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MAPPING RARE DISEASE IN 2026

CUMULATIVE PROGRESS, STRUCTURAL GAPS, AND THE ROAD AHEAD

JANUARY 2026

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This white paper is grounded in an extensive mapping effort covering more than 150 rare-disease biotech companies across the EU and the UK, including 99 private actors spanning seed-stage spinouts to commercial-stage developers. The landscape is broad and fluid; while not exhaustive, the sample captures a substantial portion of the region's current innovation capacity. As part of this work, we engaged with over 50 companies, public and private.

The field of rare diseases has evolved from a fragmented collection of scientific outliers into a coherent field with its own technologies, regulatory norms, economic logic, and industrial actors.
This transformation did not happen abruptly.
It emerged gradually, as decades of research, regulatory experimentation, patient-community engagement, and manufacturing experience accumulated into a system that is increasingly capable of advancing therapies for extremely small populations. The trajectory of the field is defined less by isolated breakthroughs than by an expanding base of shared knowledge that facilitates progress.
Yet this evolution remains incomplete.
Rare-disease innovation still faces structural constraints that cannot be solved by precedent alone: delivery technologies must become more reliable and safer, long-term evidence generation needs to keep pace with accelerated approvals, pricing frameworks must balance sustainability with access, and manufacturing needs to scale without compromising quality. The ecosystem has gained solidity, but not yet equilibrium.
This report approaches the rare-disease segment as a living system built from cumulative learning and still undergoing construction. It examines how biological insight, regulatory policy, patient networks, clinical practice, CMC know-how, and capital markets have progressively aligned around the challenges of scarcity. It also describes where the system remains fragile and where a concerted effort is now required. The combination of scientific convergence across shared pathways, institutional maturity in regulatory processes, industrial reproducibility in advanced modalities, and increasingly formal pricing governance has made the field more predictable than at any point in its history to date. At the same time, recent events like regulatory reversals on gene therapy datasets illustrate that the next phase will still demand incremental refinements of past models.
For investors, rare diseases form an attractive segment for structural reasons documented in regulatory and commercial data. Orphan-label development benefits from more focused and efficient clinical pathways, with out-of-pocket clinical costs per approval that are roughly 40% lower than for non-orphan drugs and an evidence burden averaging just 1.5 studies per drug for FDA approval (vs. 2.4 for non-orphans). This streamlined process includes a median development time of just 7.2 years (vs. 9-10 years for non-orphan programmes) and requires significantly smaller trials with a median of only c.150 patients (vs. over 500). While the overall probability of success for orphan drugs can be tricky to estimate due to the heavy concentration in difficult-to-treat cancers, the approval rate of orphan drugs outside oncology reaches 17%, more than double the 8% all indications average (excl. oncology). Specifically, in areas with well-defined genetic targets, such as rare disease gene therapies, the likelihood of approval from phase 1 can be 2-3.5 times higher than the industry average. Commercially, this translates into a significant pricing power, reflected in a median orphan drug launch price of US$219,000 vs. US$13,000 for non-orphans. These features do not eliminate risk, but they shape a setting where well-executed programmes can achieve regulatory and commercial successes.
A central contribution of this paper is a tentative to detailed mapping of Europe's rare-disease landscape. The region hosts a diverse set of actors, from de-novo innovators and platform integrators to legacy rare-disease specialists and opportunistic pharmas. Across northern and southern Europe, early-stage academic spinouts coexist with seasoned commercial organisations, forming a continuum that reflects both the maturity and the necessary heterogeneity of the ecosystem. This mapping does not present a static catalogue but a dynamic structure that shows how rare diseases have become an economic and industrial domain with depth, breadth, and continuity. This landscape is also shaped by the way capital circulates through it: M&A and licensing transactions have become a structural feature of how rare-disease innovation moves from early-stage academic origins to later-stage industrial scale, reinforcing the idea that the field operates as a connected system rather than isolated silos.
This report is also meant to act as a foundational layer. Rare diseases intersect so many scientific, regulatory and industrial domains that it is difficult to address any specific topic without first understanding how the broader system fits together. By outlining the system, how it operates, where it is robust, and where further progress is needed, this report provides the context for future analyses that will focus on more targeted themes.
The rare-disease field is more sophisticated, interconnected, and resilient than ever, yet it remains a system under active construction. It reflects decades of accumulated knowledge, institutional learning and technological refinement, while still contending with structural gaps that require sustained progress. What emerges is a landscape that is both mature and unfinished, a field capable of advancing highly specialised science, but still reliant on continued alignment across regulators, industry, patient communities and capital providers.

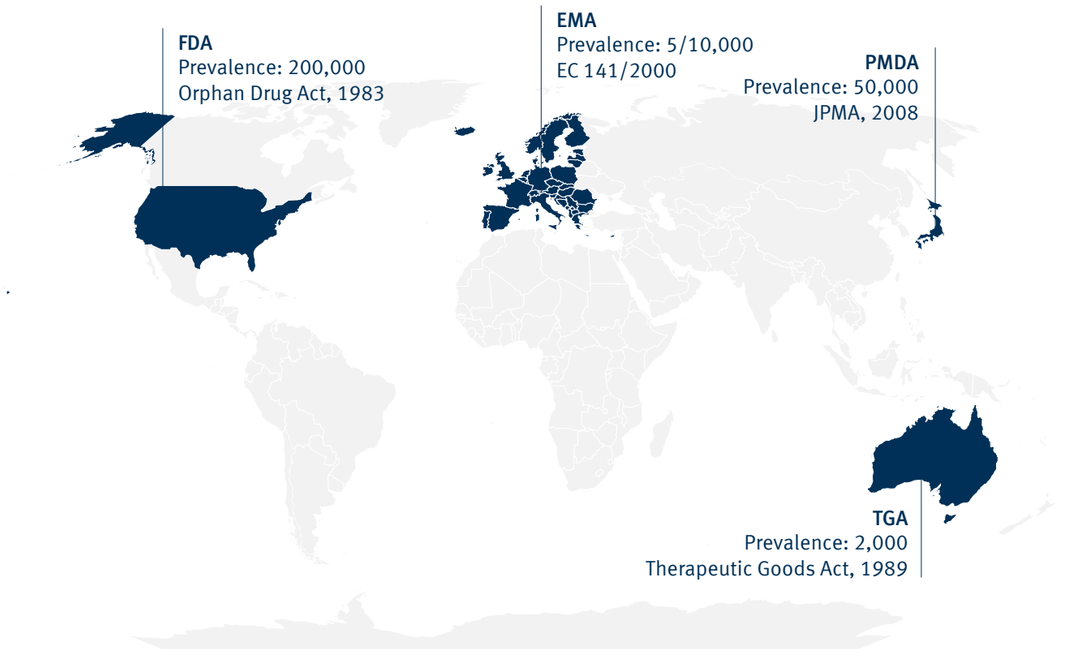
WHAT IS A RARE DISEASE IN 2026?

AN UMBRELLA TERM COVERING DEEP DIVERSITY

"Rare diseases", or "orphan diseases" are often used as a single category, but in practice the names describe a continuum of disorders that differ profoundly in prevalence, biological mechanism, and strategic dynamics.

The term itself is defined by regulation rather than biology: in the United States, a rare disease affects fewer than 200,000 people nationwide; in the European Union (EU), the threshold is no more than 5 in 10,000 individuals (corresponding to c. 225,000 people). Behind this simple definition lies a population of 6,000 to 8,000 distinct diseases, collectively affecting an estimated 300m people worldwide, with approximately 70% of these conditions manifesting in childhood. Yet, fewer than 10% have an approved treatment.

FIGURE 1: ODD CRITERIA ACROSS KEY TERRITORIES



Source: EMA, FDA, PMDA, TGA

FROM PREVALENCE TO MECHANISM

Yet in contemporary drug development, rarity has ceased to be purely a matter of numbers. As genomic sequencing fragments broad clinical categories into molecular subtypes, the definition of what constitutes a distinct “rare” disease increasingly rests on the targetable pathway rather than the patient count. A disorder may be relatively common in aggregate, but if each genotype demands its own vector, promoter, or pharmacologic mechanism, the effective population per therapy contracts to only a few dozen. Retinitis pigmentosa, a group of rare, inherited eye disorders, illustrates this shift: more than 100 different genes can cause the same clinical phenotype, yet each requires a separate construct and trial, turning a seemingly sizeable patient community into dozens of micro-cohorts.

Regulators have already adapted to this new landscape. The FDA and EMA now grant orphan designations not only to named diseases but also to molecularly defined subgroups that share a therapeutic mechanism. In practice, each pathway-specific therapy becomes its own regulatory and commercial unit, with bespoke endpoints, manufacturing standards, and post-marketing obligations.

This transition from epidemiological to mechanistic rarity underpins much of the modern orphan-drug economy. It explains the multiplication of designations for genetically defined subsets, the rise of micro-cohort trials, and the growing emphasis on platform technologies that can efficiently translate the same therapeutic logic across multiple, narrowly delineated diseases.

THE SPECTRUM OF RARITY

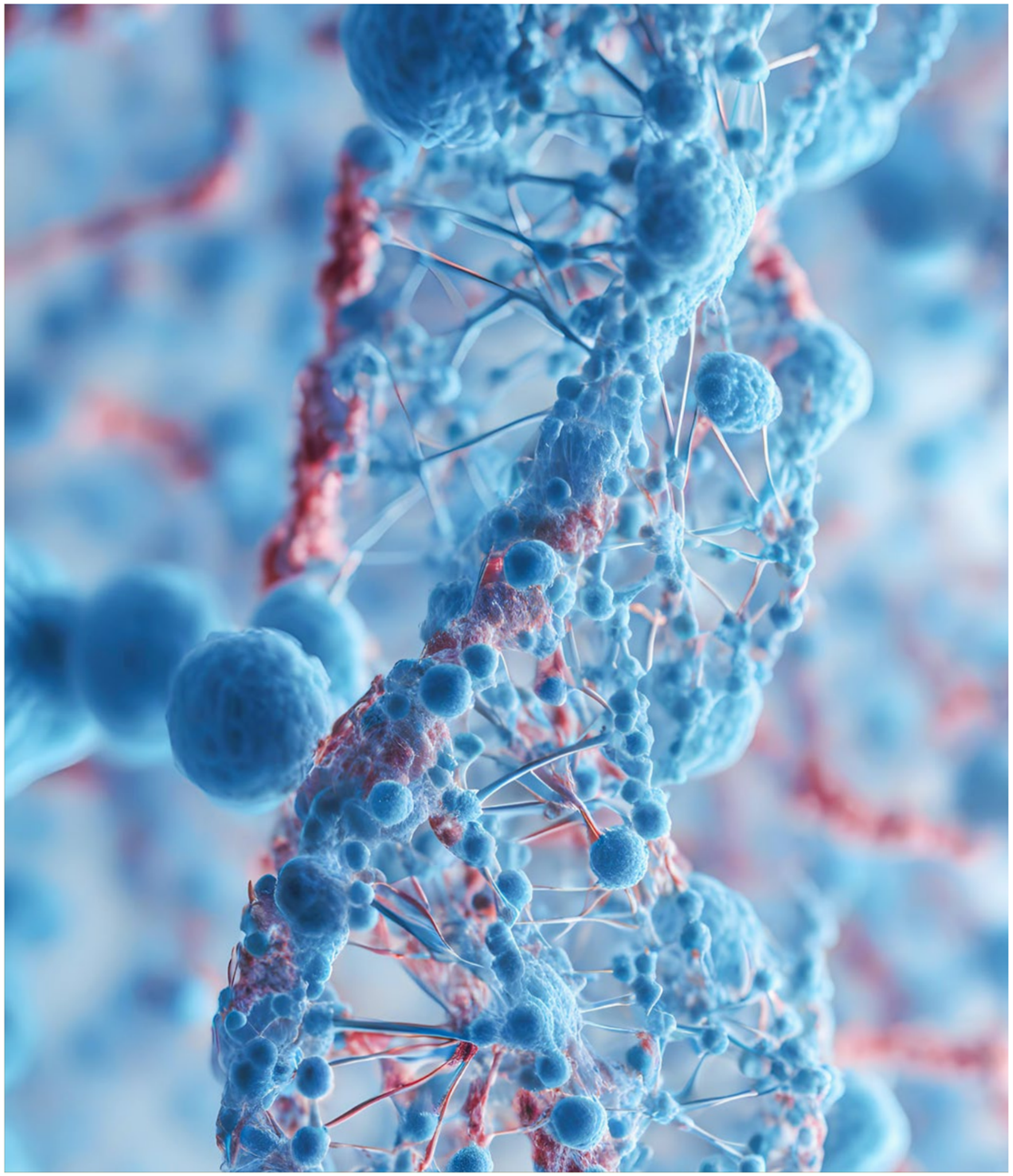
Rare diseases vary not only in prevalence but also in genetic structure, clinical trajectory, and the resources required to study them. Within the same regulatory framework, “rare” can describe disorders that affect a handful of families as well as conditions with tens of thousands of patients. This internal diversity determines how projects are conceived, tested, and sustained commercially.

At one end of the spectrum are ultra-rare genetic conditions such as aromatic L-amino acid decarboxylase (AADC) deficiency or neuronal ceroid lipofuscinosis type 2 (CLN2). These usually appear in childhood, have a single genetic cause, and suit targeted therapies like gene or RNA treatments. Development is typically small, often single-arm or natural history-controlled, and relies on international registries and support from patient groups.

A middle range includes classic orphan metabolic and neuromuscular diseases, like Pompe, or Duchenne muscular dystrophy. Populations in the hundreds or thousands support multicentre clinical studies and standardised commercial infrastructure. This segment has shaped much of the orphan-drug infrastructure. Biopharma companies often run several programmes here, using shared manufacturing and regulatory strategies.

At the broader edge are high-prevalence orphan diseases such as haemophilia A/B, paroxysmal nocturnal haemoglobinuria (PNH), or hereditary angioedema (HAE). These meet orphan thresholds but operate in established clinical and commercial systems, attracting larger pharma participants. For them, orphan incentives mainly secure exclusivity for novel mechanisms, rather than opening up rare disease R&D.

ORPHAN DRUG INITIATIVES FUELING RARE-DISEASE INNOVATION



A HIGHLY INCENTIVISED ENVIRONMENT

The economic and scientific progress of the rare-disease sector has been made possible by a series of targeted policy frameworks that transformed what was once considered commercially unviable into a viable, investable industry. The regulatory landscape in both the United States and the European Union remains highly incentivised, but it has also evolved, becoming more structured, data-driven, and, in recent years, more demanding in terms of evidence and post-marketing commitments.

The cornerstone of rare-disease policy is the Orphan Drug Act (ODA), passed in the United States in 1983 and later mirrored by the European Orphan Regulation (EC No. 141/2000) in 2000. Both sought to correct the same market failure: that the limited patient population made the traditional risk–reward ratio of drug development untenable. By offering exclusivity, tax credits, and regulatory support, the ODA created the first predictable path for companies to recover investment in ultra-small markets.

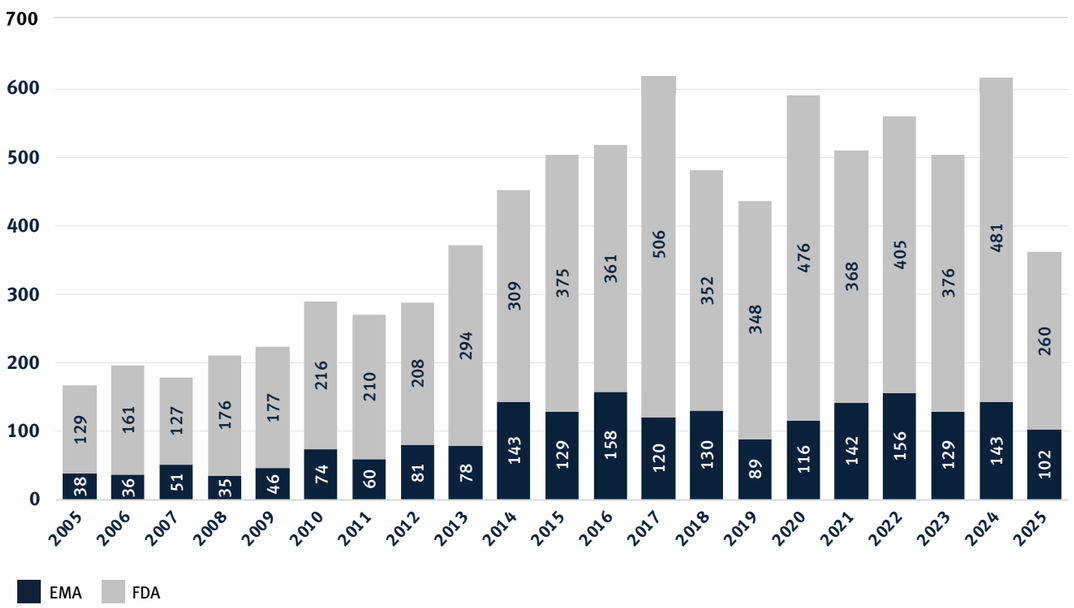
FIGURE 2: ODD: COMPARATIVE ANALYSIS OF US AND EU FRAMEWORKS

	US	EU
Legal basis	Orphan Drug Act (1983)	Regulation EC No 141/2000
Requirement	Must treat a disease affecting fewer than 200,000 people in the US or a condition without a reasonable expectation of recovering development costs	Must treat a disease affecting fewer than 5 in 10,000 people in the EU or must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development
Market exclusivity	7 years	10 years
Fee reduction	Waiver of FDA application fees	Reduced fees for regulatory activities
R&D incentives	Tax credits (up to 25% of qualified clinical testing costs)	Access to EU grants
Regulatory assistance	FDA protocol assistance and priority review eligibility	Scientific advice from EMA and protocol assistance

Source: FDA, EMA

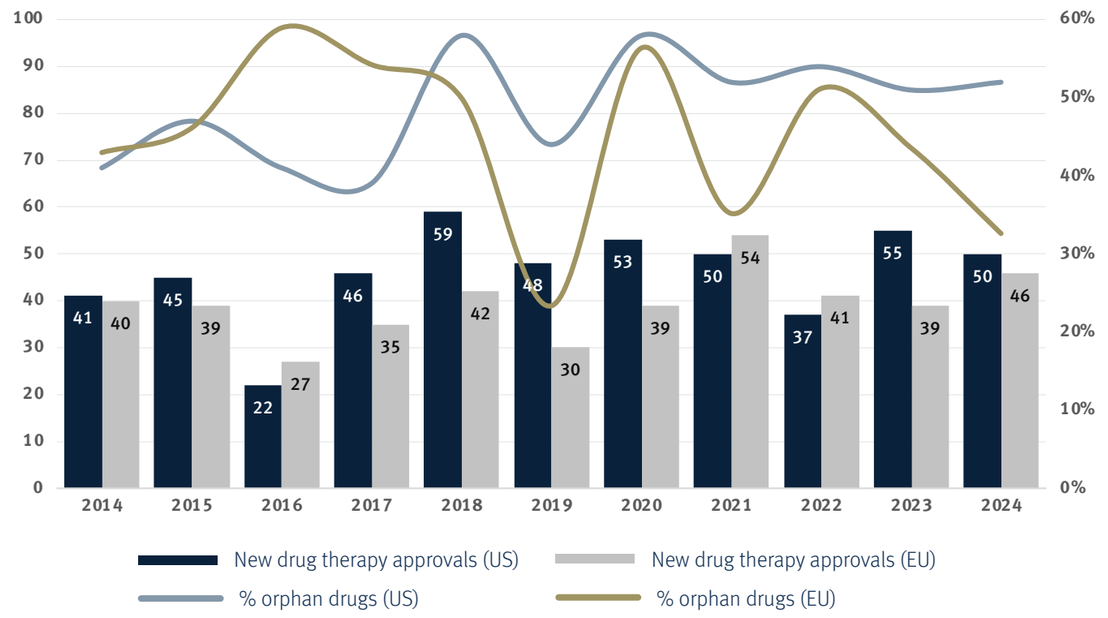
Over four decades later, the framework has yielded close to 700 FDA orphan drug approvals and over 6,000 orphan designations. In Europe, more than 180 orphan medicines have received marketing authorisation since 2000, covering over 300 rare conditions. These figures are not static: each year, between 35% and 50% of new molecular entities approved by the FDA carry orphan designation, a clear sign that orphan status has evolved from an exception to a core engine of biopharma innovation.

