to common perceptions, clinical development costs for rare disease therapies are not uniformly higher than those for non-rare diseases. Analyses of approvals show that the average cost per approved orphan drug was $166 million compared to $291 million for non-orphan drugs, with capitalized costs also lower, $291 million versus $412 million (Jayasundara, 2019). For new molecular entities specifically, orphan development costs were roughly half those of non-orphans (Jayasundara, 2019).

Rare Disease Clinical Development Costs

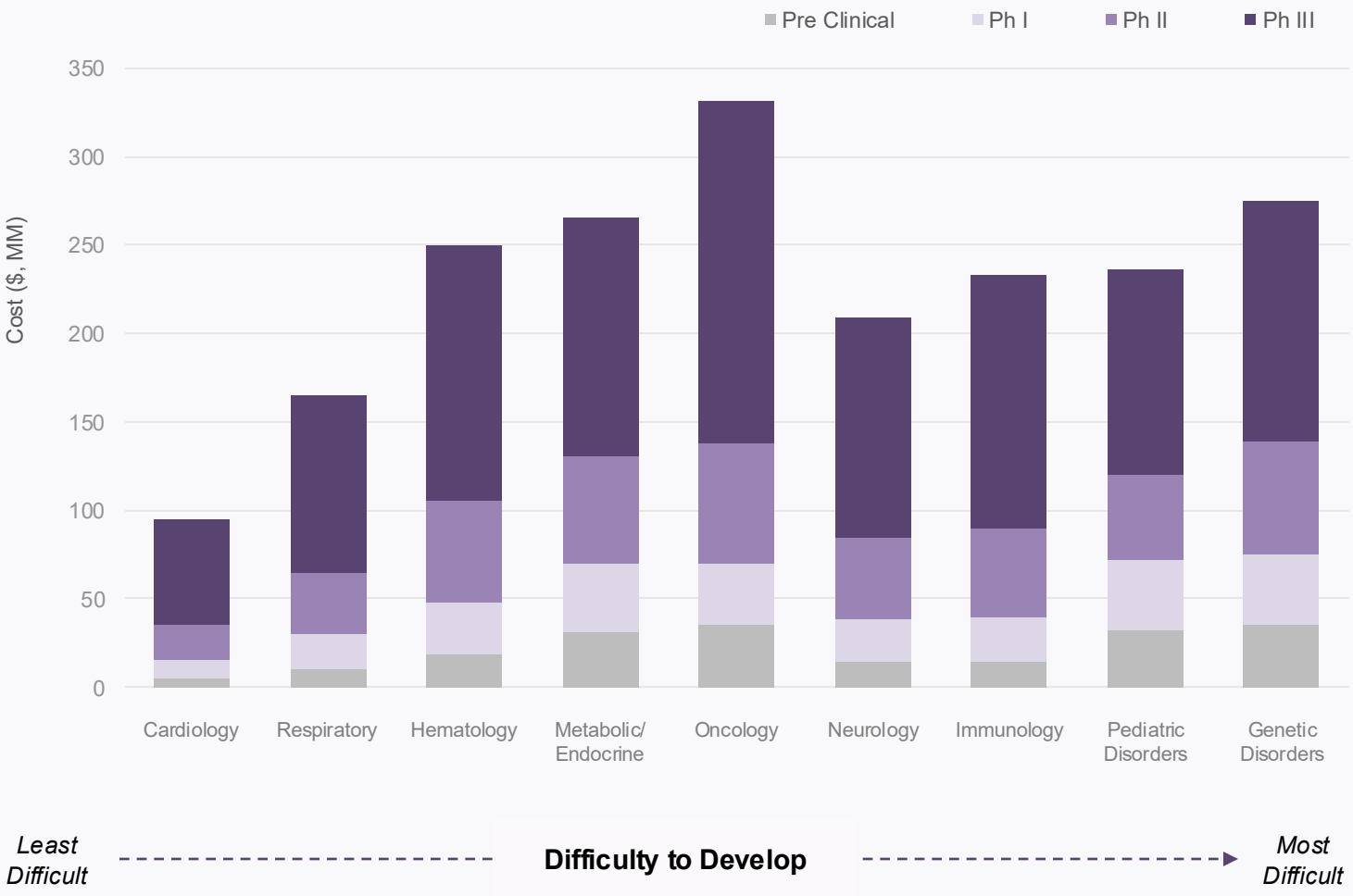


Figure 3 – Market Research analysis of industry experts (n=31) showing rare disease drug development costs by stage of development from pre-clinical to Phase III. Analysis of development costs was analyzed by therapeutic area. Experts were also asked to rank order therapeutic areas by difficulty to develop as shown here.

While clinical development costs of orphan drugs are typically less than non-rare drugs, there are significant difference between orphan drugs themselves. Market research of Industry experts (n=31) with knowledge of clinical development costs demonstrated significant difference in the development costs between different therapeutic areas. Development costs roughly correlated with therapeutic areas that were most difficult to develop. Hematology, metabolic/endocrine and oncology were more costly than difficult to develop, likely due to larger trial sizes, trial length and/or more widespread utilization of high-cost biologic therapies compared to other therapeutic areas, although publicly available data could not corroborate due to incomplete data.

On average, development costs increased about

35% ▶ **71%** ▶ **156%**

Pre-clinical to Ph I *Ph I to Ph II* *Ph II to Ph III*

between each stage of development from pre-clinical through Ph III (Fig. 3)

Clinical development of orphan drugs is generally less costly than for non-orphan drugs, largely due to differences in trial design and evidentiary standards. Orphan trials often enroll fewer patients across all phases, and regulators frequently accept approvals after Phase II using surrogate endpoints or single-arm studies, reducing the need for large Phase III programs (Richey, 2009). Regardless of trial phase, trial sizes for orphan drugs are typically smaller than those for non-orphans, though trial durations across all phases are longer on average (1,417 vs. 774 days), likely due to difficulty identifying and enrolling patients (Jayasundara, 2019). The increasing use of adaptive and/or basket trial designs has further enhanced efficiency in small populations (Li, 2022; Roes, 2016), while digital and decentralized approaches are beginning to address recruitment challenges for geographically dispersed patients (Petrini, 2022; Moore, 2022). Additional cost savings come from regulators' growing willingness to rely on expanded access program (EAP) data, which can substitute for or supplement traditional clinical trials. In fact, EAP data provided pivotal efficacy evidence in 13 approvals, nearly all involving orphan drugs (Polak, 2020).

These efficiencies help explain why, despite being resource-intensive and lengthy, rare disease R&D is not as economically prohibitive as often assumed.

The Cost and Difficulty of Rare Disease Clinical Development Challenges

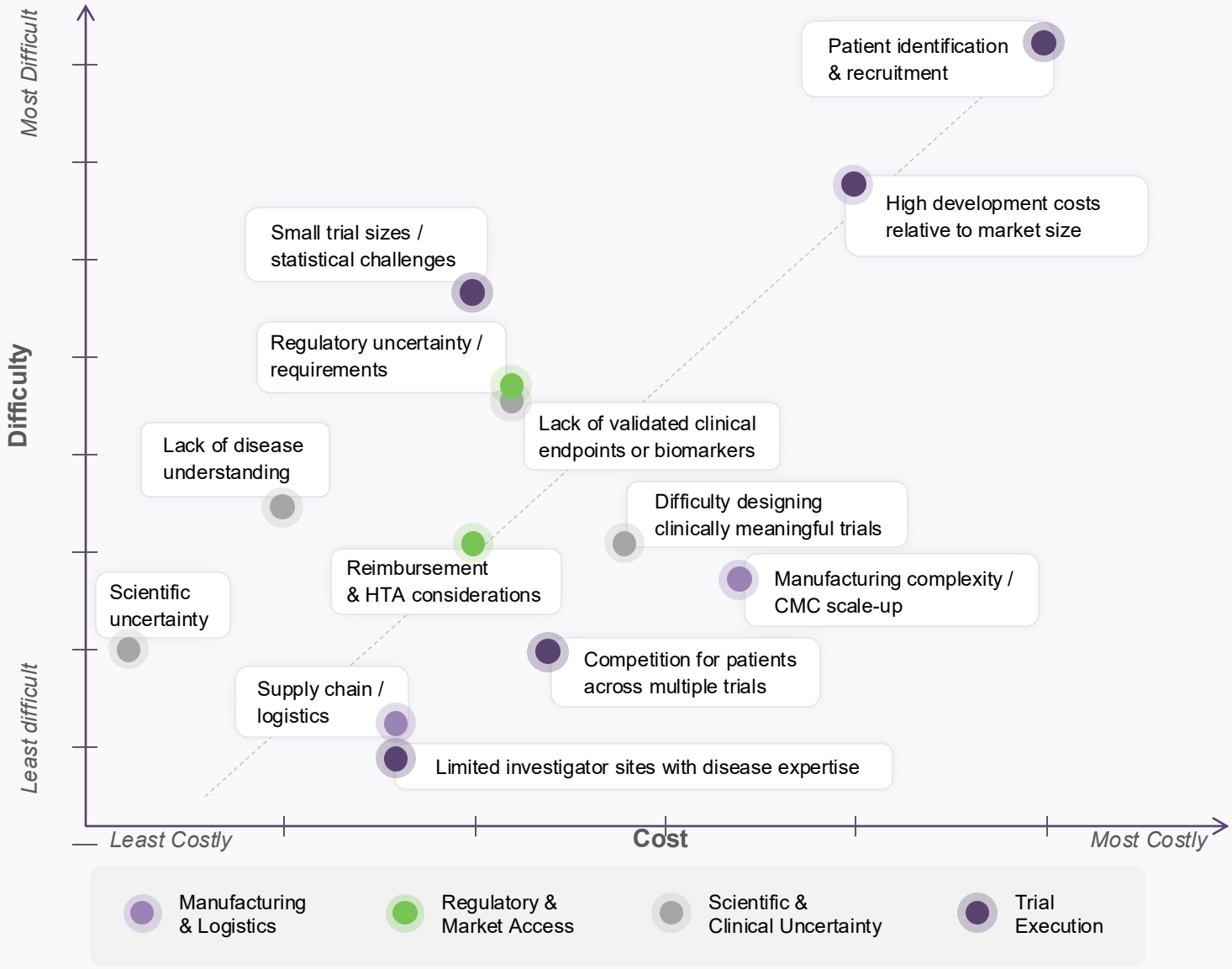


Figure 4 – Industry experts (n=31) rank ordered specific challenges related to the clinical development of rare disease drugs by difficulty and cost. The most difficult and costly hurdles are related to trial execution resulting from small patient populations. Overcoming scientific & clinical uncertainty were ranked as more difficult than costly, while manufacturing & logistics are more costly.