FIGURE 3: ORPHAN DESIGNATIONS GRANTED BY THE EMA AND THE FDA (2005-2025)



Source: FDA, EMA

FIGURE 4: NEW DRUG THERAPY APPROVALS AND ORPHAN DRUG SHARE (%)



Source: FDA, EMA, Stifel IRIS

DYNAMIC REGULATORY ENVIRONMENT FRAMEWORK

The orphan framework continues to evolve. In the United States, the 2018 Tax Cuts and Jobs Act reduced the Orphan Drug Tax Credit from 50% to 25%, but the practical impact on early-stage funding has been mitigated by the growth of venture-backed platform companies and NIH translational programmes. The Inflation Reduction Act (IRA) of 2022 initially raised fears that orphan exclusivity might not protect pricing for single-indication drugs under Medicare, but subsequent clarifications confirmed that ODA exclusivity still confers protection for therapies with one approved indication, a relief for investors in gene therapy and RNA platforms. This regulatory shield was significantly strengthened and expanded by the One Big Beautiful Bill Act (OBBBA), which addressed the statutory limitations of the original IRA. Specifically, the OBBBA broadened the Orphan Drug Exclusion, allowing therapies with one or more orphan indications to remain exempt from Medicare price negotiations as long as they are not approved for any non-orphan conditions.

FIGURE 5: KEY MILESTONES IN US RARE-DISEASE DEVELOPMENT

**Rare Paediatric PRV expired in Dec, 2024*
Source: FDA

Most recently, the framework has also expanded to address critical gaps in paediatric rare diseases. In late 2025, the House unanimously passed the Mikaela Naylon Give Kids a Chance Act, a bipartisan measure designed to modernise clinical trial requirements for paediatric cancer and restore key financial incentives.

This Act would reauthorise the Rare Paediatric Disease Priority Review Voucher (PRV) Program for five years, reviving a transferable asset class that has historically provided significant non-dilutive capital to rare disease developers.

FIGURE 6: KEY MILESTONES IN EU RARE-DISEASE DEVELOPMENT

**CMA eventually withdrawn in 2024 after confirmatory data failed*
Source: EMA

However, this legislative momentum stalled on December 19, 2025, when the measure was blocked in the Senate over broader political debate (drug-pricing reforms, funding for community centres). While it is not the end of the road for this measure, it might take longer than expected to get it through the finish line.

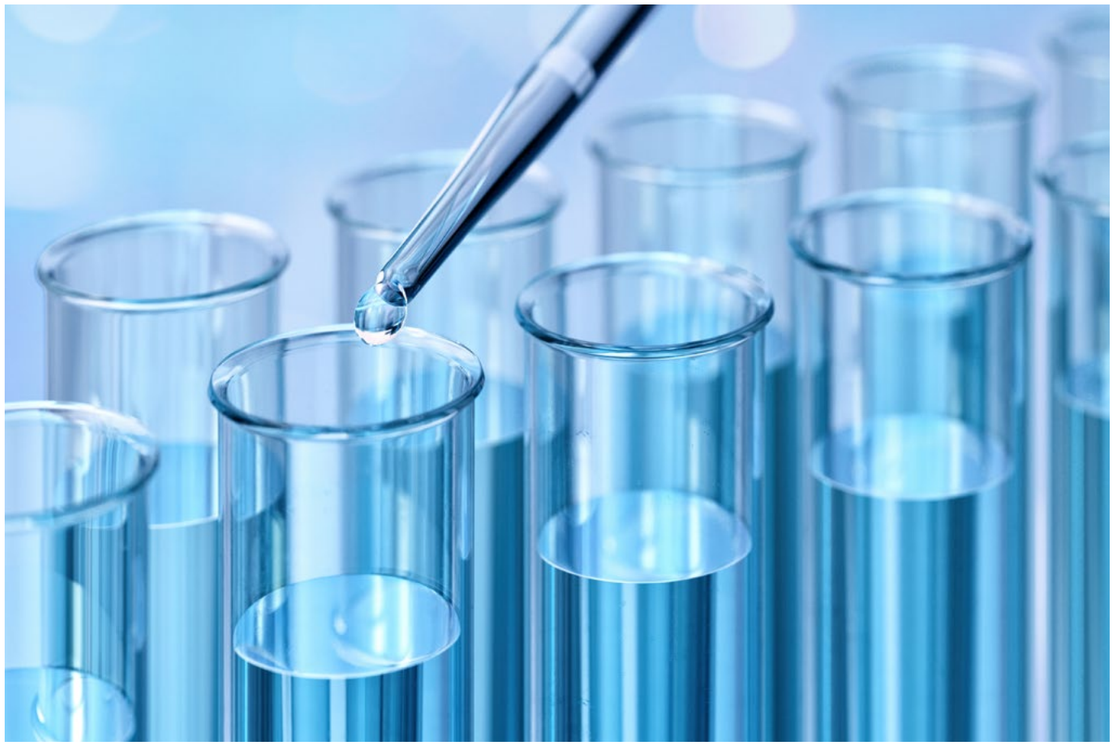
Yet, the market valuation for these regulatory assets has reached unprecedented peaks. In January 2026, Jazz Pharmaceuticals announced the sale of its PRV for US$200m in gross proceeds . This transaction

represents a significant escalation in pricing compared to historical average (US$100-150m), underscoring the premium that biopharmaceutical companies place on regulatory acceleration.

In Europe, the legislative framework is undergoing its most significant revision since 2000. The European Commission's draft Pharmaceutical Package (2023–2025) introduces a more flexible model linking market exclusivity to public-health performance: the orphan market exclusivity would be shortened (from ten to nine years) but could be extended up to 11 years for breakthrough orphan drugs (i.e. no existing treatment in the EU and a clinically relevant reduction in morbidity or mortality). This reform aims to rebalance incentives between access and innovation while maintaining the core of the orphan system.

For instance, the FDA's 2024 Draft Guidance on Platform Technology Designation aims at streamlining advanced therapy medicinal product (ATMP) development. In a landmark move, the agency granted its first-ever platform designation to Sarepta Therapeutics for its AAVrh74 vector technology. However, that designation was quickly revoked in July 2025 following reports of patient deaths and subsequent clinical holds, a stark reminder that the bar for platform validation remains exceptionally high. Despite this setback, the pathway remains viable as in October 2025, Krystal Biotech received the second-ever platform designation for its HSV-1 viral vector, demonstrating the FDA's continued commitment to the concept for technologies with a robust and consistent safety and manufacturing profile.

The EMA has also been actively exploring the concept. Presentations and discussions in late 2024 and mid-2025 confirm that the EMA is considering the use of "platform master files" as a way to reference core data and accelerate the review of subsequent products built on the same technology.

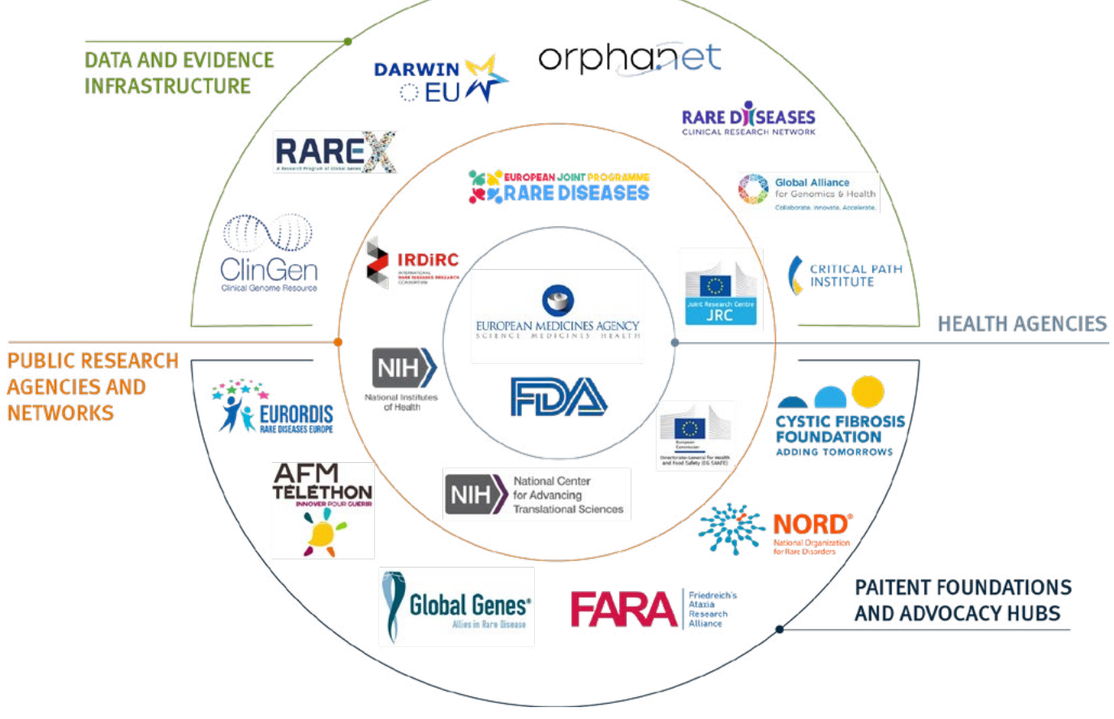


BEYOND LEGISLATION: THE RARE-DISEASE SUPPORT ECOSYSTEM

Regulation does not act in isolation. Both the US and EU have built institutional scaffolding that extends from early discovery through to post-market evidence generation.

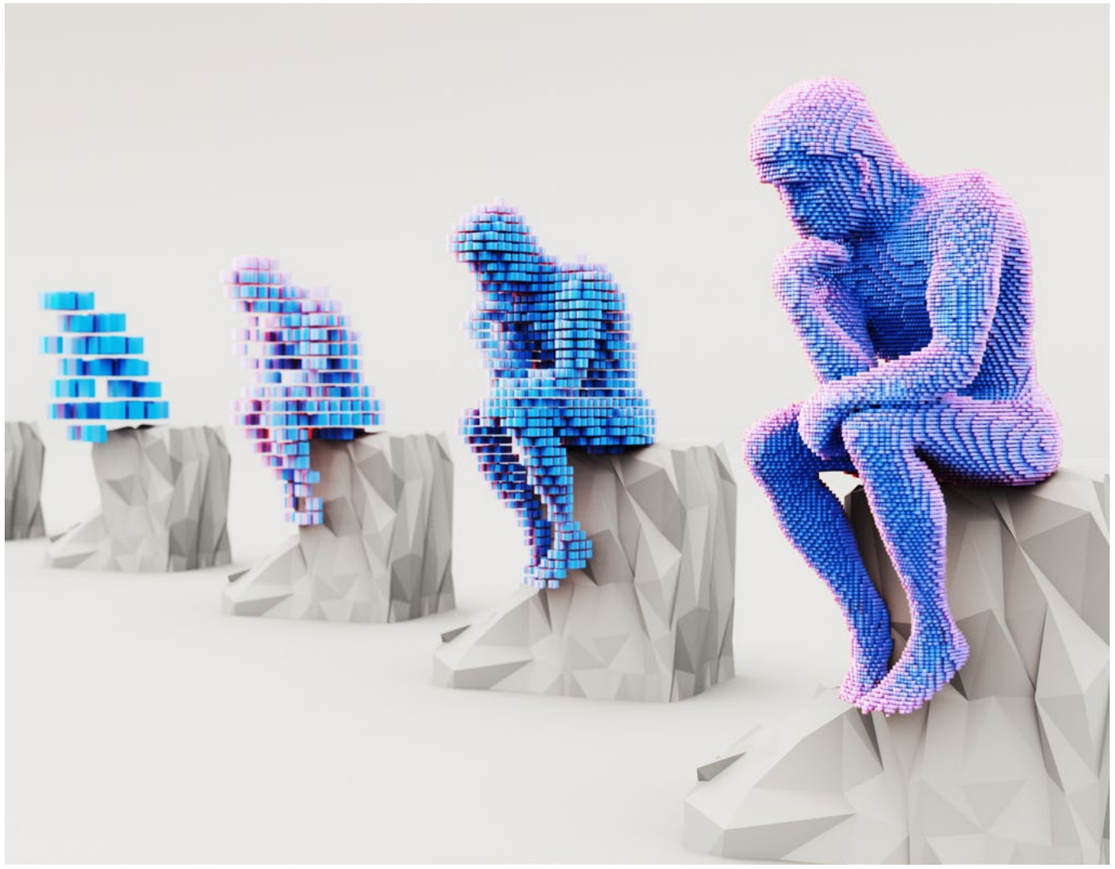
- In the US, the Rare Diseases Clinical Research Network (RDCRN), the NIH's NCATS programmes, and patient foundations such as the Cystic Fibrosis Foundation act as semi-public engines of translational science.
- In Europe, Orphanet, EURORDIS, AFM-Téléthon and national-level initiatives such as France's Plans Maladies Rares have created registries and referral networks that serve both as data infrastructure and as pre-competitive public goods.
- The Bespoke Gene Therapy Consortium (BGTC), launched in 2021 under the NIH and the Foundation for the NIH, represents a new model of public–private collaboration aimed at developing "plug-and-play" AAV platforms for ultra-rare disorders, a tangible sign that regulators are adapting to a modality-led world.

FIGURE 7: GLOBAL RARE-DISEASE ECOSYSTEM: A MAP OF KEY STAKEHOLDERS US/EU



Source: Governments and institutions reports, and Stifel IRIS

FOUR DECADES OF CUMULATIVE TRANSFORMATION



QUANTITATIVE LANDSCAPE OF ORPHAN DRUG DESIGNATION (FDA 1983-2025)

We tried to capture the structure and evolution of the orphan drug universe from the introduction of the U.S. Orphan Drug Act in 1983 through 2025, aggregating at the level of the unique active drug (regardless of how many indications it holds).

On this basis:

- 4,685 drugs have received at least one FDA orphan designation between 1983 and 2025.
- 696 of these have obtained at least one FDA approval for an orphan indication, implying a conversion rate of approximately 15%.

MAPPING THE ODD PIPELINE

The period before 2000 represents the formative stage of the orphan incentive framework. Designation volumes remained modest and technological diversity limited.

Orphan development was predominantly chemical and recombinant, with small molecules representing roughly half of all unique drugs granted an ODD and early biologics accounting for a third. Advanced modalities were still embryonic, represented by a few exploratory viral or protein-based approaches with limited regulatory traction.

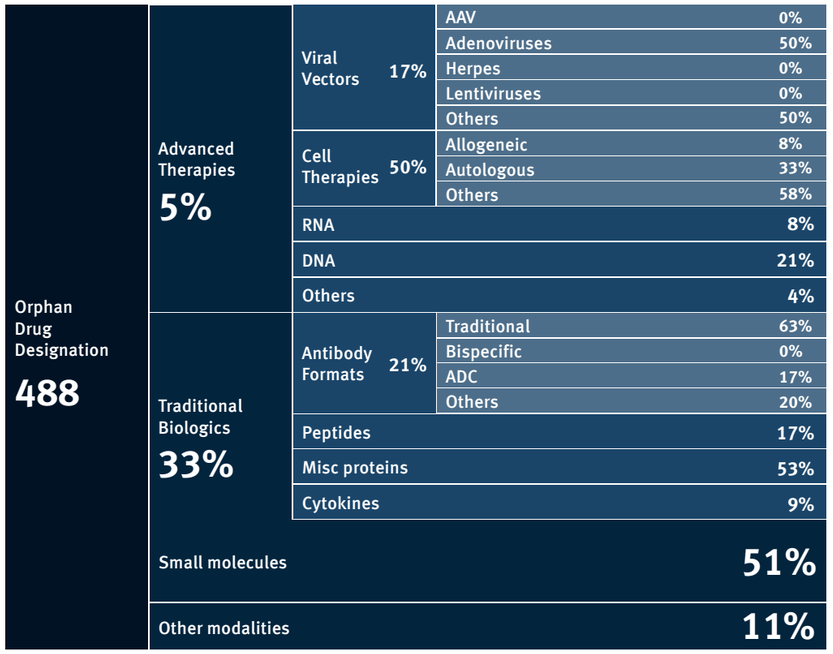
This early configuration reflects a period in which policy incentives were strong enough to attract interest, yet industrial capability remained primarily aligned with conventional chemistry. The orphan space was, in effect, an extension of existing R&D systems into smaller markets rather than a domain of technological experimentation.

The 2000–2025 window defines the consolidation of the orphan ecosystem into a fully industrialised innovation segment. The number of unique drugs granted an ODD rises above 4,000, and the technological balance shifts toward complex modalities. Small molecules still form the foundation of the orphan landscape, but their trajectory has flattened.

Traditional biologics stabilise near one-quarter of the total, while advanced therapies, i.e. gene, cell, RNA, and DNA-based constructs, expand to around one-fifth of all unique orphan-designated drug.

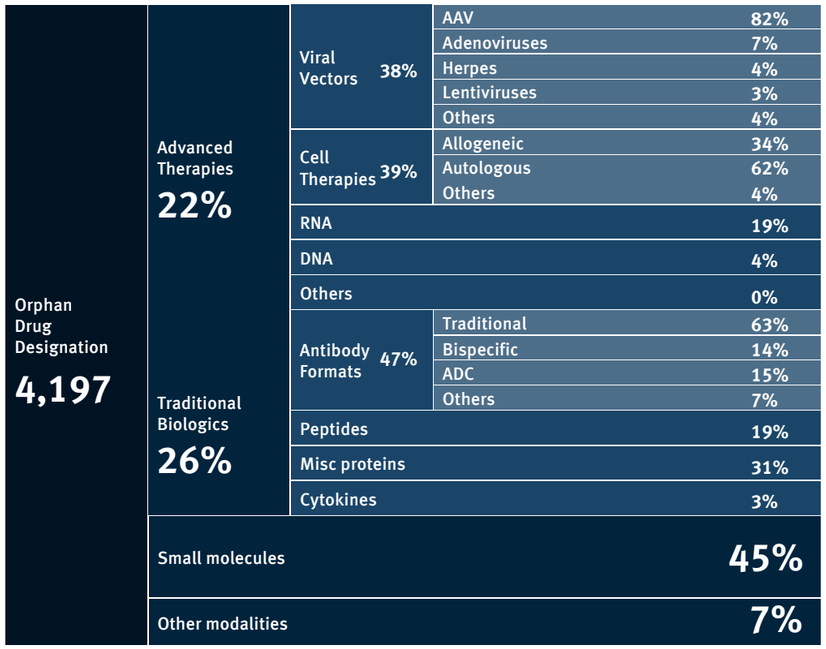
The orphan framework, originally conceived to promote discovery in neglected indications, has evolved into the primary testing ground for all therapeutic formats, from conventional chemistry to the most advanced next-gen therapeutics.