Despite significant advances, rare disease clinical development continues to face a distinct set of challenges. In a market research study of 31 industry experts with significant experience in rare disease drug development, trial execution challenges were rated as both most difficult and most costly, likely resulting from small patient populations (Fig. 4). Specifically, patient identification and recruitment was ranked as the most difficult and most costly challenge, mirroring the global needs for newborn screening and better diagnostic testing. These diagnostic gaps are not routine for most rare diseases, even when effective therapies already exist, leading to prolonged diagnostic journeys for patients. Limited natural history data further complicates development progress, with many conditions lacking robust registries or longitudinal studies to inform trial design. A shortage of validated endpoints and biomarkers poses additional barriers to both study design and regulatory approval.

Over the past several decades, rare diseases have shifted from being largely overlooked to becoming a focus of meaningful therapeutic progress. This transformation has been driven by a mix of the following that better fit the realities of small patient populations.

- Supportive policy incentives
- Rapid advances in science
- Innovative approaches to clinical development

Breakthroughs in proteomic and genetic platforms, combined with greater regulatory flexibility, have made drug development more practical and less costly. Importantly, early landmark therapies demonstrated that rare drug development was not only scientifically feasible but also commercially viable.

Together, these forces created the conditions for rare disease therapeutics to emerge as a major engine of growth for the biopharmaceutical industry.

From Niche to Blockbuster: The Commercial Triumph of Rare Diseases

While supportive policies and scientific breakthroughs were necessary conditions for rare disease development, commercial validation ultimately shifted industry perception. Blockbuster revenues, label expansions into broader markets, and successful repurposing of shelved drugs have all validated that rare disease development is not only viable but can, on its own, be a successful commercial development strategy.

The Cost and Difficulty of Rare Disease Commercial Challenges

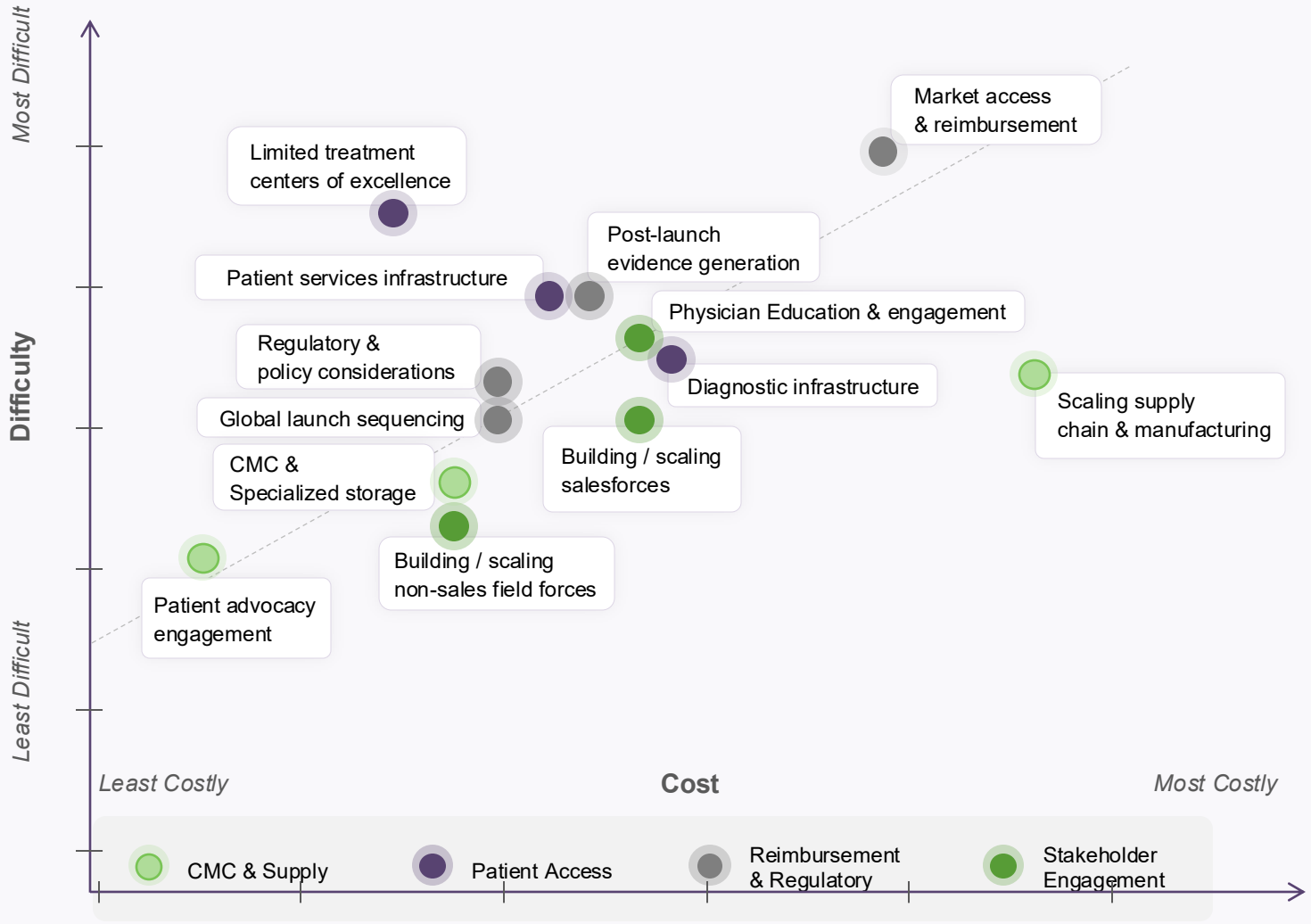


Figure 5 – Industry experts (n=31) rank ordered specific challenges related to the commercialization of rare disease drugs by difficulty and cost. Reimbursement and Regulatory Challenges were ranked as both most costly and challenging. CMC & Supply and Field Force ranked as most costly challenges. Conversely, patient access was seen as difficult but not costly. Regardless of therapeutic area or company size, there was little variation in assessments of commercialization challenge difficultly or cost *(data not shown)*.

However, commercialization of rare disease assets is not without significant costs and challenges (Fig. 5). In a market research study of 31 industry experts experienced in rare disease commercialization, reimbursement and regulatory hurdles were ranked as the most difficult and expensive. While payers acknowledge the unmet need, extremely high per-patient costs (often in the hundreds of thousands to millions per year) drive intense scrutiny of value, data quality, and long-term outcomes. Generating the real-world evidence and health economic data needed to maintain access and justify reimbursement is slow, expensive, and continues well beyond launch. Even with global orphan drug frameworks, regulatory requirements and timelines vary widely across regions, adding uncertainty and cost. Meanwhile, small, fragmented patient populations, complex diagnostic pathways, and limited treatment sites make patient access difficult to achieve. Manufacturers attempt to mitigate these barriers through robust patient and caregiver support programs, but these are resource-intensive and challenging to scale.

Commercial Costs

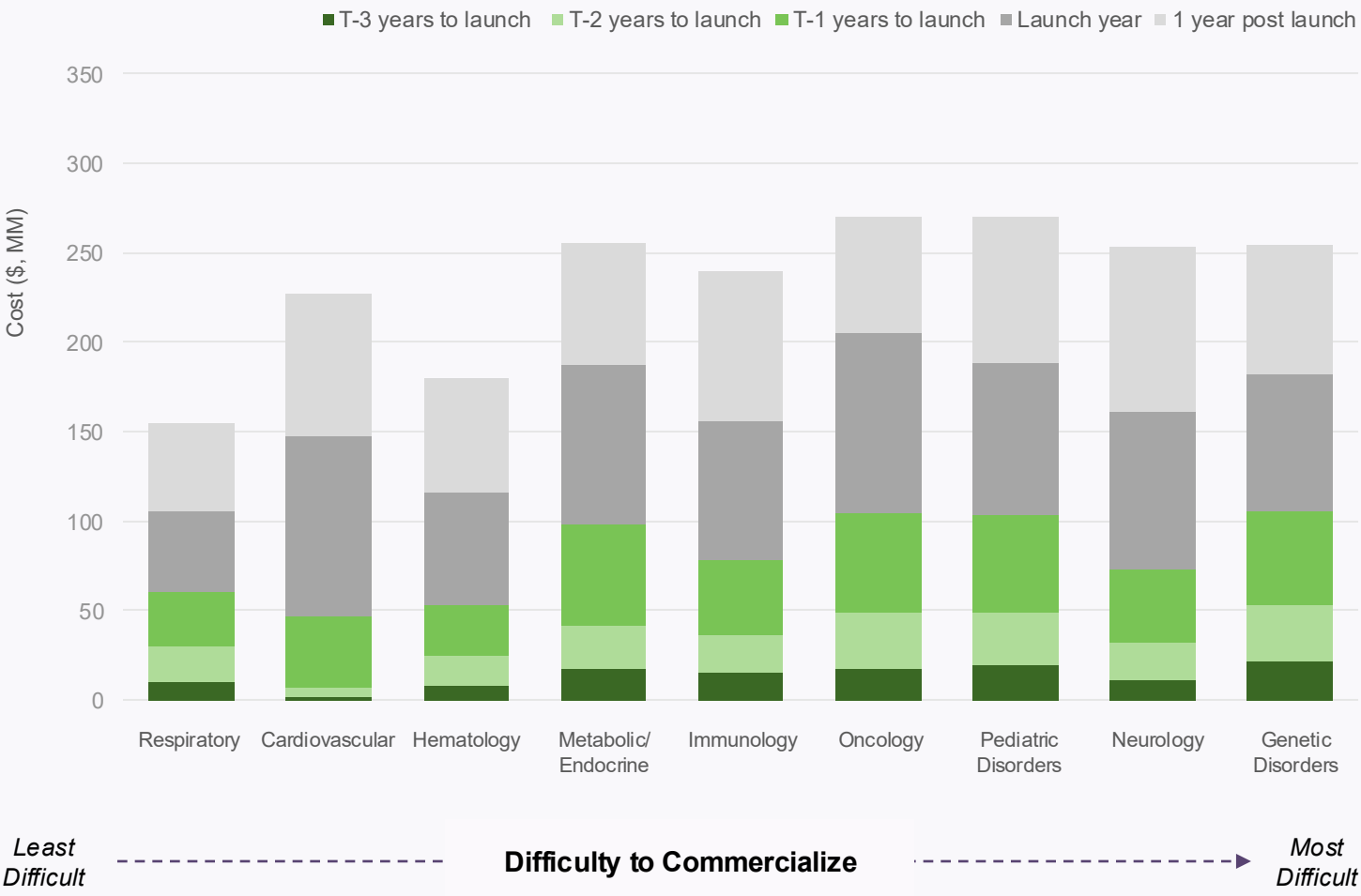


Figure 6 – Market research analysis of industry experts (n=31) showing average annual commercialization spending for rare disease assets from three years pre-launch through one-year post-launch, segmented by therapeutic area, which are ordered by difficulty to commercialize from least to most difficult.