FIGURE 8: ODD GRANTED, BY MODALITIES (1983-2000)



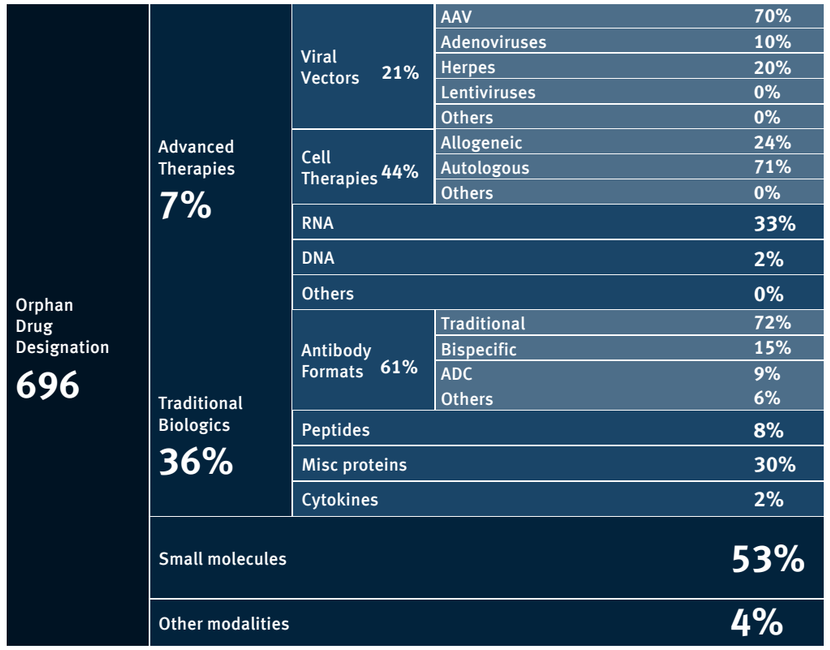
Source: FDA

FIGURE 9: ODD GRANTED, BY MODALITIES (2000-2025)



Source: FDA

FIGURE 10: FDA-APPROVED DRUGS WITH AN ODD, BY MODALITIES (1983-2025)



Source: FDA

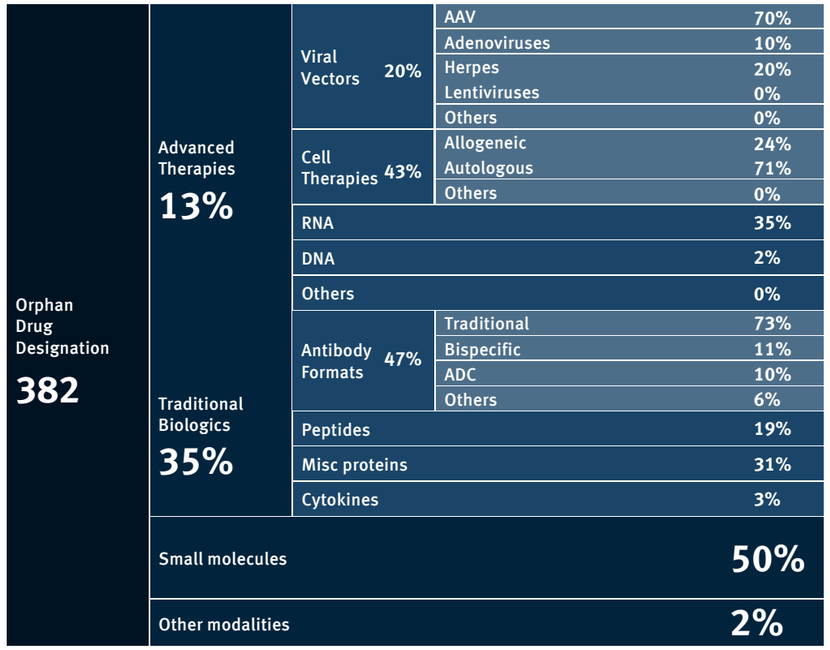
PROFILING MARKETED ORPHAN DRUGS

The universe of approved orphan drugs reflects the same balance. Across the full period, 696 unique drugs have obtained approval for at least one orphan indication, i.e. about 15% of all unique ODDs. Within that group, small molecules continue to account for the largest numerical share, illustrating their enduring role in diseases where oral or parenteral formulations remain optimal. Their approval pattern has stabilised over the years: a steady flow of molecules addressing enzymatic pathways, ion channels, or metabolic intermediates continues to sustain the segment.

By contrast, the recent decade (2015–2025) marks the surge of biologic and advanced therapy approvals, reflecting the technical and regulatory maturity of earlier R&D cycles. Gene and cell therapies now enter the approval stream with regularity, and RNA-based approaches are increasingly present in late-stage reviews.

The resulting landscape is quite balanced. Small molecules anchor the orphan space with proven mechanisms, manageable production costs, and established distribution networks, while genetic and cellular therapies extend the frontier into monogenic and ultra-rare conditions.

FIGURE 11: FDA-APPROVED DRUGS WITH AN ODD, BY MODALITIES (2015-2025)



Source: FDA

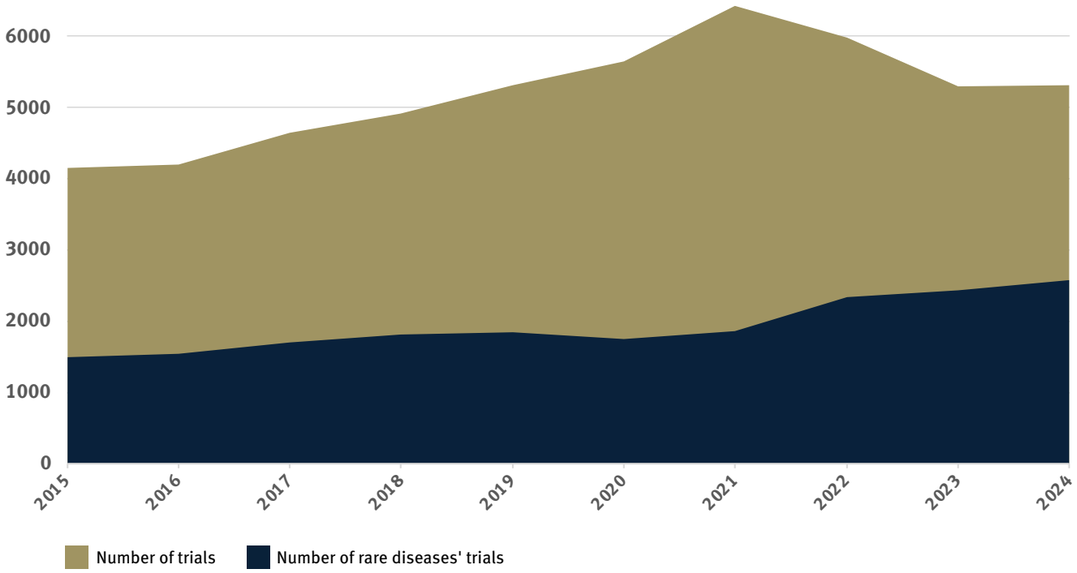
CLINICAL TRIAL ENGINE OF RARE DISEASE

The expansion of orphan-drug designations and approvals over the past two decades has been mirrored by a sharp rise in clinical activity. Rare-disease trials now represent a defined segment of the global R&D ecosystem.

BOOMING CLINICAL ACTIVITY

The data from 2015 to 2024 reveals a significant and accelerating shift in the clinical trial landscape. While the overall volume of trials has seen modest growth, rare-disease trials have expanded at more than double the rate, fundamentally reshaping the focus of clinical R&D. By 2024, rare-disease studies accounted for nearly half of all trials initiated, a dramatic increase from just over one-third in 2015.

FIGURE 12: NUMBER OF INDUSTRY-SPONSORED TRIALS LAUNCHED PER YEAR (2015-2024)



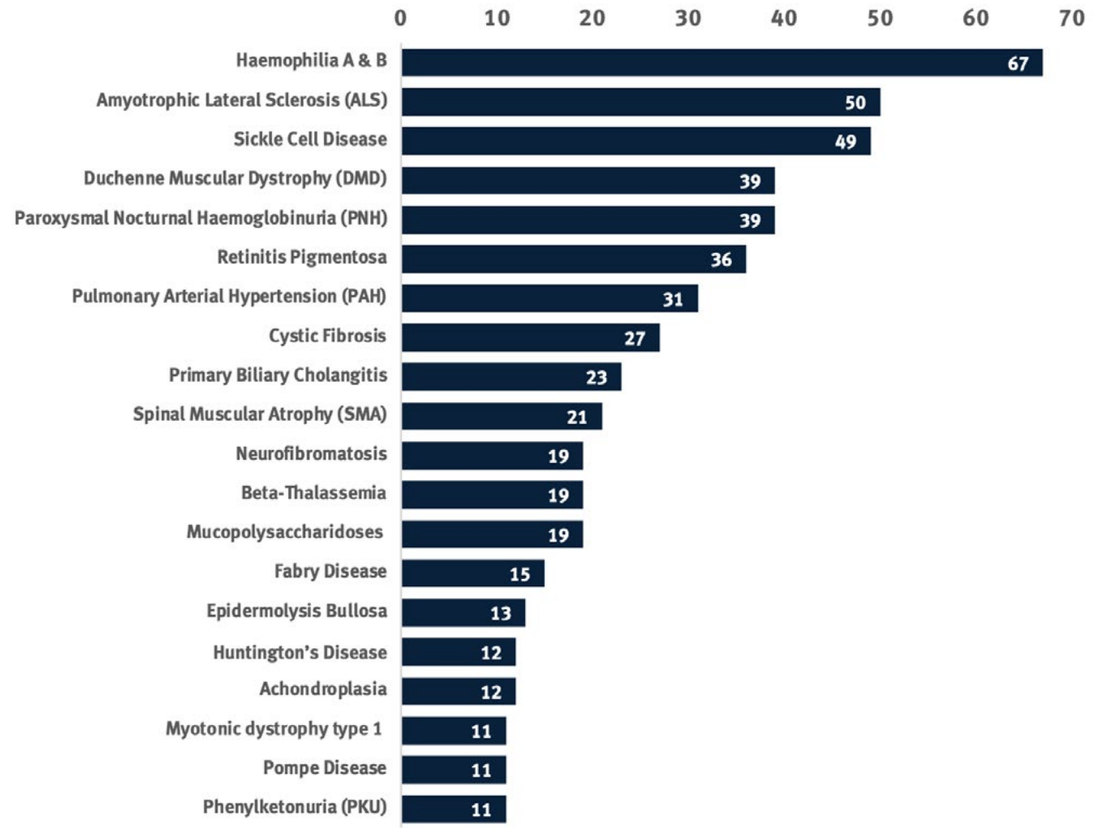
Source: IQVIA, Citeline, clinicaltrials.gov

ONCOLOGY REMAINS THE UNDISPUTED DRIVER

The rare-disease clinical trial landscape is best understood as a bifurcated universe. On one side sits the dominant force of rare oncology, which accounts for the majority of all rare-disease trial activity, up to an estimated 72%, according to IQVIA. This is a direct result of the molecular fragmentation of cancer, which has redefined many common malignancies as clusters of distinct, rare, genetically driven diseases, making them a natural fit for the orphan drug development model.

On the other side is the diverse and highly active non-oncology pipeline. An analysis of ongoing, industry-sponsored phase 1-3 trials reveals a clear and strategic concentration of R&D investment into specific, high-potential therapeutic areas.

FIGURE 13: NUMBER OF ONGOING, INTERVENTIONAL, INDUSTRY-SPONSORED PHASE 1-3 TRIALS



Source: clinicaltrials.gov

The distribution of trials across non-oncology rare diseases is heavily weighted toward indications that combine significant unmet need with scientific tractability and a viable commercial path.

- **Haematology as a powerhouse:** Genetic blood disorders dominate the pipeline. Haemophilia A and B, Sickle Cell Disease (SCD), and Paroxysmal Nocturnal Haemoglobinuria (PNH) attract intensive investment because they involve well-characterised biology, benefit from success stories in SCD and beta-thalassemia, and rely on validated biomarkers that simplify development. Yet haemophilia's high trial count hides commercial strain. BioMarin's attempt to commercialise Roctavian illustrates this: the therapy generated only US$3.5m in 2023 and US$26m in 2024, vs early projections of US$100-200m. Limited payer uptake and the need for many treated patients to return to factor therapy undermined the launch and ultimately drove BioMarin to divest the product.
- **The neuromuscular and neurology frontier:** A second critical cluster of activity targets severe neurodegenerative and neuromuscular conditions, including Amyotrophic Lateral Sclerosis (ALS),

Duchenne Muscular Dystrophy (DMD), and Spinal Muscular Atrophy (SMA). These areas carry extreme unmet need, and precedent-setting approvals such as Spinraza and Zolgensma validated the feasibility of modifying the disease course. The field now hosts intense modality competition spanning ASOs, small molecules, and next-generation AAV platforms.

- **"Classic" rare diseases:** Indications such as Cystic Fibrosis, Fabry Disease, and Pompe Disease continue to attract robust R&D activity. These indications benefit from established patient networks, long-standing registries, and clear commercial pathways opened by leaders like Vertex in CF and Sanofi/Genzyme in lysosomal storage disorders.

This landscape reflects deliberate capital concentration. Although over 7,000 rare diseases are recognised, industry resources cluster around a limited set of indications with strong scientific and regulatory footing. The 500-plus trials in the top 20 diseases delineate the most mature, commercially oriented segment of the market, while thousands of ultra-rare conditions remain largely dependent on academic groups, early de-novo innovators, and non-profit funding.

BATTLING SCARCITY: OPERATING AT THE LIMITS OF FEASIBILITY

Every rare-disease trial begins as an exercise in scarcity: too few patients, too many variables, no obvious control group. A single site may enrol only a handful of participants, yet these data integrate into shared registries that give studies coherence. Median enrolment is roughly 150 patients (compared with 500-plus in non-orphan trials), but each participant is tracked with unusual precision so that depth substitutes for scale.

Recruitment now depends less on the number of investigators and more on trust. In rare and especially ultra-rare conditions, the decisive asset is connection to patient communities. Patient Advocacy Groups have become indispensable to study design and recruitment, acting as stewards of registries, disseminators of trial information, and informal pre-screeners. Their endorsement often determines whether a study can realistically enrol.

Companies that have learned to work with them early can turn these relationships into operational assets as critical as chemistry, manufacturing and controls (CMC) know-how. The fastest trials are not only the best-funded, but those whose sponsors have built credibility with families who know every patient by name.

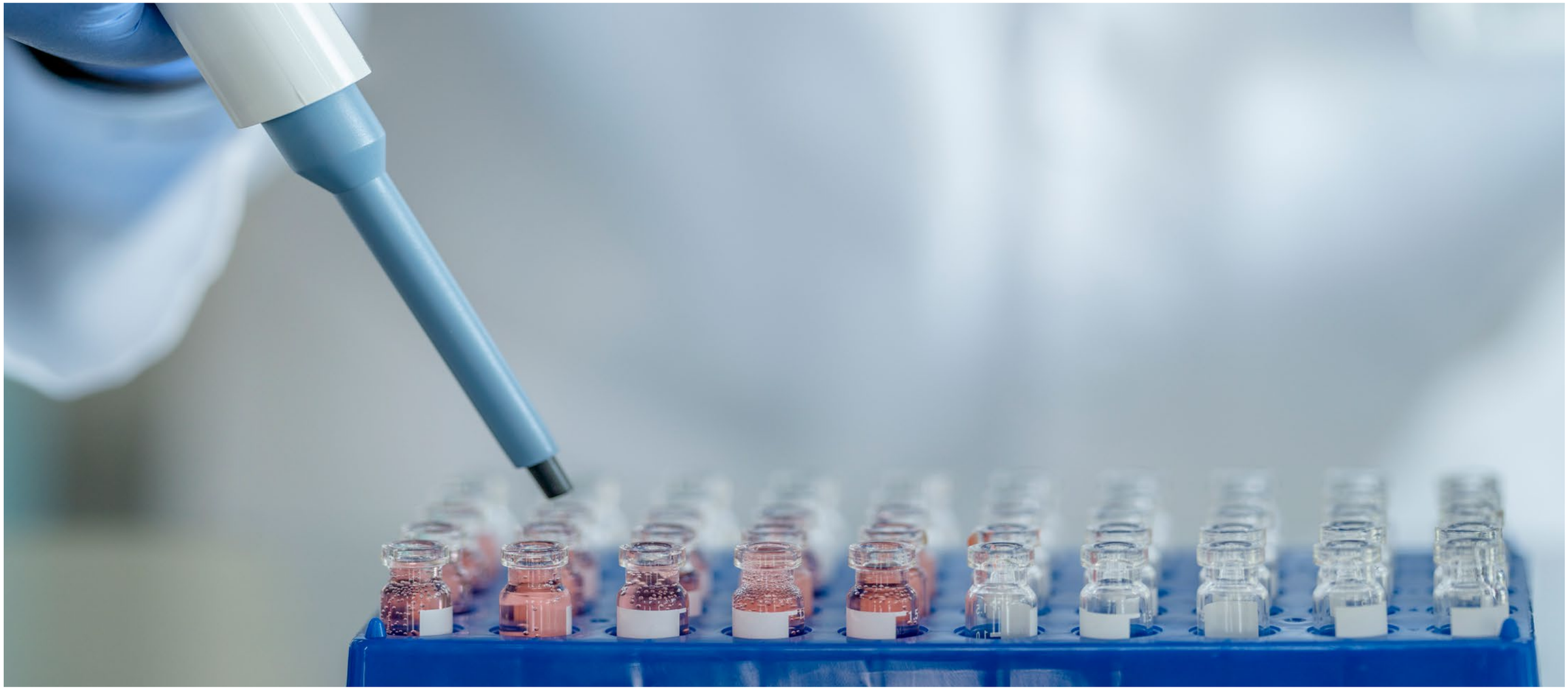


FIGURE 14: CASE STUDY – SOBI

sobi
rare strength

PATIENT-CENTRICITY AS A CORE COMPETENCY

Sobi demonstrates that, in rare diseases, real patient community integration is a vital capability. The company has turned "patient-centricity" from a slogan into scalable processes that create value.

FULL LIFECYCLE INTEGRATION

Sobi embeds patient engagement across its value chain to ensures that solutions are genuinely patient-led. Patient engagement is even a guiding principle in M&A.

DEEP COMMUNITY PARTNERSHIP

The company fosters long-term, active partnerships with advocacy groups like the World Federation of Hemophilia (WFH) and EURORDIS. It has established patient councils for direct input on clinical development and launched Unite4Rare, a global initiative co-created with patient representatives to formalise its commitment.

HOLISTIC ACCESS AND SUPPORT

Sobi's commitment extends beyond drug approval to include comprehensive Patient Support Programmes (PSPs) offering financial and educational assistance, as well as significant humanitarian aid donations. Digital tools, including those developed by its subsidiary Florio, provide next-generation solutions like florio HAEMO, florio PNH and florio ITP to help patients visualise and manage their treatment data in real time.

Source: Company reports

LESSONS FROM 40 YEARS OF TRANSLATION

Four decades after the Orphan Drug Act, the rare-disease ecosystem has travelled a long distance from fragile proofs of concept to an organised framework of translation. Progress in rare-disease development has come in waves: moments of sudden breakthrough followed by periods of adjustment, when enthusiasm met the limits of data, infrastructure, or cost.

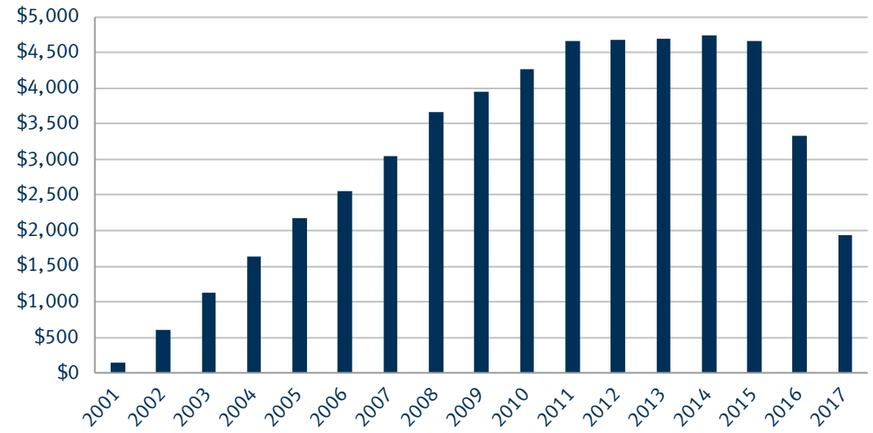
FIRST WAVE: BREAKTHROUGHS AND OVERPROMISES

The early 2000s delivered a sequence of landmark approvals that validated the vision behind the Orphan Drug Act. These therapies proved that rare-disease research could generate life-changing benefit, and that small-population innovation could sustain industrial investment.