While the clinical development costs of rare disease assets have been well studied, there is limited publicly available data on commercialization costs. In market research with industry experts, annual commercialization spending from three years pre-launch through one year post-launch was analyzed by therapeutic area (Fig. 6). Experts reported relatively little variation in costs across therapeutic areas, though spending increased by roughly 80% year over year. Interestingly, commercialization costs did not correlate with how difficult each therapeutic area was to commercialize, but there was a strong correlation between the difficulty of clinical development and the difficulty of commercialization. This consistency in commercialization investment likely reflects the shared structural challenges of rare disease launches across all therapeutic areas – small, dispersed patient populations, complex diagnostic and referral pathways, and stringent payer demands. Every rare disease asset requires a high-touch, resource-intensive commercialization model with similar infrastructure for patient support, stakeholder outreach and education, and evidence generation. As a result, commercialization costs tend to converge around $250M over the five years assessed, regardless of indication. While mechanism of action and drug class were not specifically assessed, it is likely that small molecules are less costly to commercialize than biologics, and that complex biologics (e.g., cell and gene therapies) require significantly higher investment.

A growing number of rare disease therapies have achieved blockbuster status, with annual sales exceeding $1 billion. These examples demonstrate that serving small populations does not preclude large commercial returns.

SPINRAZA®

An antisense oligonucleotide for spinal muscular atrophy (SMA), surpassed $2 billion in annual revenues within just three years of launch.

zolgensma®

Zolgensma, a one-time gene therapy for SMA, became a commercial juggernaut despite its ultra-high upfront cost of $2.1 million per dose (Michaeli, 2023; Ollendorf, 2018).

Together, these therapies highlight two complementary rare disease business models

High chronic revenue (Spinraza)  VS  Ultra-premium curative pricing (Zolgensma)

Beyond the success of SMA therapies, other therapies have also crossed the billion-dollar threshold, demonstrating that rare disease blockbusters are not indication specific or one-off success stories. Soliris for paroxysmal nocturnal hemoglobinuria (PNH) and Cerezyme for Gaucher disease have both reached multi-billion-dollar revenues. Elevidys (delandistrogene moxeparvovec) for Duchenne muscular dystrophy is emerging as a blockbuster candidate. Despite ongoing safety concerns, providers continue prescribing it for selective patient populations, suggesting little slowing in revenue projections. These commercial proof points overturned the myth that orphan drugs could not sustain global-scale returns.

Maximum Annualize Revenue of Orphan Designated Drugs from 2000 to 2024

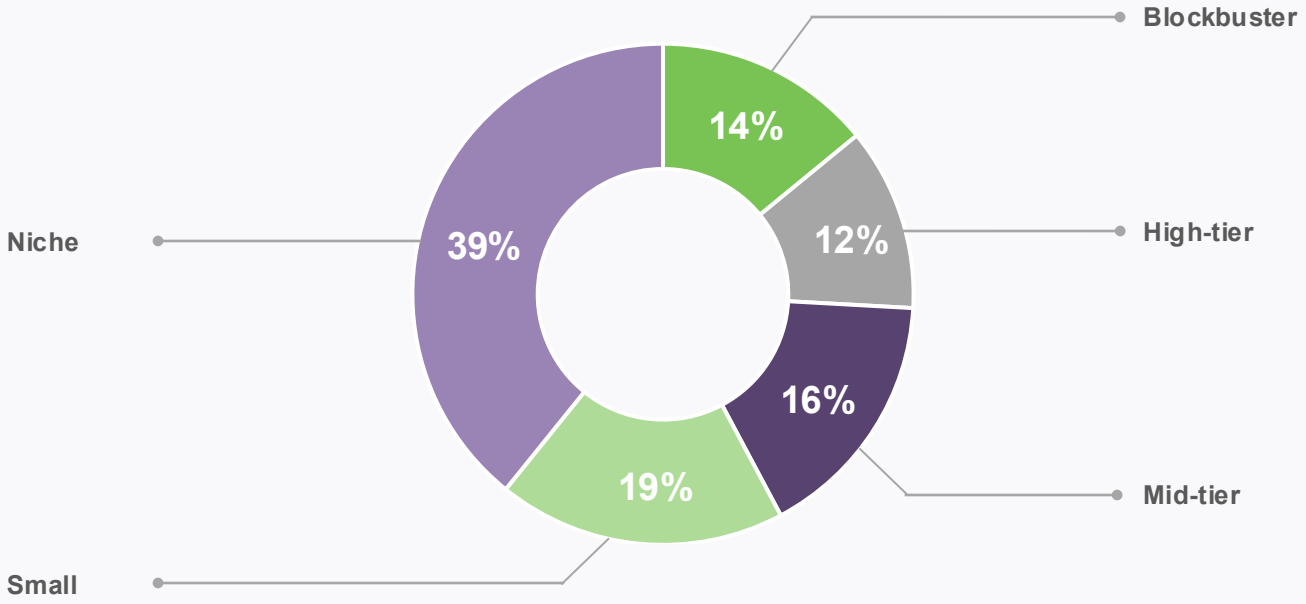
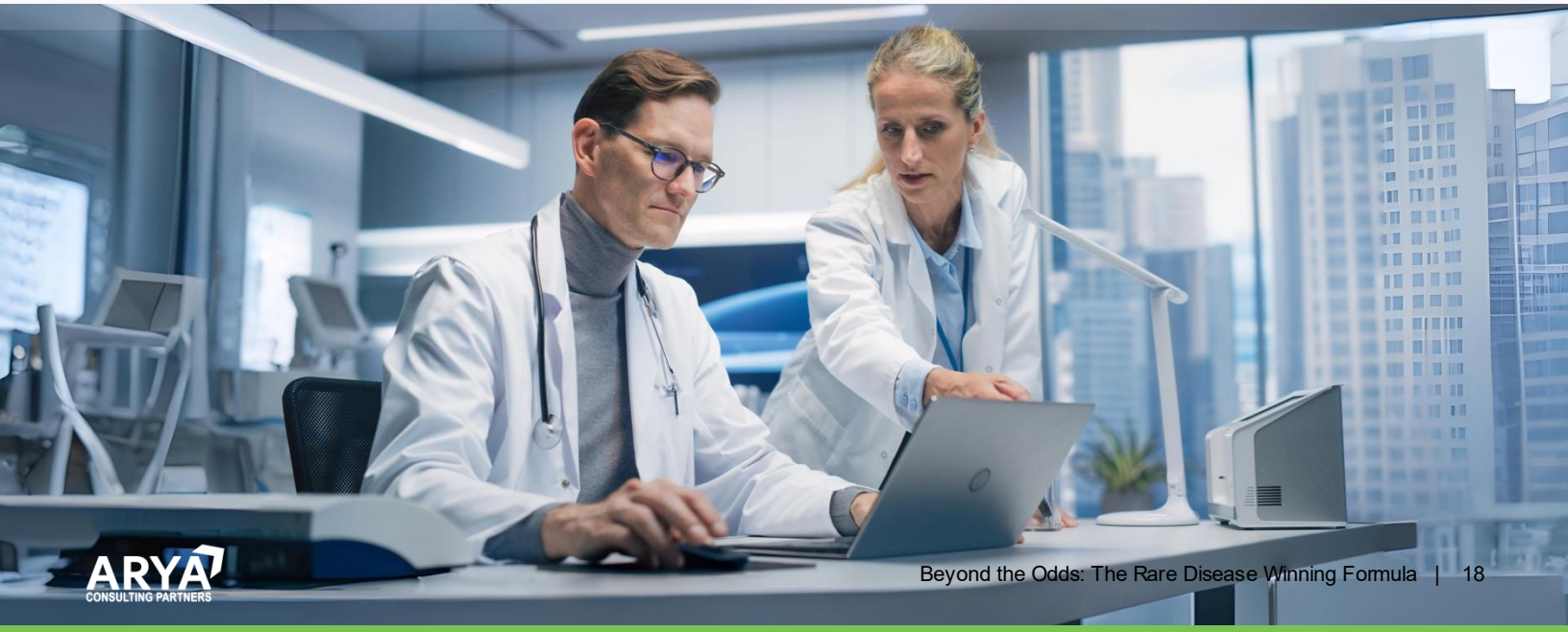


Figure 7 – Peak annual revenue analysis of orphan-designated drugs approved in the U.S. between 2000 and 2024 (n=398). Drugs are categorized by peak annual sales into Blockbuster (≥$1B), High-tier ($500M–<$1B), Mid-tier ($250M–<$500M), Small ($100M–<$250M), and Niche (<$100M). Revenue estimates may include ex-U.S. sales. This analysis highlights that while a minority of orphan drugs achieve blockbuster or high-tier revenue, a substantial proportion of therapies remain mid-tier or niche, reflecting the diverse commercial potential within the rare disease space.



While there is an increasing reliance by big pharma on blockbuster drug revenue, it is important to note that most approved therapies never achieve blockbuster status, and many fail to recoup their full development investment. Only about 14% of orphan designated drugs achieve blockbuster status, with another ~12% classified as high-tier revenue products generating between $500M and $1B annually (Fig. 7). Analyses of post-launch performance of FDA approved therapies highlight this reality. In a review of therapies approved between 2000 and 2019, the total revenues over the first three years post-launch were examined for both orphan and non-orphan drugs (Fig. 8). Therapies approved exclusively for orphan indications showed a steady upward trend in early revenues over this period, suggesting that rare disease designations increasingly correlate with strong initial commercial performance. In contrast, drugs that never received an orphan designation exhibited declining three-year post-launch revenues, reflecting the intense competition, crowded therapeutic landscapes, and higher development costs faced by non-orphan products.