Gleevec (imatinib, Novartis, 2001), was the defining model. It transformed chronic myeloid leukaemia (CML) into a manageable chronic condition, and demonstrated that targeting a specific genetic driver could deliver dramatic clinical benefits. Gleevec's success demonstrated that small, genetically defined populations could justify industrial-scale research and still deliver blockbuster returns, anchoring the logic of precision medicine.

Luxturna (voretigene neparvovec, Spark Therapeutics / Roche, 2017) consolidated the transition from experiment to discipline. Approved for biallelic RPE65 mutations, it demonstrated that hospital-based gene therapy could meet industrial-grade CMC standards,

FIGURE 15: GLEEVEC SALES (US$M)



Source: Evaluate Pharma

long-term follow-up requirements, and structured site certification. It created the template that later retinal programmes would follow.

Beyond those two drugs, that period was a period of firsts:

- **Soliris** (acluzimab, Alexion, 2007) introduced complement inhibition for the rare and lethal paroxysmal nocturnal haemoglobinuria (PNH) and paved the way for other complement-targeting drugs like Ultomiris (ravulizumab-cwvz, Alexion, 2018) and Empaveli (pegcetacoplan, Apellis, 2021).
- **Spinraza** (nusinersen, Biogen/Ionis, 2016) demonstrated that intrathecal antisense oligonucleotide (ASO) therapy could safely alter gene splicing in spinal muscular atrophy (SMA).
- **Onpattro** (patisiran, Alnylam, 2018): (patisiran, Alnylam, 2018) validated RNA interference (RNAi) and established GalNAc-siRNA delivery for hepatic disorders.
- **Zolgensma** (onasemnogene abeparvovec, Novartis, 2019) became the first systemic AAV gene replacement therapy for SMA, and the first medicine to cross the US$2m price mark.

These breakthroughs were enabled by regulatory flexibility: small sample sizes, reliance on surrogate biomarkers, and expedited programmes such as Breakthrough Therapy Designation, Accelerated Approval, and the EU's PRIME pathway. Both the FDA and EMA accepted that early programmes could not rely on large randomised trials, and post-marketing evidence remained largely descriptive while the field established proof of concept.

REGULATORY TIGHTENING AND OPERATIONAL LEARNINGS

The first two decades of orphan approvals for advanced therapies confirmed the promise of gene and RNA technologies but also exposed the limits of an overly permissive system. Early programmes were approved on the strength of small, single-arm trials, often relying on surrogate endpoints and short-term biomarker data. As the number of such therapies grew, regulators in both the US and Europe began to recognise recurring vulnerabilities: durability of benefit, manufacturing comparability, and the lack of structured long term follow-up. Thus, by the turn of the 2020s, the cumulative experience of these pioneering programmes had re-shaped the regulatory contract with both the FDA.

FIGURE 16: CASE STUDY – SAREPTA

SAREPTA THERAPEUTICS	**THE CASE** • First drug for Duchenne Muscular Dystrophy (DMD), approved on surrogate endpoint (dystrophin increase) via Accelerated Approval (2016) • First DMD therapy to reach market despite limited clinical DATA • Delay in required confirmatory trial (completed Nov 3, 2025, failure to meet primary endpoint)
EXONDYS 51 (eteplirsen) Injection	**THE LESSON** • **AA reforms:** aimed to strengthen the FDA's enforcement of post-marketing studies (mandatory timelines, regular reporting…) • **Precedent:** sparked industry-wide debate on balancing speed, evidence quality, and affordability in rare disorders

Source: Company reports

FIGURE 17: CASE STUDY – UNIQURE

uniQure	**THE CASE** • First gene therapy approved in Europe (2012) for lipoprotein lipase deficiency • **Price:** €1m per patient, making it the most expensive drug at the time • Approved on extremely limited data (27 patients), never approved in the U.S • **Commercial failure:** only one commercial sale before withdrawal in 2017
Glybera®	**THE LESSON** • **Cautionary tale:** high price + ultra-rare indication + weak evidence = unsustainable model, with companies like GSK (Strimvelis) explicitly pricing their gene therapies significantly lower to avoid Glybera's fate

Source: Company reports

Although many of these lessons were crystallised in the regulation of gene and RNA therapy, their influence has since permeated every class of orphan drugs reshaping expectations for small molecules and biologics alike.

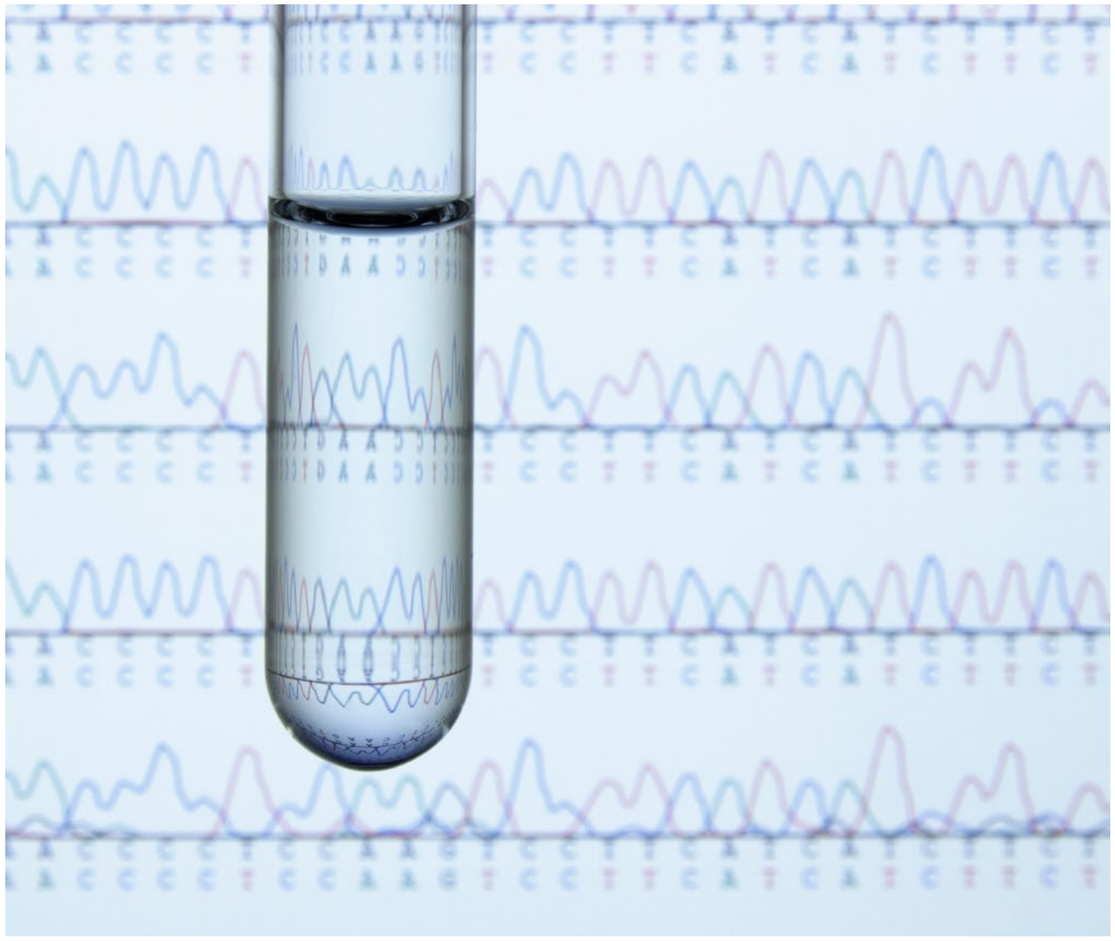
In the US, the Food and Drug Omnibus Reform Act (FDORA; 2022) formalised the FDA's Accelerated Approval Council and mandated clearer guidance on surrogate endpoints and post-approval commitments, turning earlier informal practice into structured policy. The evolution continued in November 2025 with the introduction of a "plausible mechanism pathway" aimed at bespoke gene-editing therapies, allowing approvals on the basis of very small datasets for selected severe genetic diseases.

In the EU, the EU Health Technology Assessment Regulation (EU) 2021/2282 established EU-level Joint Clinical Assessments (JCAs) Assessments to harmonise evidence reviews for pricing and reimbursement, beginning with advanced therapy medicinal products (ATMPs) and oncology. Member-state rules also moved: Germany's GKV-FinStG (2022) reduced the orphan-drug revenue threshold from €50m to €30m (i.e. threshold to lose orphan privilege), tightening price negotiations once uptake grows.

In parallel, both agencies have reinforced post-authorisation data infrastructure (beyond orphan disease). The FDA's Sentinel and Rare Disease Cures Accelerator (RDCA-DAP) platforms, and the EMA's DARWIN EU network, now support long-term evidence generation independent of sponsors.

The field therefore operates under a more structured balance: accelerated pathways persist, but regulators expect continuous evidence to sustain them.

THE DUAL DYNAMICS OF INNOVATION IN RARE DISEASE



R&D in rare disease appears to evolve through two opposing but complementary movements. Fragmentation multiplies the number of recognised entities as sequencing exposes new gene-level distinctions. Convergence reconnects them by revealing shared biological circuits that run across organs and phenotypes.

Together they form the structure of modern rare-disease innovation: precision at the molecular level, scalability at the mechanistic one.

FRAGMENTATION: ONE DISEASE BECOMES MANY

Advances in sequencing and biochemical profiling have revealed that many conditions once treated as single rare diseases actually encompass a constellation of genetically distinct entities. This can be seen in inherited retinal disorders, neuromuscular and metabolic disorders, where overlapping phenotypes mask wide molecular diversity.

Limb-girdle muscular dystrophies (LGMDs) illustrate the point. More than thirty genes can produce a similar pattern of progressive muscle weakness. Each subtype requires its own biological rationale, vector design, and patient registry. Programmes currently in development include gene therapy for mutations in the DYSF, SGCA/B/C genes, myosin-modulating small molecules for mutations in the FKRP gene, but also cell therapy approaches aiming to regenerate healthy muscle by engineering muscle stem cells with the CRISPR/Cas9 tool. A single phenotype has thus splintered into dozens of mechanistically distinct entities.

FIGURE 18: GENETIC CLASSIFICATION OF LIMB-GIRDLE MUSCULAR DYSTROPHIES (LGMD)

AUTOSOMAL RECESSIVE

NAME	GENE	PROTEIN
LGMD R1 (formerly LGMD2A)	*CAPN3*	Calpain-3
LGMD R2 (formerly LGMD2B)	*DYSF*	Dysferlin
LGMD R3 (formerly LGMD2D)	*SGCA*	α-sarcoglycan
LGMD R4 (formerly LGMD2E)	*SGCB*	ß-sarcoglycan
LGMD R5 (formerly LGMD2C)	*SGCG*	y-sarcoglycan
LGMD R6 (formerly LGMD2F)	*SGCGD*	б-sarcoglycan
LGMD R7 (formerly LGMD2G)	*TCAP*	Telethonin
LGMD R8 (formerly LGMD2H)	*TRIM32*	TRIM32
LGMD R9 (formerly LGMD2I)	*FKRP*	FKRP
LGMD R10 (formerly LGMD2J)	*TTIN*	Titin
LGMD R11 (formerly LGMD2K)	*POMT1*	POMT1
LGMD R12 (formerly LGMD2L)	*ANOS*	Anoctamin 5
LGMD R13 (formerly LGMD2M)	*FKTN*	Fukutin
LGMD R14 (formerly LGMD2N)	*POMT2*	POMT2
LGMD R15 (formerly LGMD2O)	*POMGnT1*	POMGnT1
LGMD R16 (formerly LGMD2O)	*DAG1*	a and ß dystroglycans
LGMD R17 (formerly LGMD2Q)	*PLEC*	Plectin
LGMD R18 (formerly LGMD2S)	*TRAPPC11*	TRAPPC11
LGMD R19 (formerly LGMD2T)	*GMPPB*	GMPPB
LGMD R20 (formerly LGMD2U)	*ISPD*	ISPD
LGMD R21 (formerly LGMD2Z)	*POGLUT1*	Protein O-glucosyltransferase 1
LGMD R22	*COL6A1, -A2, -A3*	Collagen VI
LGMD R23	*LAMA2*	Laminin a2 (merosin)
LGMD R24	*POMGNT2*	POMGNT2
LGMD R25 (formerly LGMD2X)	*BVES*	POPDC1
LGMD R26	*POPDC3*	POPDC3
LGMD R27	*JAG2*	Jagged-2
LGMD R28	*HMGCR*	HMG-CoA reductase

AUTOSOMAL DOMINANT

NAME	GENE	PROTEIN
LGMD D1 (formerly LGMD1D)	DNAJB6	DNAJB6
LGMD D2 (formerly LGMD1F)	TNPO3	Transportin 3
LGMD D3 (formerly LGMD1G)	HNRNPDL	hnRNPDL
LGMD D4 (formerly LGMD1I)	CAPN3	Calpain-3
LGMD D5 (formerly LGMD2A)	COL6A1, -A2, -A3	Collagen α1, 2, 3(VI) chain

Source: AFM telethon

FIGURE 19: CASE STUDY – ATAMYO

atamyo therapeutics

A PRECISION PORTFOLIO FOR LGMD

Atamyo Therapeutics, a clinical-stage biotechnology company and spin-off of gene therapy pioneer Genethon, exemplifies the precision-medicine strategy required to tackle fragmented rare diseases. Instead of pursuing a single, broad therapy for Limb-girdle muscular dystrophy (LGMD), Atamyo is building a portfolio of distinct gene replacement therapies, each engineered to correct a specific underlying genetic mutation.

TARGETED STRATEGY

Atamyo's approach directly confronts the genetic fragmentation of LGMDs by developing multiple, highly specific AAV-based therapies. Each product is a separate biological solution for a distinct patient sub-population.

CLINICAL-STAGE PIPELINE

The company has advanced multiple candidates into the clinic, each targeting a different genetic cause of LGMD:

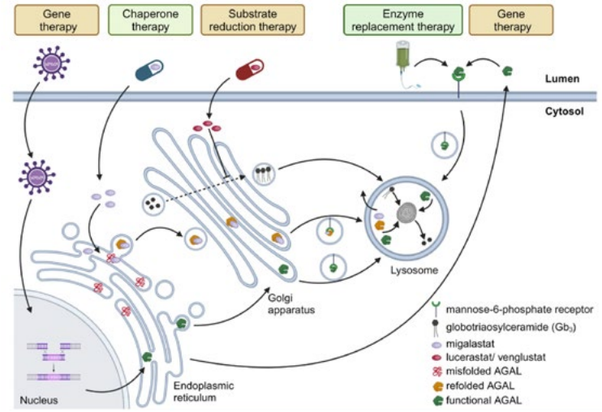
- **ATA-100:** LGMD-R9 (LGMD2I), in Phase 1b/2 trial.
- **ATA-200:** LGMD-R5 (LGMD2C), in a Phase 1b/2 trial.
- **ATA-300:** LGMD-R1 (LGMD2A), in preclinical.

Source: Company reports

Fabry disease shows the same tendency in metabolic disorders, now hosting at least four mechanistic strategies, each adapted to patient-specific genotypes and tissue distribution:

- **Enzyme replacement therapies** (ex. agalsidase beta, Fabrazyme, Sanofi): provide a working form of the defect enzyme.
- **Pharmacological chaperones** (migalastat, Galafold, Amicus Therapeutics): stabilise certain mutant enzymes so they fold correctly and reach the lysosome.
- **Substrate-reduction therapies** (ex. Venglustat, ceramide analog, Sanofi): lower biosynthesis of accumulated substrate.
- **Gene therapies** (ex. AMT-191, AAV5 gene therapy, uniQure): seek to restore endogenous enzyme production.

FIGURE 20: APPROVED THERAPEUTIC APPROACHES AND CURRENT DEVELOPMENT IN FABRY'S DISEASE



Source: Lenders, et al. Progress and Challenges in the Treatment of Fabry Disease. BioDrugs. 2025.

Here, the field advances through subdivision, not aggregation.

CONVERGENCE: MANY DISEASES BECOME ONE MECHANISM

However, while diagnostics divide, biology recombines. Distinct rare disorders, scattered across organs and phenotypes, can share a single molecular pathway, allowing data, manufacturing, and regulatory experience to circulate between them. Complement activation, PI3K/AKT signalling, and mitochondrial metabolism illustrate how these cross-organ circuits turn disconnected conditions into coherent mechanistic families.

Complement inhibition shows how one pathway can sustain an entire rare-disease portfolio. Eculizumab (Soliris, Alexion/AstraZeneca) began with PNH in 2007, then expanded to atypical haemolytic uremic syndrome (aHUS), generalised myasthenia gravis, and neuromyelitis optica spectrum disorder (NMOSD). Its long-acting follow-on, ravulizumab (Ultomiris), has replicated this pattern. Each indication affects a different tissue but relies on the same biological logic and similar analytical infrastructure.

Argenx offers another model. By targeting the neonatal Fc receptor, which recycles pathogenic immunoglobulin G antibodies, it built a multi-indication franchise around efgartigimod (Vyvgart), approved for generalised myasthenia gravis (gMG) and chronic inflammatory demyelinating polyneuropathy (CIDP) and in late-stage trials across neurology, haematology, and dermatology.

The PI3K/AKT/mTOR axis bridges developmental overgrowth disorders and oncology. Alpelisib, first approved as Piqray (Novartis, 2019) for PIK3CA-mutated breast cancer, later received accelerated approval as Vijoice (2022) for PIK3CA-related overgrowth spectrum (PROS), showing how pathway-defined diseases can support two-way translation between rare and common settings.

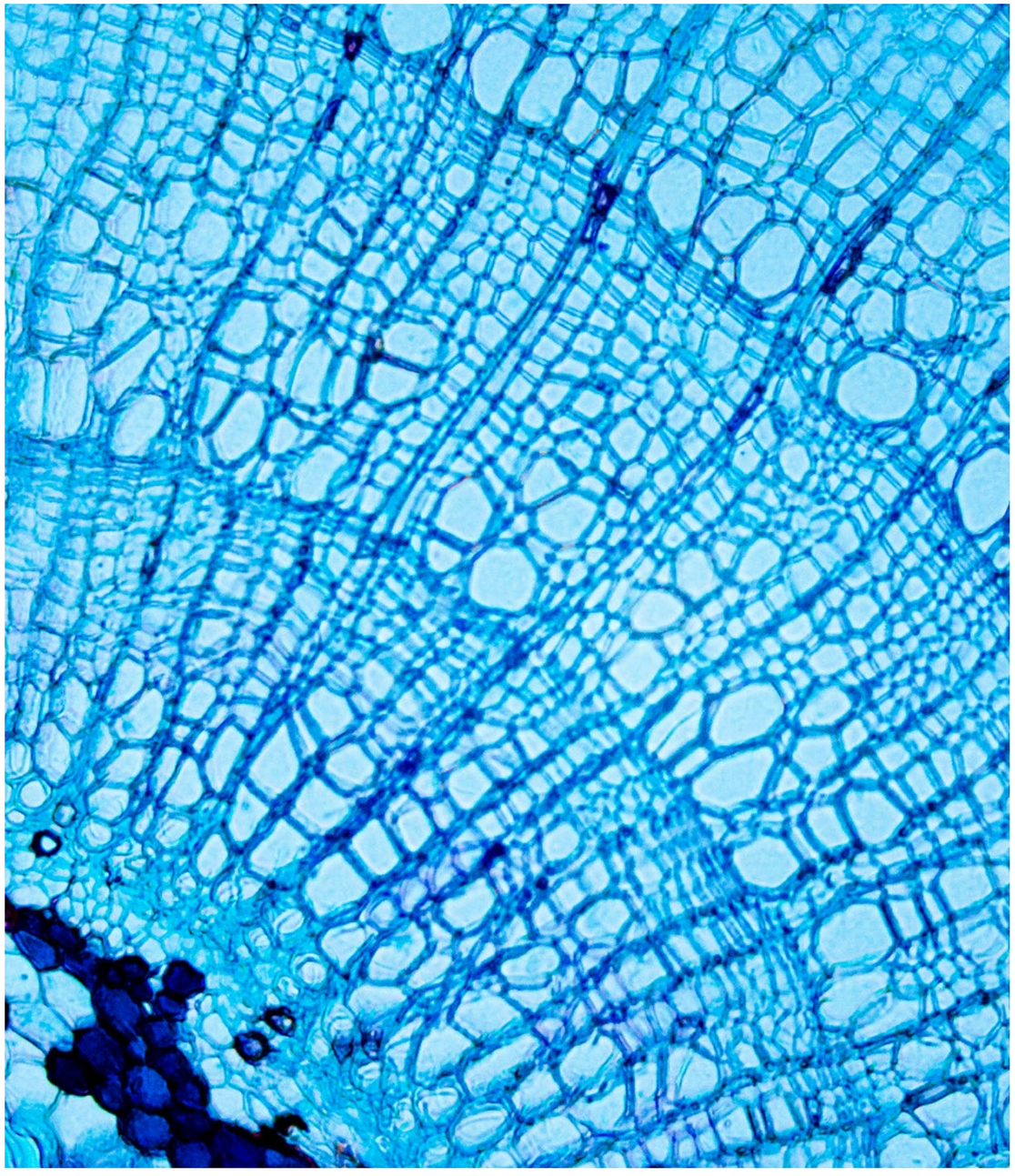
Mitochondrial dysfunction, arising from diverse genetic defects, drives phenotypes across neurology, cardiology, and ophthalmology. Programmes from Khondrion, Stealth BioTherapeutics, and Minovia Therapeutics all aim to stabilise energy metabolism across different phenotypes, relying on shared mechanistic biomarkers such as adenosine triphosphate production and oxygen-consumption rate to validate their approach, creating cumulative regulatory familiarity.

Pathway convergence enables rare-disease portfolios to function as modular systems, allowing multiple rare indications to share one scientific backbone and thereby justify sustained investment.

These dual dynamics are not in conflict: fragmentation provides the molecular precision to deliver transformative outcomes, while convergence enables the mechanistic scalability required to build sustainable enterprises.

THE STRATIFYING RARE-DISEASE ECOSYSTEM

Taking a closer look at the European rare-disease landscape, we tried to find a way to classify the actors navigating the field. There are many valid ways to look at it, be it by modality, therapeutic area, or corporate stage.



PURE RARE-DISEASE SPECIALISTS VS. OPPORTUNISTIC ACTORS

Companies differ not only by the rarity of the conditions they target but by how central the orphan model is to their identity. Some were conceived to serve small populations as an end in itself; others discovered rare disease as a natural extension of deeper scientific coherence (an organ system, a delivery platform, or a therapeutic modality that incidentally spans both orphan and common indications).

At one extreme are the pure rare-disease specialists: companies conceived for the orphan model from the outset. Their scientific and operational architecture (CMC, regulatory design, clinical strategy) is built around the constraints of low-prevalence diseases. They develop narrow, defined indications, maintain constant dialogue with regulators, and often rely on early academic or patient-foundation alliances rather than scale. This category also includes rare disease-focused distributors.

FIGURE 21: CASE STUDY – MINORYX

minoryx therapeutics

THE PURE-PLAY ORPHAN CNS SPECIALIST

Minoryx Therapeutics, founded in 2011, is designed for the orphan model, focusing on novel therapies for severe, rare CNS diseases. Its strategy aligns with the unique challenges of low-prevalence neurodegenerative conditions.

SINGULAR FOCUS ON ORPHAN CNS

Minoryx's pipeline targets rare neurological diseases. Its lead asset, leriglitazone, is a novel, brain-penetrant PPAR-gamma agonist being developed for X-linked Adrenoleukodystrophy (X-ALD). This focus enables deep expertise and efficient operations.

ORPHAN-CENTRIC DEVELOPMENT PATH

Leriglitazone reflects a classic orphan drug approach, securing Orphan Drug Designation from both the FDA and EMA, plus Fast Track and Rare Pediatric Disease designations from the FDA.

DEEP PATIENT & ACADEMIC ALLIANCES

Minoryx works closely with advocacy groups like ULF and Stop ALD Foundation, ensuring patient and clinician input shapes its clinical programs.

STRATEGIC PARTNERSHIPS FOR COMMERCIALISATION:

Partnerships, including with Neuraxpharm for leriglitazone's European launch, allow Minoryx to focus on R&D while ensuring therapies reach patients.

Source: Company reports

FIGURE 22: CASE STUDY – THX PHARMA

THX pharma

A PLATFORM-DRIVEN PIVOT TO RARE DISEASE

THX Pharma (formerly Theranexus) demonstrates a strategic shift from a platform for common neurological disorders to a rare disease focus. The company began by modulating glial cells to enhance current CNS drugs for conditions like narcolepsy and Parkinson's.

FROM PLATFORM TO INDICATION

THX Pharma started with a drug discovery platform targeting neuron-glial cell interactions, enabling work in both common and rare CNS diseases.

STRATEGIC PIVOT TO RARE

In 2022, Theranexus shifted focus to rare neurological diseases, driven by the progress of Batten-1 (miglustat) for Batten disease (CLN3). Now as THX Pharma, it is also developing an ASO platform dedicated to rare diseases.

REPURPOSING AND ALLIANCES

The development of Batten-1 showcases a classic orphan drug strategy:

- Drug Repurposing: Batten-1 is a reformulated miglustat, a drug already approved for other rare conditions, significantly de-risking its development pathway.
- Patient-Foundation Partnership: The programme is developed with the Beyond Batten Disease Foundation (BBDF), which co-sponsors clinical trials and provides critical patient community engagement.

Source: Company reports

At the opposite end are the opportunistic actors, i.e. large or diversified organisations that maintain orphan programmes because these align with existing portfolio strengths or complement therapeutic franchises, not because rare disease itself defines their model. Their rare divisions are structured, often well-funded, and scientifically credible, yet function as portfolio pillars rather than strategic nuclei. In the European landscape, several legacy pharmas and multinational healthcare groups have intermittently played this role, using orphan designations as regulatory fast lanes or as vehicles for repositioning under-utilised assets.

FIGURE 23: CASE STUDY – RECORDATI

RECORDATI

THE DIVERSIFIED PLAYER AND STRATEGIC ACQUIRER

Recordati is an "opportunistic actor," running a large, diversified business where its Rare Diseases unit serves as a high-growth pillar alongside a sizeable Specialty & Primary Care (SPC) franchise. This dual model lets Recordati use cash flow from primary care to fund high-value rare disease acquisitions.

A TALE OF TWO BUSINESSES

Recordati's identity is not defined solely by rare diseases. In 1H25, the SPC segment, accounted for 61% of group revenue while Rare Diseases contributed 39%, highlighting its role as a crucial but complementary part of a larger, diversified organization.

GROWTH VIA M&A

Recordati has expanded its rare disease presence through bolt-on acquisitions of de-risked, revenue-generating assets. Key deals include:

- Orphan Europe (2007): Entry into rare disease
- EUSA Pharma (2022): A €750m deal for a new rare oncology franchise.
- Enjaymo (2024): An $825m upfront for Sanofi rare hematology drug.

PORTFOLIO SYNERGY

The rare disease division spans endocrinology, metabolic, and hemato-oncology, complementing Recordati's group strengths. Acquisitions are chosen for their fit with existing expertise and commercial infrastructure.

Source: Company reports

Between these poles lies an increasingly fluid middle ground where specialisation and strategy intertwine. The trajectory of those strategic entrants typically begins within the orphan space but evolve toward broader indications through therapeutic-area or modality consistency. They use the high-precision, data-rich environment of rare disease as a launchpad, validating a mechanism or technology before expanding to more prevalent conditions. What defines this category is scientific coherence across scales: their orphan programmes remain core to validation and learning, but the companies themselves are in active transition from precision rarity to wider market application. In doing so, they provide the connective tissue between discovery-stage biotechnology and mainstream biopharma, a proof that industrial maturity can emerge directly from orphan innovation.

FIGURE 24: CASE STUDY – BEACON THERAPEUTICS

beacon therapeutics

RARE DISEASE AS A LAUNCHPAD

Beacon Therapeutics uses rare disease as a launchpad to validate AAV gene therapy in eye diseases. Its pipeline shows a progression from addressing rare, precise indications to broader ophthalmic applications, unified by its focus on eye health.

ORPHAN DISEASE AS THE PROVING GROUND

Beacon's lead asset, laru-zova, targets X-Linked Retinitis Pigmentosa (XLRP), a rare form of blindness, providing a clear clinical and regulatory path to demonstrate its AAV platform. Another program addresses the also rare Cone-Rod Dystrophy (CRD).

PIVOTING TO PREVALENT CONDITIONS

Beacon's pipeline includes a preclinical program for dry Age-related Macular Degeneration (dAMD), showing a strategic shift from rare genetic disease (XLRP) to a major, common condition (dAMD).

MODALITY-FIRST, NOT DISEASE-FIRST

Beacon is defined by ophthalmic gene therapy expertise. It leverages rare retinal disorders to de-risk its AAV platform before expanding into broadly prevalent eye diseases.

Source: Company reports

FIGURE 25: CASE STUDY – BIOXODES

Bioxodes

A MECHANISM-DRIVEN BRIDGE FROM RARE TO COMMON DISEASE

Bioxodes exemplifies using a rare, acute condition to validate a novel therapeutic approach with broad potential. Its lead candidate, BIOX-101, a peptide inspired by tick saliva, targets thrombo-inflammation. By starting with an orphan disease, Bioxodes aims to de-risk a platform that could address both rare and common conditions.

ORPHAN INDICATION AS A GATEWAY

Bioxodes' lead programme targets intracerebral haemorrhage (ICH), a severe form of stroke for which it has received an ODD. It provides a clear regulatory to demonstrate BIOX-101's novel effect on thrombosis and neuroinflammation.

SCIENTIFIC COHERENCE ACROSS A THERAPEUTIC AXIS

Bioxodes' identity is rooted in its therapeutic approach, as the mechanism of BIOX-101 is the foundation for a pipeline targeting thrombo-inflammatory disorders.

MODALITY-FIRST, NOT DISEASE-FIRST

Bioxodes already plans to develop BIOX-101 for acute ischemic stroke and additional thrombo-inflammatory indications, scaling the platform from a rare condition to larger markets.

Source: Company reports

The result is a reciprocal dependence: discovery-driven companies rely on the industrial maturity of opportunistic actors, while larger companies depend on the originality and regulatory agility of smaller innovators to refresh their pipelines.

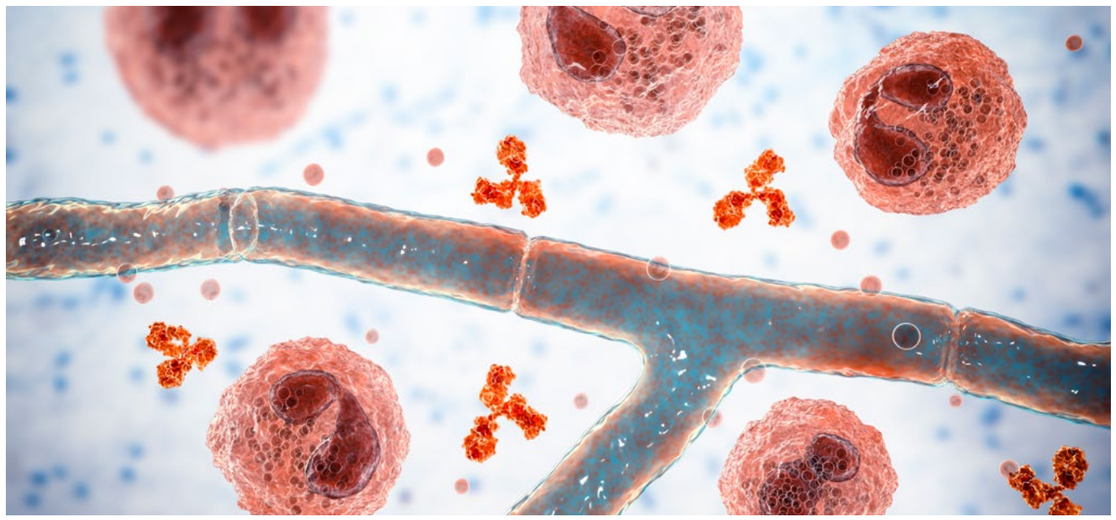


FIGURE 26: STRATEGIC SEGMENTATION OF THE EUROPEAN RARE-DISEASE MARKET – RARE-DISEASE SPECIALISTS VS. OPPORTUNISTIC ENTRANTS

Source: Company reports and Stifel IRIS

TYPOLOGIES OF COMPANIES

Looking at another angle, we identified four recurring archetypes: de-novo innovators, repurposers, integrators, and legacy or hybrid pharmas. These are not rigid boxes but stereotypes that help make sense of an increasingly complex ecosystem.

- **De-novo innovators:** These are the originators, i.e. companies often built around a single scientific breakthrough and spun out of academic labs. Their goal is to establish initial biological validation without necessarily seeking commercial breadth.

FIGURE 27: CASE STUDY – ARTHEX BIOTECH

ARTHEx biotech

AN ACADEMIC SPIN-OUT FOCUSED ON A NOVEL MECHANISM

ARTHEx Biotech is a quintessential de-novo innovator, built around a singular scientific breakthrough from the University of Valencia. Its entire focus is on validating a novel therapeutic approach for Myotonic Dystrophy Type 1 (DM1), a rare, progressive neuromuscular disease.

ACADEMIC ROOTS AND SINGULAR FOCUS

ARTHEx's mission is to use ASO to inhibit microRNAs (miRNAs) involved in DM1. The company's lead and sole clinical-stage asset, ATX-01, embodies this focused approach.

GOAL OF BIOLOGICAL VALIDATION

The main objective is to validate its miRNA-targeting approach. The Phase I/IIa ArthemiR™ trial for ATX-01 is underway to demonstrate safety and efficacy.

VENTURE-BACKED ORIGINATOR

ARTHEx's funding history, including a recent upsized Series B financing ($87m led by new investor Bpifrance), is characteristic of a biotech originator reliant on venture capital to translate a promising academic discovery into a clinical-stage asset.

Source: Company reports

FIGURE 28: CASE STUDY – BOOST PHARMA

BOOST PHARMA

A NOVEL APPROACH TO BRITTLE BONES

BOOST Pharma is a classic "De-Novo Innovator," founded specifically to translate a scientific breakthrough from an academic setting into a clinical reality. Spun out of the Karolinska Institute in Sweden, the company is built around a single, high-potential asset: a novel mesenchymal stem cell (MSC) therapy for Osteogenesis Imperfecta (OI), or brittle bone disease.

TRANSLATING ACADEMIC EXCELLENCE

The company originated from years of collaborative research at the Karolinska Institutet, a world leader in cell therapy.

ADDRESSING THE GENETIC ROOT

BOOST's core innovation is BT-101, a first-in-class mesenchymal stem cell therapy. Unlike traditional treatments that only manage symptoms, BT-101 targets the underlying genetic cause of OI by providing healthy cells that can differentiate into bone-forming osteoblasts and produce normal collagen.

STRONG EARLY CLINICAL SIGNAL

In the landmark Phase I/II BOOSTB4 trial, BT-101 demonstrated a c.78% reduction in fracture rates over a two-year period. OI currently lacks any approved therapy that modifies the course of the disease; these results suggest BT-101 could be that breakthrough. These data positions the company for deal-making and further development, fulfilling the primary goal of the de-novo innovator archetype.

Source: Company reports

- **Repurposers / redeployers:** At the opposite end are the companies that create value through intelligent reuse of known assets. We included here both classical repurposing and broader forms of data-driven redeployment, where new therapeutic relevance is extracted from existing pharmacology or abandoned assets are given a second chance.

FIGURE 29: CASE STUDY – OAK HILL BIO

Oak Hill Bio

THE ASSET REDEPLOYER

Oak Hill Bio follows the redeployment model by acquiring clinical-stage assets deprioritized by larger pharma and repurposing them for rare diseases. Its strategy centers on in-licensing molecules with established pharmacology, not internal discovery.

RESCUING ABANDONED ASSETS

Oak Hill's pipeline is built entirely on assets acquired from big pharma like rugonersen for Angelman syndrome, in-licensed from Roche after the programme was halted.

VALUE CREATION THROUGH REDEPLOYMENT

Oak Hill finds new uses for existing molecules, leveraging prior manufacturing, safety, and clinical data to lower development time and cost. The emphasis is on clinical execution over novel discovery.

A LEAN, EXTERNALLY FOCUSED MODEL

Operating with a lean structure, Oak Hill specializes in identifying and advancing undervalued assets from larger companies, aiming for efficient regulatory approval in new, often orphan, indications.

Source: Company reports

FIGURE 30: CASE STUDY – ADVICENNE

advicenne

THE REFORMULATION SPECIALIST

Advicenne creates value by smartly repurposing well-known compounds, focusing on new, pediatric-friendly formulations of approved drugs for rare kidney diseases to address unmet patient needs

FOCUS ON NOVEL FORMULATION

Advicenne's lead product, Sibnayal (potassium citrate/ potassium bicarbonate) was developed as an extended-release granule formulation to treat distal renal tubular acidosis (dRTA), a rare genetic kidney disorder. The ingredients are common, but the formulation is novel and designed for chronic use in both children and adults.

SOLVING AN UNMET NEED WITH AN EXISTING COMPOUND

Previously, dRTA patients relied on unapproved, less tolerable preparations. Advicenne addressed this by repurposing known alkalinising agents into a more effective, patient-friendly treatment.

EXPANDING THE REPURPOSING PIPELINE

Advicenne uses the same model for ADV7103 in cystinuria, another rare kidney disease, establishing a repeatable approach of novel formulations in rare conditions.

Source: Company reports

FIGURE 31: CASE STUDY – UNIQURE

uniQure

THE AAV GENE THERAPY INTEGRATOR

uniQure illustrates the "Integrator“ model, turning its core AAV gene therapy platform into a repeatable engine for new therapeutics. With over 20 years’ experience, the company has achieved commercial validation and now leverages this expertise to advance a broad pipeline.

A VALIDATED, MODULAR PLATFORM

uniQure's core strength is its AAV platform, encompassing vector design, manufacturing, and analytics. This platform is a reproducible engine for creating gene therapies for liver-directed and central nervous system (CNS) disorders.

PROOF OF REPRODUCIBILITY: A MULTI-PROGRAMME PIPELINE

Platform maturity is shown by multiple assets:

- HEMGENIX (etranacogene dezaparvovec): The first FDA-approved gene therapy for Haemophilia B, validating the platform from R&D to commercialization.
- AMT-130: Late-stage Huntington’s disease program, highlighting versatility.
- Early-stage pipeline: All new assets derive from this core technology.