Orphan vs Non-Orphan Drug Designation Revenue

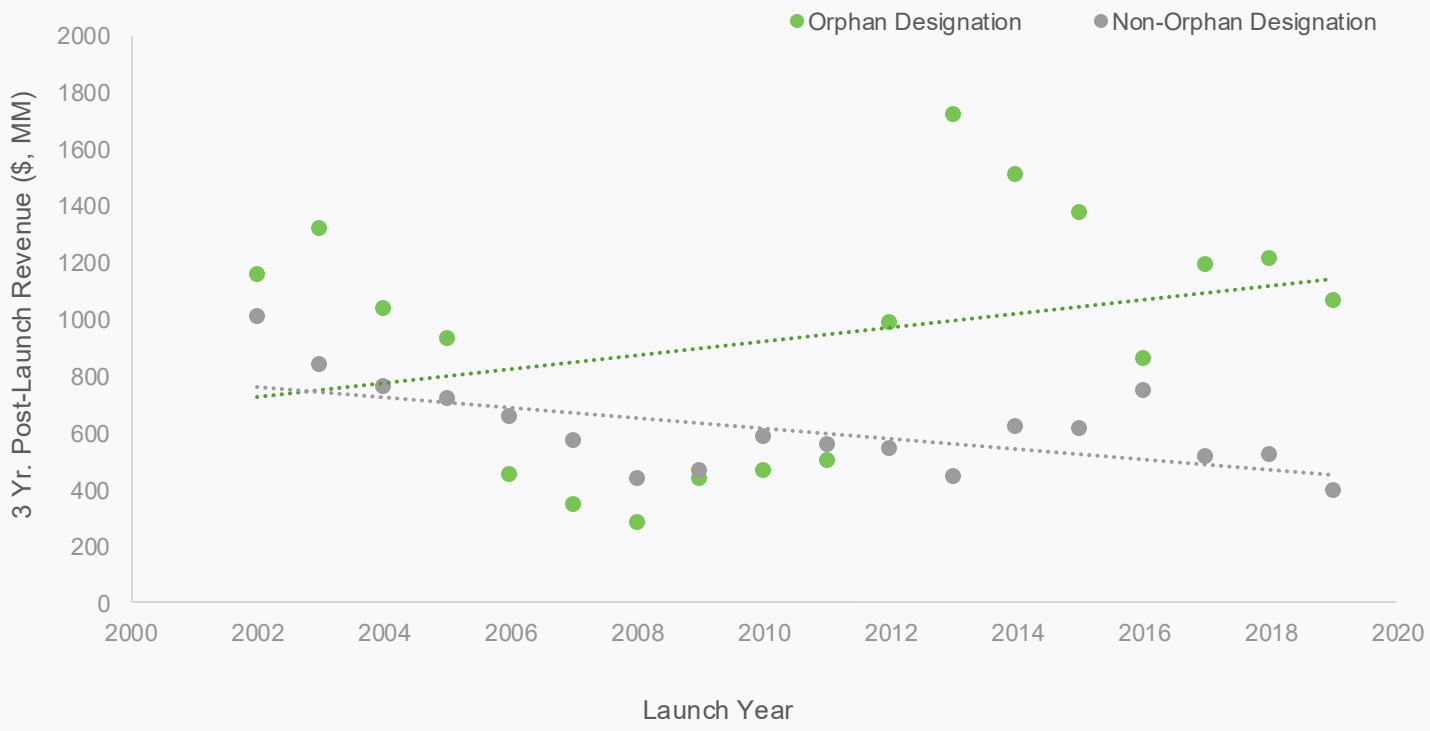


Figure 8 – Analysis of 3-year post launch revenue for assets that were approved for only orphan indications (rare; n=318) or only non-orphan indications (non-rare; n=2106) between 2000-2024 in the US. Revenue may include ex-US revenue. Assets were excluded if no sales data was available. Asset Orphan indications approval median (range) 1 (1-29). Non-orphan indications median (range) 1 (1-36).

Although roughly 40% of orphan drugs are niche products with maximum annual sales under $100M (Fig. 7), these therapies often achieve net positive returns over their life cycle, benefiting from limited competition and low risk of generic or biosimilar entry. These findings underscore the strategic appeal of orphan development for pharmaceutical companies. Even small patient populations can generate meaningful early returns, particularly when paired with strong pricing, reimbursement strategies, and patient access programs. At the same time, the data highlights the inherent risk in relying solely on blockbuster potential, as the majority of products, rare disease or not, do not reach multi-billion-dollar revenue levels, reinforcing the need for careful portfolio diversification and commercial planning.

Orphan-first strategies are attractive not only because of reduced early competition, but also because of expansion potential. Systematic reviews confirm that 25-30% of orphan therapies eventually gain additional non-orphan indications (Chambers, 2023). This strategy turns niche programs into broad commercial platforms. Imatinib is a canonical example. Originally approved for chronic myeloid leukemia, an orphan disease, it later expanded into gastrointestinal stromal tumors and other cancers, building a multibillion-dollar franchise. However, expansion from rare to non-rare is not without concerns. Analyses of FDA approvals show subsequent non-orphan indication expansions rely on weaker trial designs or smaller data sets than other class competitors (Michaeli, 2022). This raises questions about whether orphan incentives are being used beyond their intended scope.

Rare disease indications have also unlocked commercial potential by reviving shelved drugs.

Propranolol

Once a generic beta-blocker, was repurposed for infantile hemangioma

Fenfluramine

Previously withdrawn as a weight-loss agent, was reintroduced for Dravet syndrome

Alpelisib

A PI3K inhibitor, gained approval for PIK3CA-related overgrowth spectrum (Jonker, 2024).

Repurposing is also being accelerated by computational tools. Gene-target mapping and trial data mining have uncovered thousands of repositioning opportunities, for example linking multiple sclerosis with Crohn's disease and other immune-mediated conditions (Sakate, 2021).

These practices reflect both the creativity and tensions within rare disease development, as incentives designed for small patient populations sometimes fuel broader commercial expansion.

The Rare Disease Success Formula

Over four decades of rare disease drug development reveals a consistent formula for success:

Each component of this success story has been essential. Landmark policies such as the Orphan Drug Act and expedited regulatory pathways lowered barriers to entry; therapeutic innovations including ERTs, monoclonal antibodies, and cell and gene therapies demonstrated feasibility and unlocked new possibilities; and changes to trial design and regulatory flexibility enabled efficient translation from science to patients (Ollendorf, 2018; Michaeli, 2023; Chambers, 2023). This formula has delivered tangible results. Orphan drugs have achieved blockbuster-level sales in rare diseases, and today roughly one-third of all FDA-approved drugs carry an orphan designation, demonstrating both commercial viability and sustained momentum in this field.

Patient advocacy has been central to this trajectory. Advocacy groups generate natural history data, enable decentralized trials, and shape both regulatory and reimbursement strategies. In doing so, they reduce development risk and accelerate pathways to approval and adoption (Bechara, 2023). This has led to a shift where in rare diseases, patient centricity is now operational, not aspirational.

The commercial model that emerged from this foundation has been validated repeatedly by capital markets. Small and mid-cap biotechs typically drive proof-of-concept, with large pharma scaling commercialization and global launch sequencing once clinical success is established (Bechara, 2023). This sequencing reflects both capital efficiency and strategic fit, aligning with the industry-wide shift from volume-based to value-based innovation, where small, highly effective therapies can generate outsized impact even in small patient pools (Michaeli, 2023). Investor enthusiasm has reinforced this cycle. Studies show that orphan designation announcements generate significant positive abnormal returns of approximately 3.4% for biotech firms (Miller, 2017). Moreover, valuation analyses confirm that orphan and multi-indication assets consistently attract higher acquisition prices and stronger returns relative to non-orphan assets (Chambers, 2023). These market trends highlight that rare disease strategies are not only scientifically feasible, but also highly financially attractive.

What began as a policy experiment has matured into a cornerstone of pharmaceutical growth.

Incentives catalyzed initial investment

Scientific advances proved feasibility

Commercial validation attracted further capital.

The result is a self-reinforcing cycle that ensures rare disease development remains central to biopharma strategy (Miller, 2017; Chambers, 2023). At the same time, the field continues to evolve in ways that are both creative and contested. Multi-indication expansion has maximized clinical and commercial value, but has sparked scrutiny about whether incentives are being applied beyond their intended scope. Repurposing and computational repositioning have revived shelved assets and generated thousands of new opportunities (Sakate, 2021). Increasingly high launch prices fuel payer resistance, raising concerns about long-term sustainability.

These lessons set the stage for the next paper in this series, where we turn from success to sustainability. Part 2 will explore the pricing and access landscape of rare disease therapies, analyzing payer dynamics, affordability challenges, and innovative contracting models that will shape the next decade of rare disease commercialization.

Future Questions for Rare Disease Development

Policy & Incentives

How will U.S. and EU regulators address concerns that orphan incentives are being extended to broader, non-rare indications with weaker data packages?

Pricing & Sustainability

What innovative payment and contracting models (e.g., outcomes-based agreements, annuity-style payments) will be needed to sustain patient access to ultra high-cost therapies?

Global Market Access

How will differences in HTA frameworks across Europe, Asia-Pacific, and emerging markets influence launch sequencing, pricing, and long-term commercial viability?

Clinical Trial Innovation

Can decentralized and hybrid trial models solve the recruitment and diagnostic gap challenges in ultra-rare indications?

BD&L & Globalization

As next-generation modalities (gene, RNA, cell therapies) proliferate in Asia, how will global R&D geography shape U.S. and European partnership, licensing, and investment strategies?

Methodology

Figure 2, 7 and 8: Analysis for Figures 2, 7, and 8 was conducted using data accessed from Global Data (September 2025), following the subsequent methodologies. Total Orphan Designations reflects the total count of unique drugs that received an FDA Orphan Designation for any indication, organized by the year in which their first designation was received; excludes drugs which pursued any indication in which they did not receive an Orphan Designation. Orphan Approvals by Year reflects the total count of unique drugs that received an FDA Orphan Designation for any indication and were approved in that indication, organized by the year in which their first approval was received; also excludes drugs which pursued any indication in which they did not receive an Orphan Designation. This figure was further sub-divided based on molecule type, using the dichotomous classification of Small Molecule and Biologic. Figure 7 reflects the total number of unique drugs that received an FDA Orphan Designation for any indication and were subsequently approved in that indication between the years 2000 and 2024; excludes any drugs for which sales data was not available. This sample is further subdivided by peak annual sales into Blockbuster (≥$1B), High-tier ($500M–<$1B), Mid-tier ($250M–<$500M), Small ($100M–<$250M), and Niche (<$100M); the figure represents the drugs within each category of peak annual sales as a percentage of the overall sample. Figure 8 reflects the average revenue over the first 3 years post-approval for all unique drugs that received their first approval for any indication in the US between 2000 and 2020; excludes drugs for which sales data was unavailable. This sample is further subdivided based on FDA Orphan Designation into two categories: 'Orphan Only Designation' represents drugs that received an FDA Orphan Drug Designation in any indication, were approved in that indication, and were not approved in any indication in which an FDA Orphan Drug Designation was not received; 'Non-orphan Designation' represents drugs that did not receive an FDA Orphan Drug Designation in any indication.

Figure 3-6: Figures 3-6 are based on data collected through an online survey designed to capture quantitative insights into the clinical development and commercialization of products in the rare disease space. Respondents were required to meet specific qualification criteria, including holding a senior position title, having a minimum of 5 years industry experience, and possessing strong or extensive knowledge of the costs associated with clinical and commercial development. The survey comprised 15 closed-ended questions utilizing multiple choice, matrix tables, and ranking formats. The survey was conducted between September 19 and September 25, 2025, and included a final sample of 31 qualified respondents (n=31). All data shown represents averages across respondents. Cost averages from two respondents were excluded because either no cost increases were reported between pre-clinical and Phase III clinical trials or costs were greater than 400% lower than calculated average.

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