MANUFACTURING AS A CORE COMPETENCY

uniQure’s manufacturing is industry-leading. The FDA confirmed that new candidates like AMT-130 can leverage prior experience from HEMGENIX, demonstrating a mature, repeatable process.

Source: Company reports and Stifel IRIS

FIGURE 32: COMPANY ARCHETYPES IN THE EUROPEAN RARE-DISEASE ECOSYSTEM

Source: Company reports and Stifel IRIS

- **Integrators/platform maturers:** This group sits at the point where experimentation turns into reproducibility. Integrators are the companies that have learned to deliver multiple programmes from one validated process.
- **Legacy or hybrid pharmas:** The last category gathers the incumbents that now anchor the rare-disease economy, combining financial scale with operational depth. They acquire or partner with innovators once proof of concept is secured, scale manufacturing, and sustain complex market-access negotiations over years. Their conservatism provides structural stability: without them, few smaller companies could navigate global compliance, pricing, and distribution for long-term orphan markets.Culpa sus pari cuptature

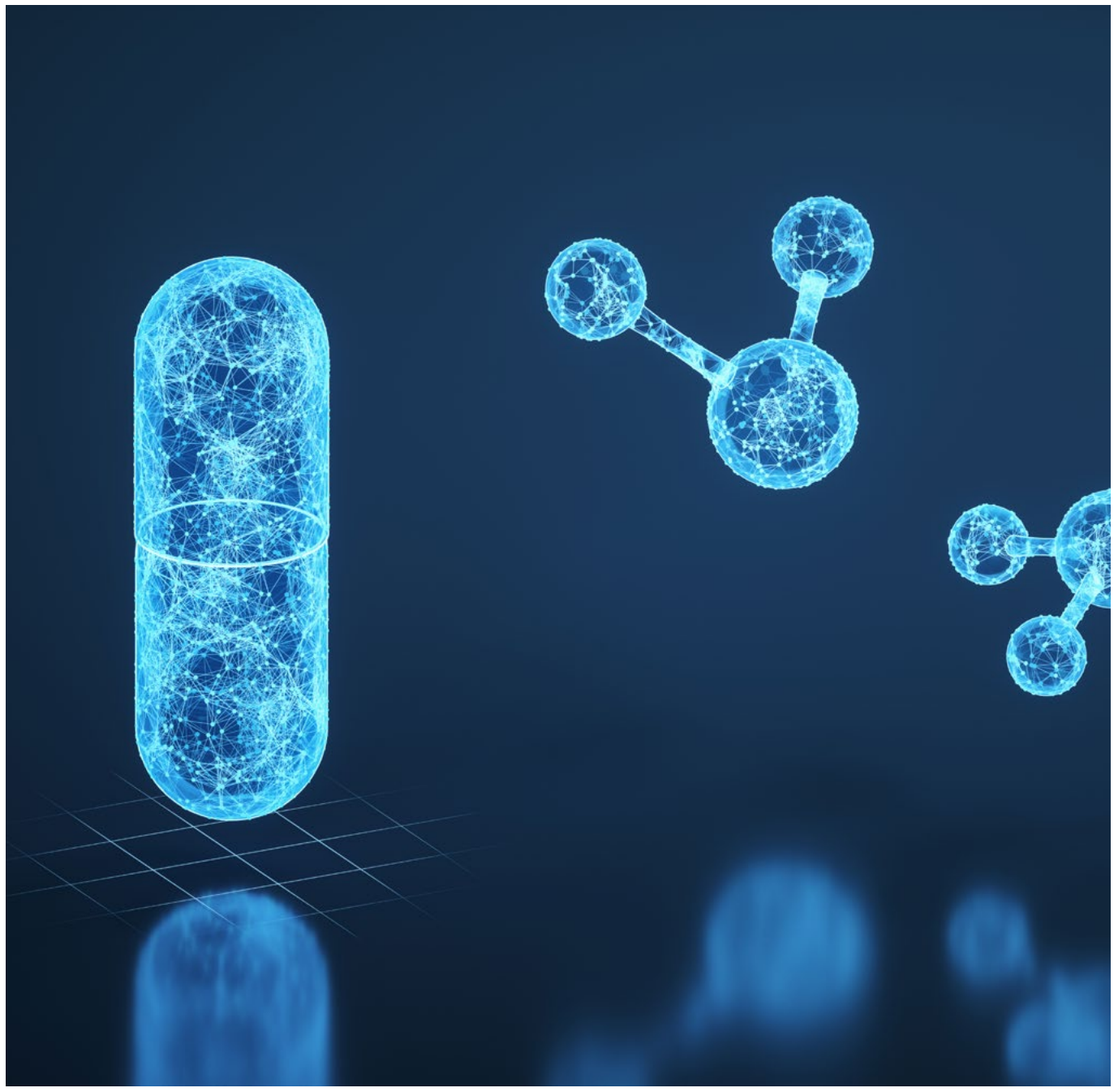
This classification is interpretive, not prescriptive. We attempted to impose order on a field that constantly shifts, knowing that companies often evolve across categories. A repurposer can become an integrator; an integrator may be acquired by a legacy group; some hybrids straddle all four roles at once.

Our purpose is not taxonomy for its own sake but to show that maturity in rare diseases has become structural, defined by a company’s function within the collective system.

De-novo innovators expand the frontier, repurposers accelerate translation, integrators secure reproducibility, and legacy companies ensure permanence.

MATURING FRAMEWORKS

Over the past decade, the rare-disease ecosystem has moved from isolated breakthroughs towards a more structured model of reproducible innovation. Scientific novelty remains essential, but maturity now lies in a company's ability to generate successive successes from the same technological and procedural foundations. Two complementary forms of progress define this phase: technological continuity, where validated modalities evolve into repeatable platforms, and institutional continuity, where accumulated expertise turns individual programmes into scalable operating systems.



CUMULATIVE LEARNINGS

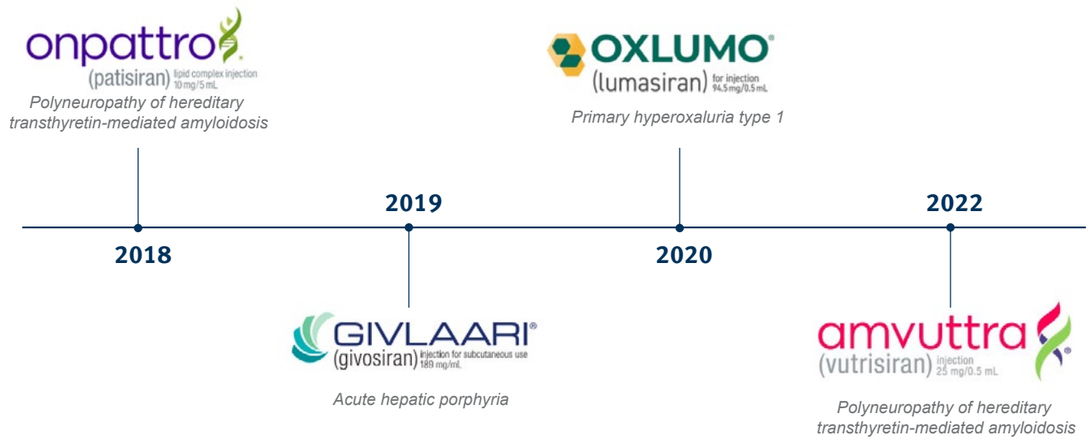
The first sign of maturity in the rare-disease sector is the shift from singular invention to cumulative learning. Where early pioneers built one-off solutions around untested technologies, the most advanced actors now generate a sequence of successes from the same scientific and procedural base. Knowledge, infrastructure, and regulatory familiarity have become transferable assets: once a modality proves safe and effective, it can be iterated.

MATURITY THROUGH TECHNOLOGICAL CONTINUITY

Some rare-disease pioneers have reached a stage where a validated modality can be reused across multiple programmes without re-negotiating its fundamentals.

Alnylam Pharmaceuticals epitomises this transition. Following the first approval of Onpattro (patisiran) in 2018, the company delivered three further products, Givlaari, Oxlumo, and Amvuttra, built on the same siRNA chemistry and hepatocyte-targeted delivery system. Each programme targeted a distinct pathway but shared a similar technological and regulatory template, including biomarker validation, CMC architecture, and long-term safety design. The rapid succession of approvals proved that once a rare-disease modality achieves clinical validation, innovation can shift from invention to industrial-scale iteration.

FIGURE 33: BUILDING AN RNA PLATFORM



Source: Company reports

MATURITY THROUGH INSTITUTIONAL LEARNING

Other organisations achieved maturity not through a common technology, but through the institutionalisation of competence. This engine is defined by a set of repeatable, cross-functional capabilities designed to overcome the structural challenges of the orphan drug market: small, dispersed patient populations, complex reimbursement landscapes, and high logistical burdens.

Two companies, Genzyme and Alexion, serve as the archetypes for this strategy. They achieved market leadership not by deploying a single, universal technology, but by building a powerful commercial and clinical apparatus that could be aimed at successive rare-disease targets. Their core asset was the organisation itself.

FIGURE 34: CASE STUDY – GENZYME (NOW PART OF SANOFI)

SANOFI GENZYME

THE ARCHITECT OF THE ORPHAN DRUG PLAYBOOK

Genzyme pioneered the modern commercial model for rare diseases, building a dominant franchise in enzyme replacement therapies (ERTs). Success relied on mastering the full product ecosystem, a competence replicated across indications.

PATIENT-CENTRIC COMMERCIAL MODEL

Genzyme recognised success in rare diseases required more than just an effective drug. Its strategy relied on deep collaborations with patient communities and physicians, involving patient's identification, diagnosis and high-touch support services.

MASTERING THE REIMBURSEMENT LANDSCAPE

Genzyme excelled at navigating reimbursement for high-cost therapies. By proving the transformative value of treatments like Ceredase (1994) for Gaucher disease, the company established the economic viability of the orphan drug model.

BUILDING A SUSTAINABLE ENGINE

Focusing on lysosomal storage disorders (LSDs) created a center of excellence. Knowledge was systematically reapplied across programmes, creating a self-reinforcing cycle of competence supported by over 30 years of registry data.

Source: Company reports

FIGURE 35: CASE STUDY – ALEXION (NOW PART OF ASTRAZENECA)

ALEXION®

MASTERING MARKET CREATION AND LIFECYCLE MANAGEMENT

Alexion built a multi-billion dollars franchise around a single mechanism of action: complement inhibition. The company's maturity was demonstrated by its ability to systematically expand the utility of its lead asset, Soliris, by defining its role in new diseases and expertly managing the franchise lifecycle.

DEEP SCIENTIFIC AND COMMERCIAL FOCUS

Alexion's deep expertise in the complement system led to Soliris (eculizumab), then expanded its use from PNH to aHUS, gMG, and NMOSD, building a blockbuster from multiple rare diseases.

NAVIGATING REGULATORY AMBIGUITY

Alexion forged regulatory paths in uncharted indications by leveraging robust data and strong ties with health authorities.

LIFECYCLE MANAGEMENT AS A COMPETENCY

Alexion defended its franchise by launching Ultomiris (ravulizumab), a long-acting Soliris successor, and executed a successful switch strategy to sustain market leadership.

Source: Company reports

The Genzyme and Alexion models demonstrate that for rare-disease companies, the most durable competitive advantage is often operational, not technological. The "platform" is the organisation's ability to execute a complex, multi-faceted strategy.

A third example of organisational maturity is demonstrated by companies that can successfully pivot from a clinical or regulatory failure by repurposing the strategic assets built during the process. Santhera's path from idebenone to vamorolone in Duchenne muscular dystrophy (DMD) serves as a prime example. This pathway underscores how maturity in the rare-disease sector increasingly resides in the ability to operationalise learning rather than simply avoid failure.

The company's multi-year effort to develop idebenone for DMD, despite ultimately falling short of regulatory approval in key markets, was not a total loss. Instead, the programme served as a crucible for forging durable, indication-specific competencies.

FIGURE 36: CASE STUDY – SANTHERA

santhera
THEIR FUTURE - OUR FOCUS

PIVOTING FROM FAILURE BY OPERATIONALISING LEARNING

Santhera demonstrates maturity through its ability to pivot and learn from failure. After the clinical-stage setback of idebenone in DMD, Santhera leveraged strategic assets from that effort to secure approval for vamorolone (AGAMREE®), showing how failed programs can enable later success.

THE CRUCIBLE OF FAILURE: THE IDEBENONE PROGRAMME

Santhera invested years and significant capital in developing idebenone for DMD. Despite promising early data, the pivotal SIDEROS study was stopped in 2020 after an interim analysis showed it was unlikely to meet its primary endpoint.

HARVESTING COMPETENCIES FROM A SETBACK

This multi-year effort built key experience in DMD clinical trial design, and fostered strong ties with key opinion leaders, trial sites, and patient groups.

THE STRATEGIC PIVOT TO VAMOROLONE

Santhera had already acquired vamorolone, a dissociative steroid, in 2018. After idebenone failed, it quickly shifted focus, using its DMD expertise to accelerate VISION-DMD, secure regulatory submissions, and win approval for vamorolone.

Source: Company reports

CONVERGENCE ON PREDICTABLE DEVELOPMENT MODELS

As experience accumulated, a second axis of maturity emerged through the progressive standardisation of development pathways. Early programmes relied on improvisation, but many rare-disease modalities now follow a reproducible framework shared by regulators, sponsors, and patient networks.

Novel diseases still require substantial groundwork to establish precedents and validate endpoints. Yet for well-understood modalities, an informal template has taken shape. This structure originated in the first wave of AAV programmes, when the lack of historical controls forced developers and agencies to build methods step by step. Over time, these practices consolidated into a workable model for monogenic conditions.

For rare genetic diseases, the standard sequence now includes:

- A natural-history study to define baseline trajectory
- A single-arm pivotal trial using functional or biomarker endpoints
- A predefined post-authorisation registry and five-to-fifteen-year follow-up

Each component now benefits from guidance on endpoint selection, patient characterisation, and evidence standards. Patient organisations often provide registry foundations early, allowing even small companies to plan registrational studies with clearer alignment to regulatory expectations.

FIGURE 37: CASE STUDY – SPUR THERAPEUTICS

SPUR THERAPEUTICS

LEVERAGING THE STANDARDISED AAV DEVELOPMENT PATHWAY

Spur Therapeutics (formerly Freeline Therapeutics) illustrates the benefits of a standardised approach in the rare-disease space. By applying an established template for AAV gene therapies in monogenic disorders, Spur advances efficiently into late-stage development.

ADHERENCE TO THE AAV PLAYBOOK

Spur's lead programme, avigbagene parvec (FLT201) targets Gaucher disease type 1, a classic single-gene lysosomal storage disorder, making it an ideal candidate for AAV gene therapy.

REGULATORY ALIGNMENT

With positive Phase 1/2 data, Spur is set to launch a single-arm Phase 3 trial in 2026, already aligned with the FDA on the design to support accelerated and full approval, highlighting the increasing predictability of this pathway.

BUILDING ON ESTABLISHED PRECEDENTS

By focusing on a proven modality for a well-understood disease, Spur can leverage existing clinical and regulatory knowledge. While each programme still requires some tailoring, they can follow the path successfully navigated by other AAV therapies, giving confidence in the registrational strategy.

Source: Company reports

SCALING INDUSTRIAL CAPABILITIES AND KNOWLEDGE TRANSFER

The third expression of maturity is operational. Advanced-therapy production, once confined to academic centres, has been industrialised across both continents. Specialised manufacturers such as YposKesi (a SK pharmteco company), Oxford Biomedica, SK pharmteco, and Viralgen, alongside industrial scale actors like ThermoFisher, have created end-to-end platforms covering plasmid supply, viral-vector production, and fill–finish operations under GMP standards. These facilities allow small developers to access industrial-grade capacity without internalising prohibitive costs, while agencies gain confidence from consistent documentation and cross-site comparability data.

Knowledge transfer now occurs across programmes and sponsors. Manufacturing templates validated for one product class are used as blueprints for others, and release-testing protocols are harmonised through shared vector reference materials and potency standards. The same principle applies to clinical operations: data-sharing through global registries such as Orphanet, DARWIN EU, and RDCA-DAP ensures that natural-history, durability, and safety data accumulate continuously across products and diseases. In short, the field is learning collectively rather than independently.

TOWARD AN INTEGRATED ECOSYSTEM

The rare-disease field is gradually assembling into a connected ecosystem, where discovery, regulation, and manufacturing operate with increasing interdependence. Experience from one programme increasingly informs others, creating a shared language of endpoints, assays, and regulatory expectations. This progress is uneven. Mature areas exist alongside domains still shaped by trial-and-error, and alignment varies across therapeutic classes and agencies.

Across EU, the most advanced clusters (neuromuscular, haematologic, and metabolic disorders) benefit from established registries, regulatory precedents, and CDMO infrastructure that give smaller sponsors access to industrial standards. Ultra-rare and first-in-class indications often remain tied to academic processes and fragmented oversight. Regulatory convergence is partial; conditional approvals and RMAT designations help, but evidence thresholds and post-approval duties still diverge across regions.

Even so, the orphan field is less defined by fragility and more by continuity across the research, regulatory, and manufacturing cycle. This maturity does not eliminate uncertainty but allows it to be managed within increasingly predictable boundaries.

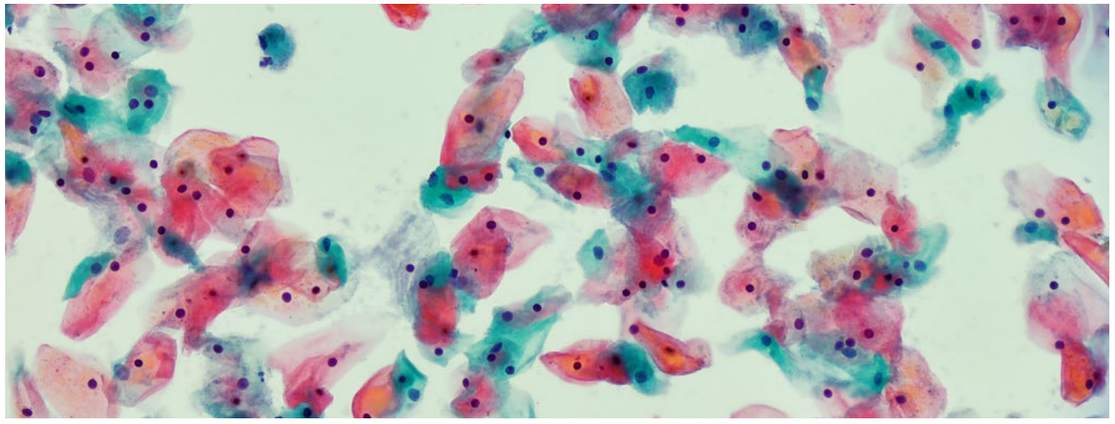


FIGURE 38: THE RARE-DISEASE DEVELOPMENT LANDSCAPE IN EUROPE – A SNAPSHOT OF PUBLIC AND PRIVATE COMPANY PIPELINES

Companies are classified by the stage of development of their most advanced rare-disease asset
Source: Company reports

This landscape of companies stratified by their stage of development provides a clear snapshot of the rare-disease ecosystem's structure and dynamism. While this figure is illustrative, as it is difficult to capture the entirety of the dynamic European ecosystem, especially the multitude of young, under-the-radar startups that populate the preclinical stage, it reveals a clear and telling distribution. The landscape is not a classic pyramid with a massive early-stage base and a tiny apex. Instead, it showcases the hallmarks of a maturing and highly productive industrial sector with two features:

1. **A well-populated mid-stage:** The significant concentration of companies in P2, the most populated clinical phase on this map, demonstrates that a substantial number of assets are successfully navigating early discovery and safety studies. This "belly" of the pipeline is a sign of a healthy ecosystem capable of consistently advancing novel science into clinical validation.
2. **A robust late-stage and commercial cohort:** The high density of companies in P3 and on the market is the most compelling sign of the sector's maturity. Far from being a niche corner of biotech, the rare-disease field now has a critical mass of companies, from specialised companies to focused distributors and global pharmas, capable of navigating the final hurdles of pivotal trials, regulatory approval, and complex commercial launches.

This distribution visualises the sector's success: it has created a sustainable conveyor belt that not only fosters early-stage innovation but, crucially, has become proficient at translating that innovation into late-stage and commercial-stage assets.

THE ECONOMICS OF RARITY

THE FOUR PILLARS OF VALUE CREATION IN RARE DISEASE

In rare diseases, economics follows biology. As molecular definitions become more precise, patient groups shrink, yet programmes must still fund GMP manufacturing, toxicology, chemistry-manufacturing-controls work, and pivotal studies. High fixed costs spread over tiny populations define the economics of rarity.

The market therefore depends on a different architecture. Scale is replaced by reusable development and manufacturing modules, value concentrates in a small number of high-impact transactions, regulators operate as partners, and patient communities act as part of the infrastructure. These elements explain how precision-driven science can remain economically viable despite extreme scarcity.

FIGURE 39: FOUR PILLARS TO SUPPORT THE BUSINESS MODEL

SCALE SUBSTITUTION

Shared platform and « indication piling » spread fixed cost across small programmes.

AAV portfolios (uniQure, REGENXBIO) or RNAi chemistry (Alnylam) reuse the same infrastructure and assays across multiple diseases

REGULATORY ENGAGEMENT

Early engagement and systematic leveraging of government incentives designed to de-risk and accelerate orphan drug development.

Market exclusivity, R&D grants, tax credits, fast-track review pathways...

VALUE CONCENTRATION

High per-patient pricing, outcome-based agreements and pay-over-time models allow to capture value through pricing rather than sales volume.

Novartis offers a five-year payment plan for Zolgensma

PATIENT-CENTRIC ECOSYSTEM

Creation of an ecosystem around the patient journey, with support from advocacy groups

Alnylam created the "Alnylam Act®", a programme offering no-cost genetic testing and counseling to suspected patients, effectively building the market from ground up

Source: Stifel IRIS

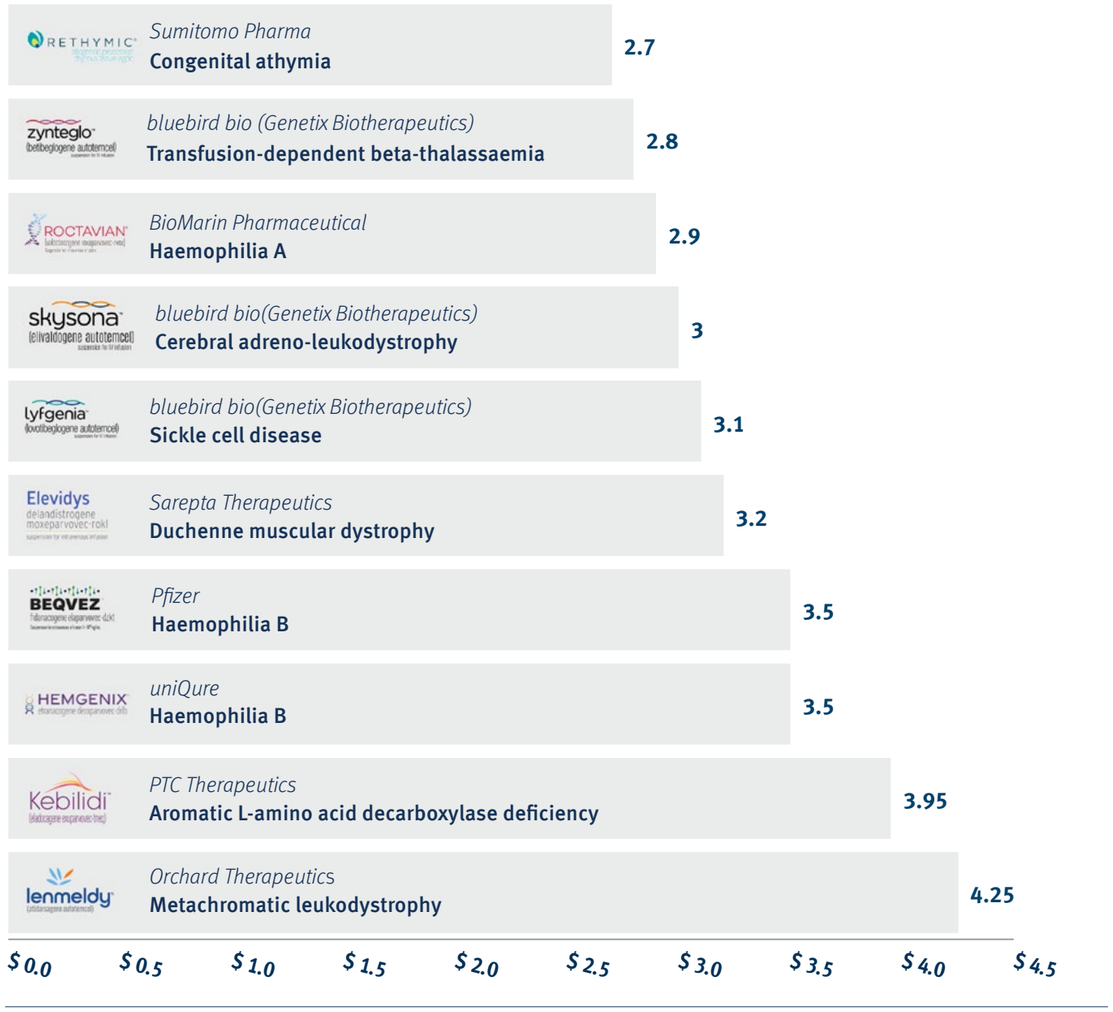
SCALE SUBSTITUTION – THE POWER OF REUSABLE PLATFORMS

In traditional drug development, scale is achieved by applying a successful drug to a large patient population. In rare diseases, where patient populations are inherently small, this model is inverted. Instead, scale is achieved by applying a reusable technological platform to multiple different rare diseases. This "scale substitution" allows companies to distribute the high fixed costs of research, process development, and manufacturing across a portfolio of products.

VALUE CONCENTRATION – HIGH IMPACT, HIGH PRICE

Because the costs of development are spread across a very small number of patients, the economic model for rare diseases requires that the value of the therapy be highly concentrated. This translates to extremely high per-patient prices for transformative, often curative, treatments. This model is only sustainable if the therapy provides a profound, life-altering benefit that justifies its cost to payers and health systems.

FIGURE 40: HIGHEST PRICED ORPHAN DRUGS (US$M)



Source: Company reports, Evaluate

REGULATORY ENGAGEMENT – COLLABORATIVE PATHWAYS

The traditional, sometimes adversarial relationship between sponsors and regulators is replaced in rare diseases by a more collaborative process, problem-solving partnership. Given the high unmet need, small patient populations, and lack of established clinical precedents, regulators often work closely with companies to find pragmatic solutions. This collaborative approach does not eliminate regulatory risk, but it transforms it. Instead of a simple pass/fail hurdle, the process becomes a joint effort to define the path forward. This engagement is formalised through a variety of mechanisms designed to de-risk and accelerate development.

PATIENT-CENTRIC ECOSYSTEMS – EMPOWERING PARTNERSHIPS

In rare diseases, the traditional lines between drug developer, physician, and patient become blurred. The final pillar of the rare-disease operating model is the recognition that patients and their families are not passive recipients of care but are active, essential partners in the drug development and commercialisation process. Given the small, geographically dispersed nature of these populations, patient advocacy groups often become the central nodes for disease expertise, clinical trial recruitment, and market access. Successful companies do not merely engage with these communities; they integrate them directly into their operational infrastructure, creating a powerful, patient-centric ecosystem.

PRICING GOVERNANCE AND PAYER ADAPTATION

The financial architecture of rare-disease innovation has matured as much as its science. Once negotiated case-by-case, pricing for orphan drugs now unfolds within a formalising governance system where health-technology assessment (HTA), real-world evidence (RWE), and managed-access frameworks interact continuously.

In Europe, the **Joint Clinical Assessment (JCA)**, under the new EU HTA Regulation, will standardise the evidentiary core for high-cost therapies. While it will not replace national price decisions, it reshapes their terms by forcing companies to justify premium pricing against a shared clinical baseline. However, its implementation is phased:

- **From January 2025:** The JCA will apply to new cancer drugs and all advanced-therapy medicinal products (ATMPs).
- **From 2028:** The scope will expand to include all orphan drugs.

National payers have already adapted by building dynamic reimbursement contracts that treat price as a variable, not a fixed endpoint.

- In **Italy**, AIFA's outcome-based registries link payment directly to patient-level follow-up, with "payment-at-result" models that claw back funds when endpoints are unmet.
- In **France**, the autorisation d'accès précoce (AAP) framework (which replaced the former ATU system) combines early access with mandatory data collection.
- In **Germany**, the GKV-FinStG reform tightened the revenue threshold at which an orphan drug's privileged pricing status expires to €30m (down from €50m), anchoring long-term price to market uptake and demonstrated benefit.

In the United States, the CMS Cell and Gene Therapy (CGT) Access Model extends this logic to one-time

curative therapies. It enables states to join pooled, outcomes-based contracts that pay over time, contingent on patient health outcomes. This represents a structural shift: payers no longer debate the sticker price but the reliability and durability of the therapeutic effect.

For companies, these changes impose a new discipline. The sustainability of high orphan drug prices now depends on the continuity of evidence. This means feeding post-approval data into registries like Europe's DARWIN EU and the FDA-linked RDCA-DAP to confirm the persistence of benefit. Pricing has become a performance contract measured in years, not negotiations. The frontier of pricing power more than the launch dossier, it becomes the real-world dataset that follows it.

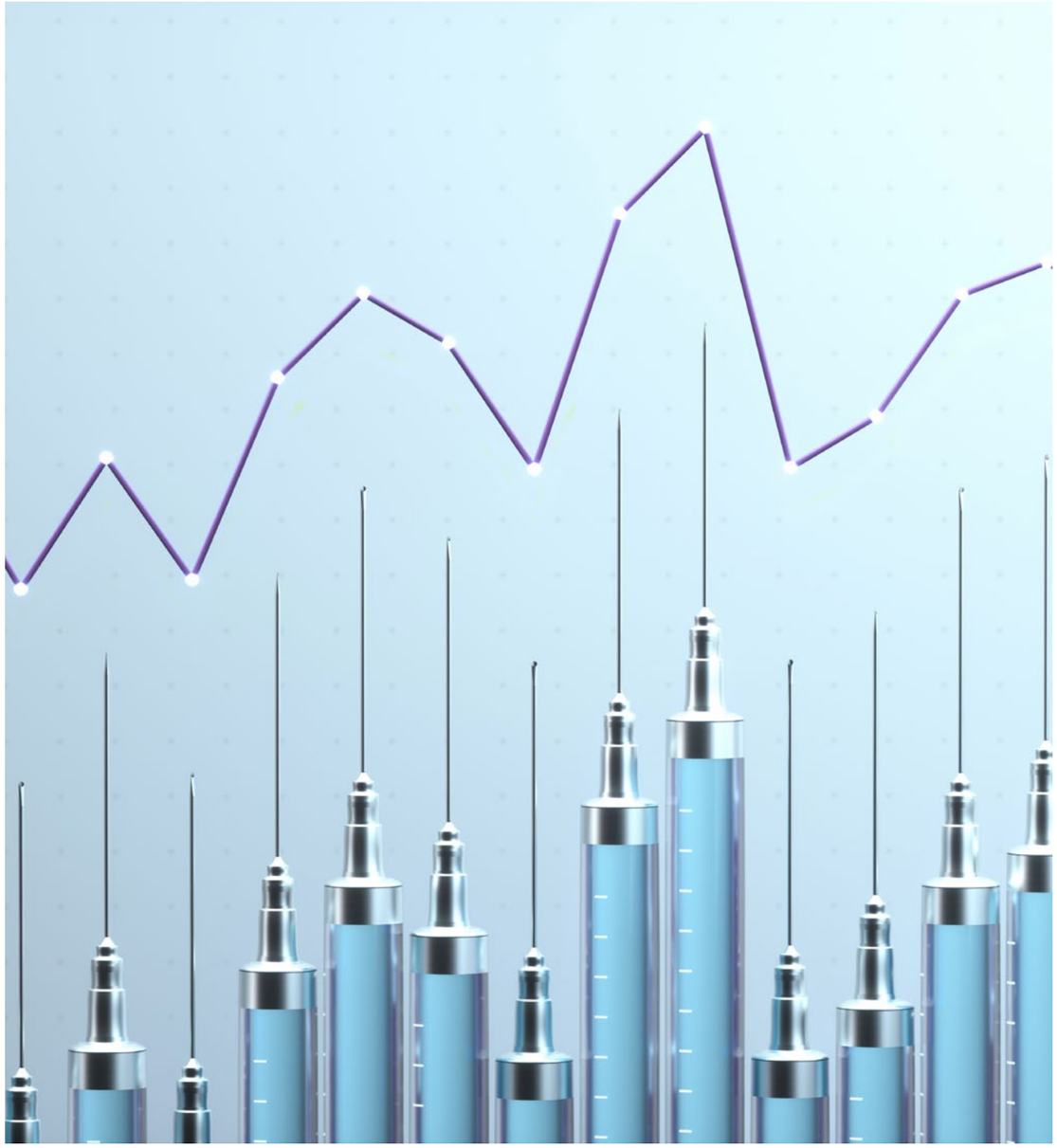
And while HTA frameworks are now clearer, access remains uneven. Fragmented national assessments in Europe can delay launches by one to three years for the same therapy, and outcome-based arrangements are still hindered by inconsistent definitions of clinically meaningful endpoints. The trajectory is obviously compelling, but there remains progress to be made.

THE SECONDARY MARKET FOR ORPHAN ASSETS

As the sector matures, a second layer of economics has emerged: the after-market of rarity. Products that once symbolised frontier innovation now circulate between owners much like durable industrial assets. Their value lies less in growth potential than in the steady annuity of a small, loyal patient base and a long tail of follow-up revenues.

Specialised acquirers have built part of their strategy around this phenomenon. They acquire non-core orphan brands from larger groups or license late-stage assets from smaller innovators, extending exclusivity and maintaining patient support to ensure stable demand. Recordati's October 2024 agreement to acquire the rare-disease drug Enjaymo from Sanofi, or Advanz Pharma's acquisition of two orphan-designated drugs from Eisai in April 2019, illustrate how these assets gain a second industrial life once their original sponsors shift focus.

TRANSACTIONS AND CAPITAL ACTIVITY



SELECTIVE M&A DRIVING GROWTH

The last years saw robust M&A activity in rare diseases, including several blockbuster acquisitions by big pharma as well as targeted takeovers by mid-sized specialists. Notably, rare-disease dealmaking hit a high point in 2021. In 3Q21, total disclosed rare-disease M&A value topped US$29 billion (a 241% YoY increase) as companies like Merck, Sanofi, Pfizer and Novo Nordisk all inked ›US$1bn acquisitions in this space. The momentum continued with a mix of mega-deals and bolt-on acquisitions in subsequent years, with several key trends:

- **Surge in Big-Ticket Deals (2021–2023):** Rare diseases became the focal point of some of pharma's largest deals. 2021 was a breakout year. Beyond AstraZeneca/Alexion (nearly US$40bn), that year saw multiple ›US$1bn deals by Merck, Sanofi, and others, signalling a wave of consolidation in orphan drugs. This culminated in Amgen's US$27.8bn Horizon acquisition in 2022, the year's largest pharma deal. In 2022, despite an overall slowdown in biotech M&A, rare-disease focused takeovers remained prominent (with Amgen, Pfizer, and others snapping up orphan drug companies). By 2023, big pharma continued paying a premium for rare-disease specialists, exemplified by Biogen's multi-billion dollar move for Reata and Novartis's US$3.5n bid for Chinook (rare renal) amid competitive bidding.
- **Shift to Mid-Sized Bolt-on Acquisitions (2024):** Entering 2024, as market valuations of biotechs cooled, the trend tilted toward mid-cap acquisitions. Many deals fell in the US$1–5bn range, still sizeable but mostly focused on single assets or late-stage candidates. Vertex's US$4.9bn Alpine Immune buy and Gilead's US$4.3bn CymaBay deal typify this, each securing one high-potential orphan drug. Rather than pursuing entire diversified companies, acquirers targeted one-disease firms with compelling late-stage data or recently approved product. This bolt-on approach allowed pharma companies to fill specific portfolio gaps with less risk than a transformative merger. The rare-disease area was perfectly suited to this strategy, given many biotechs in the space are relatively small but have one-of-a-kind therapies.
- **Broad dynamics and signals of larger deals (2025):** In 2025, the trend of executing numerous deals under US$5bn continued, emphasising a strategy centred around selective asset acquisition and risk mitigation. However, Novartis's US$12bn acquisition of Avidity Biosciences late October could be a signal of renewed interest in larger-scale deals, particularly for assets with significant therapeutic potential and strategic fit.

LICENSING DYNAMICS

For biotechnology companies, licensing is a critical strategic lever, providing non-dilutive capital, external validation, and access to the global development and commercialisation infrastructure of larger partners. This dynamic is particularly nuanced in the rare-disease space. While the focused patient populations of orphan indications can make a "go-it-alone" strategy seem feasible, the complexities of global patient identification, specialised reimbursement, and post-market studies often make partnering with an established rare-disease company the optimal path.

FIGURE 41: SELECTED M&A TRANSACTIONS

Date	Payer	Country	Payee	Country	TDV (up to $bn)	Premium	Technology	Therapeutic area	Stage of development
Dec-25	BIOMARIN	US	Amicus Therapeutics	US	4.8	33%	Small molecules	Rare metabolic disorders, nephrology	Commercial
Dec-25	Orphalan	EU	ORPHELIA	EU	Undisclosed		Small molecules	Neurology/oncology	Commercial
Oct-25	NOVARTIS	CH	AVIDITY	US	12	46%	Antibody oligonucleotide conjugates	Neuromuscular disorders, cardiology	Regulatory
Oct-25	Lilly	US	ADVERUM	US	0.3		Gene therapy	Ophtalmology	Phase 3
Oct-25	Alkermes	EU	Avadel	EU	2.4	28%	Small molecules	Neurology	Commercial
Oct-25	biocryst	US	astria	US	0.7	53%	Monoclonal antibody	Immunology, dermatology	Phase 3
Sep-25	Biogen	US	ALCYONE THERAPEUTICS	US	0.1		Drug delivery	Neurology	Clinical stage (medical device)
Jun-25	SANOFI	EU	blueprint	US	9.1	30%	Small molecules	Hematology	Commercial
May-25	BIOMARIN	US	inozyme	US	0.3	182%	ERT	Rare metabolic and mineral imbalance diseases	Phase 3
Apr-25	NOVARTIS	CH	REGULUS	US	1.7	108%	Antisense oligonucleotides	Nephrology	Phase 1b
Apr-25	MERCK	EU	SpringWorks	US	3.9	26%	Small molecules	Oncology	Commercial
Apr-25	NORGINE	EU	theravia	EU	Undisclosed		Small molecules	Rare diseases	Commercial
Mar-25	Bristol Myers Squibb	US	seventybio	US	0.3	88%	CAR-T cell therapy	Oncology	Commercial
Jan-25	GSK	UK	IDRx	US	1.2		Small molecules	Oncology	Phase 1/2b
Dec-24	Immedica	EU	MARINUS	US	0.2		Small molecules	Neurology	Commercial
Dec-24	Pharming	EU	ABLIVA	EU	0.1	48%	Small molecules	Primary mitochondrial diseases	Phase 2
Oct-24	Ludtech	EU	LONGBOARD	US	2.6		Small molecules	Neurology	Late-stage
Jul-24	Biogen	US	HI-Bio	US	1.8	54%	Monoclonal antibody	Immunology and autoimmune diseases	Phase 3 ready
Apr-24	ONO PHARMA	JP	decipher	US	2.4	75%	Small molecules	Oncology	Commercial
Apr-24	ESTEVE	EU	HRA Pharma	EU	0.3		Small molecules	Rare diseases	Commercial
Apr-24	VERTEX	US	ALPINE ImmuneSciences	US	4.9	67%	Protein-based immunotherapy	Immunology and autoimmune diseases	Phase 3 ready
Mar-24	AstraZeneca	UK	AMOLYT	EU	1.1		Peptides	Rare diseases	Phase 3
Feb-24	GILEAD	US	CYMABAY	US	4.3	27%	Small molecules	Hepatology	Regulatory
Jan-24	SANOFI	EU	INHIBRX	US	2.2	23%	Fusion protein	Endocrinology and metabolic disorders	Phase 2
Jul-23	Biogen	US	REATA	US	7.3	59%	Small molecules	Neurology	Commercial
Jun-23	NOVARTIS	CH	CHINOOK	US	3.5	67%	Small molecules	Nephrology	Phase 3
May-23	Ironwood	US	VectivBio	CH	1	43%	Peptide analogue	Gastrointestinal diseases	Phase 3
May-23	SOBI	EU	cti	US	1.7	89%	Small molecules	Hematology	Commercial
Jan-23	Chiesi	EU	AMRYT	UK	1.5	107%	Peptide	Rare diseases	Commercial
Jan-23	IPSEN	EU	Albireo	US	0.9 (+ CVR)	104%	Small molecules	Hepatology	Commercial
Dec-22	AMGEN	US	HORIZON	EU	27.8	20%	Various	Rare diseases	Commercial
Aug-22	Pfizer	US	GBT	US	5.4	43%	Various	Hematology	Commercial
Aug-22	AMGEN	US	ChemoCentryx	US	3.7	116%	Small molecules	Inflammation, nephrology	Commercial
Jan-22	ucb	EU	ZOGENIX	US	1.9	72%	Small molecules	Neurology	Commercial
Nov-21	novo nordisk	EU	Dicerna	US	3.3	80%	RNAi-based therapies	Various	Phase 3
Sep-21	MERCK	US	ACCELERON	US	11.5	34%	Fusion protein	Pulmonary disorders	Phase 3
Sep-21	SANOFI	EU	Kadmon	US	1.9	79%	Small molecules	Transplant-related disorders	Commercial
Aug-21	SANOFI	EU	TranslateBIO	US	3.2	56%	mRNA	Various	Phase 1/2
Jul-21	AstraZeneca	UK	ALEXION	US	39	45%	Monoclonal antibody	Rare diseases	Commercial

Source: Company reports, LABIOTECH deal tracker, and Stifel IRIS

The December 2024 licensing agreement between Novartis and PTC Therapeutics for a Huntington's disease candidate, which included a US$1bn upfront payment, set an aggressive tone for 2025. While the scale of that transaction's metrics remained unmatched, 2025 still saw a significant number of high-value deals, reinforcing the market's appetite for de-risked assets in specialised therapeutic areas.

A notable concentration of these partnerships has targeted neurology, immunology, and ophthalmology: fields rich with rare and orphan diseases. Beyond paying premiums for clinically validated assets, partners are also playing the long game, actively seeding their pipelines by placing strategic, early-stage bets on the next wave of scientific innovation.

FIGURE 42: SELECTED LICENSING TRANSACTIONS IN 2025-2026

Date	Payer	Country payer	Payee	Country payee	Upfront ($m)	Milestones (up to, $m)	TDV (up to, $m)	Technology	Therapeutic area
Jan-26	Nxera	JP	santhera	CH	40*	165	205	Small molecules	Neurology
Dec-25	Akebia	US	32BIO	US	12	580	592	Fusion protein	Nephrology
Dec-25	REGENERON	US	TESSERA	US	150*	125	275	Gene editing	Metabolic Disorders
Nov-25	Chiesi	EU	ALIADA	US			Undisclosed	BBB crossing platform	Metabolic Disorders
Nov-25	Lilly	US	MEIRAGTx	US	75	400	475	Gene therapy	Ophthalmology
Oct-25	AVIADOBIO	UK	UgeneX Therapeutics	CN			413	Gene therapy	Ophthalmology
Oct-25	Chiesi	EU		US	115	2000	2115	Gene editing	Hepatology
Sep-25	VectorY	EU	ShapeTX	US			1200	Gene therapy	Neurology
Sep-25	Kwangdong	KR	ocugen	US	8	180	188	Gene therapy	Ophthalmology
Sep-25	VERTEX	US	Enlaza	US	45	2000	2045	T-cell engager	Immunology and Autoimmune Diseases
Jul-25	KISSEI	JP	VIRIDIAN	US	70	315	385	Monoclonal antibody	Immunology and Autoimmune Diseases
Jul-25	ALEXION	US	JCR	KR			825	Drug delivery	Genetic and Genomic Medicine
Jun-25	VOR	US	RemeGen Biosciences	CN	125	4000	4125	Fusion protein	Immunology and Autoimmune Diseases
Jun-25	Chiesi	EU	KEY2BRAIN	EU			Undisclosed	BBB crossing platform	Metabolic Disorders
May-25	Angelini Pharma	EU	GRIN	US	50	520	570	Small molecules	Neurology
May-25	Lilly	US	ALCHEMAB	UK			415	Monoclonal antibody	Neurology
Apr-25	Amicus	US	Dimerix	AU	30	560	590	Small molecules	Nephrology
Apr-25	Lilly	US	Creyon	US	13	1000	1013	Antisense oligonucleotides	Rare and Common Diseases
Apr-25	ferrer	EU	prilenia	EU			569	Small molecules	Neurology
Mar-25	MERCK	EU	Abbisko	CN	85	521	606	Small molecules	Oncology
Mar-25	AstraZeneca	UK		CN	75	3400	3475	Protein therapeutics	Autoimmune and Metabolic Diseases
Mar-25	ONO PHARMA	JP	IONIS	US	280	660	940	Antisense oligonucleotides	Oncology
Feb-25	Biogen	US	STOKE	US	165	385	550	Antisense oligonucleotides	Neurology
Feb-25	VANDA	US	AnaptysBio	US	10	35	45	Monoclonal antibody	Dermatology
Jan-25	日本新薬	JP	AB2	US	36	150	186	Protein therapeutics	Immunology and Autoimmune Diseases
Jan-25	novo nordisk	EU	IMMvention	US			Undisclosed	Small molecules	Hematology and Chronic Diseases
Jan-25	日本新薬	JP	REGENXBIO	US	110	700	810	Gene therapy	Metabolic Disorders
Jan-25	Lilly	US	Mediar Therapeutics	US	99	687	786	Monoclonal antibody	Pulmonology
Jan-25	Lilly	US	ALCHEMAB	UK			Undisclosed	Monoclonal antibody	Neurology
Jan-25		CN	CLIMBBIO	US	9	Undisclosed	Undisclosed	Monoclonal antibody	Immunology and Autoimmune Diseases
Jan-25	ALESTA	EU	BicBio	US			Undisclosed	Small molecules	Metabolic Disorders

Source: Company reports, LABIOTECH deal tracker, and Stifel IRIS

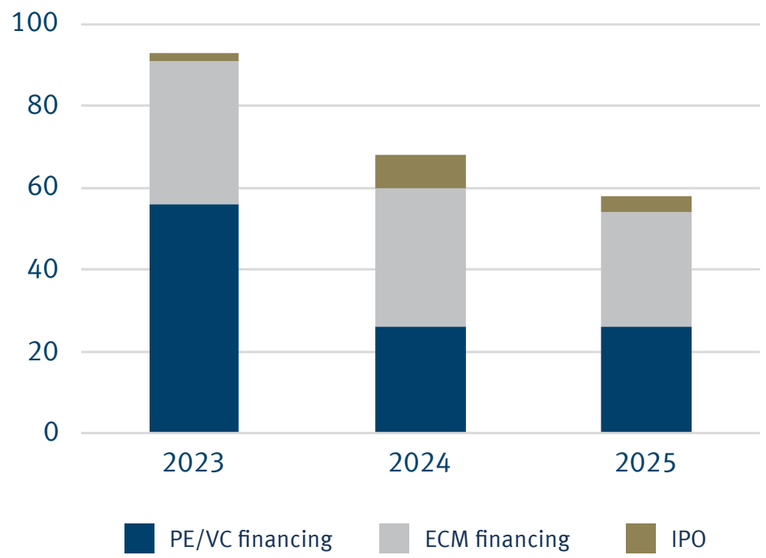
FINANCING FLOWS

The rare-disease sector represents one of the most dynamic and compelling areas within the biopharmaceutical landscape. Far from a niche market, it has evolved into a powerhouse of innovation and a focal point for investment, driven by a powerful combination of high unmet medical need, favourable regulatory frameworks, and attractive commercial models. For investors, it offers exposure to an area where transformative therapies for patients generate both societal value and resilient commercial upside.

MACRO PATTERNS IN CAPITAL FORMATION

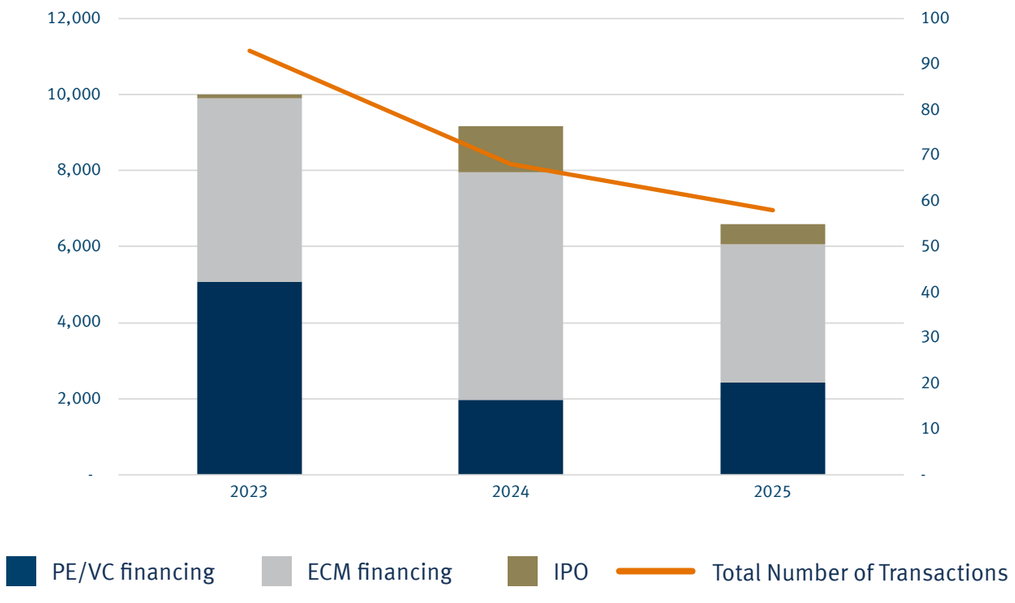
Despite a challenging macroeconomic environment that saw a contraction in broader biotech and healthcare venture capital, the rare-disease sector demonstrated notable resilience and strategic adaptation in its financing landscape from 2023 to 2025. While overall funding volumes moderated, key indicators point to sustained investor confidence and a positive underlying momentum. Most notably, the IPO window for rare-disease companies cracked open in 2024, raising more than US$1bn in a market where IPOs remained scarce, a stark contrast to the US$108m proceeds raised in 2023. Furthermore, after an initial dip, private equity and venture capital financing began to rebound in 2025, signalling a potential return of early-stage investment ahead of broader market trends. This strategic pivot towards public markets and the recovery in private funding underscore the sector's durable appeal, as investors continue to recognise the long-term value in addressing high unmet medical needs, even as they navigate a more selective investment climate.

FIGURE 43: NUMBER OF TRANSACTIONS BETWEEN 2023 AND EARLY NOVEMBER 2025



Source: PitchBook and Stifel IRIS

FIGURE 44: AMOUNT RAISED (US$M) BETWEEN 2023 AND EARLY NOVEMBER 2025



Source: PitchBook and Stifel IRIS

2025 IS SHOWING SIGNS OF RECOVERY

The financing landscape for rare-disease therapeutics showed remarkable resilience through the first three quarters of 2025 (January to early-November), with companies raising nearly US$7bn across 58 transactions. While the average deal size of approximately US$116m was skewed by a handful of mega-deals, a deeper look reveals a highly selective, bifurcated market. Large, de-risked public companies with late-stage assets commanded significant capital, as evidenced by major follow-on offerings from Insmed (US$750m), Cogent Biosciences (US$400m), and uniQure (US$345m).

In contrast, the IPO window remained narrow but showed signs of life, with only a few successful debuts. The US saw three rare disease-oriented IPOs:

- **Aardvark Therapeutics** (US$94m) in February for metabolic disorders, starting with Prader-Willi syndrome
- **Ascentage Pharma** (US$143m) in January for oncology, which includes rare cancers
- **Sionna Therapeutics** (US$219m) in February for its cystic fibrosis pipeline

In Europe, BioVersys went public on the SIX Swiss Exchange (CHF77m), raising capital to advance its pipeline that includes the orphan drug designated fixed combination of alpibectir and ethionamide in tuberculosis.

Geographically, while the United States continues to dominate fundraising, European biotechs are able to secure substantial nine-figure rounds, signalling increasing investor confidence.

FIGURE 45: TOP 20 LARGEST FINANCING IN RARE DISEASE IN 2025 (NOVEMBER 2025)

Date	Company	Amount ($m)	Funding type	Therapeutic area	Geography
Jun-25	insmed	750	ECM financing	Pulmonology, Rare Diseases	
Sep-25	uniQure	345	ECM financing	Genetic and Genomic Medicine, Hematology	
Sep-25	KRIYA THERAPEUTICS	320	PE/VC financing	Ophtalmology, Metabolic Disorders, Neurology	
Jan-25	disc medicine	226	ECM financing	Hematology	
Feb-25	sionna	219	IPO	Pulmonology	
Jul-25	SOLENO THERAPEUTICS	200	ECM financing	Rare Diseases	
May-25	Taysha GENE THERAPIES	200	ECM financing	Neurology	
Feb-25	abcuro	200	PE/VC financing	Musculoskeletal Diseases	
Sep-25	MBX Biosciences	200	ECM financing	Endocrinology and Metabolic Disorders	
Oct-25	Ovid Therapeutics	175	ECM financing	Neurology	
Sep-25	AMYLYX	175	ECM financing	Endocrinology and Metabolic Disorders	
Jul-25	PHARVARIS	175	ECM financing	Bradykinin-Mediated Diseases	
Jun-25	VOR BIOPHARMA	175	ECM financing	Immunology and Autoimmune Diseases	
Mar-25	SURROZEN	175	ECM financing	Ophthalmology	
Oct-25	HEMOB	157	PE/VC financing	Hematology	
Apr-25	AiRNA	155	PE/VC financing	Genetic and Genomic Medicine	
Apr-25	ATSENA THERAPEUTICS	150	PE/VC financing	Ophthalmology	
May-25	azafaros	147	PE/VC financing	Endocrinology and Metabolic Disorders	
Nov-25	AAVANTGARDE	141	PE/VC financing	Ophthalmology	
Jun-25	SPLICEBIO	135	PE/VC financing	Ophthalmology, Genetic and Genomic Medicine	
Jan-25	Ascentage	126	IPO	Oncology	

Source: Company reports, LABIOTECH funding tracker, and Stifel IRIS

WHO INVESTS IN RARE DISEASE?

DEDICATED RARE DISEASE AND ORPHAN DRUG FUNDS

This is a niche but growing category of investors with an explicit mandate to fund companies in the rare-disease space. They combine deep scientific expertise with a specific focus on the unique clinical and commercial pathways of orphan drugs. This specialisation allows them to underwrite risks that generalist funds might avoid.

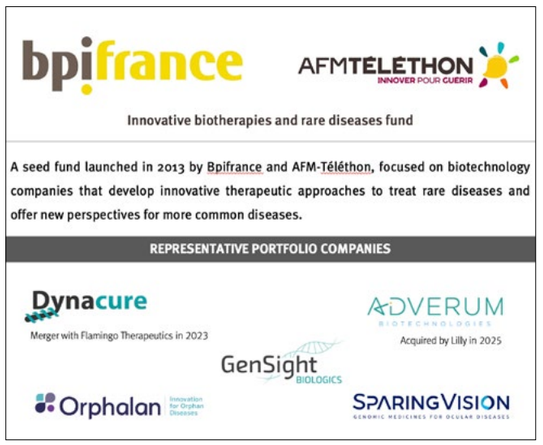
FIGURE 46: SNAPSHOT OF SOFINNOVA TELETHON FUND PORTFOLIO

Source: Sofinnova Partners

FIGURE 47: SNAPSHOT OF CHIESI VENTURES PORTFOLIO

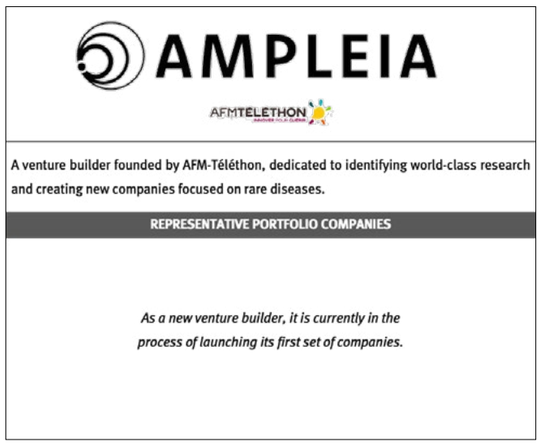
Source: Chiesi Ventures

FIGURE 48: SNAPSHOT OF THE INNOVATIVE BIOTHERAPIES AND RARE DISEASES FUND PORTFOLIO



Source: BPI France, AFM Télethon

FIGURE 49: SNAPSHOT OF THE VENTURE BUILDER AMPLEIA



Source: Ampleia

PATIENT-LED AND DISEASE-FOUNDATION VENTURE FUNDS

Pioneered by organisations like the Cystic Fibrosis Foundation, this model sees patient advocacy groups acting as direct investors. They leverage their deep disease knowledge, patient networks, and long-term capital to de-risk and accelerate programmes, often taking equity stakes to create a self-sustaining "evergreen" funding cycle.

FIGURE 50: SNAPSHOT OF THE CYSTIC FIBROSIS FOUNDATION PORTFOLIO

Source: Cystic Fibrosis Foundation

FIGURE 51: SNAPSHOT OF CURE DUCHENNE PORTFOLIO

Source: Cure Duchenne

FIGURE 52: SNAPSHOT OF THE CHARCOT-MARIE-TOOTH ASSOCIATION PORTFOLIO

Source: Charcot-Marie-Tooth Association

FIGURE 53: SNAPSHOT OF THE RETINAL DEGENERATION FUND PORTFOLIO

Source: Retinal Degeneration Fund

TRADITIONAL LIFE SCIENCE VCS

These are the blue-chip venture capital firms that, while not exclusively focused on rare diseases, are the primary architects of the biotech startup ecosystem. Their deep pockets and company-building expertise make them essential partners for any rare-disease company. They are often the lead investors in large Series A and B rounds.

FIGURE 54: SNAPSHOT OF ATLAS VENTURE PORTFOLIO

Source: Atlas Venture

FIGURE 55: SNAPSHOT OF FORBION PORTFOLIO

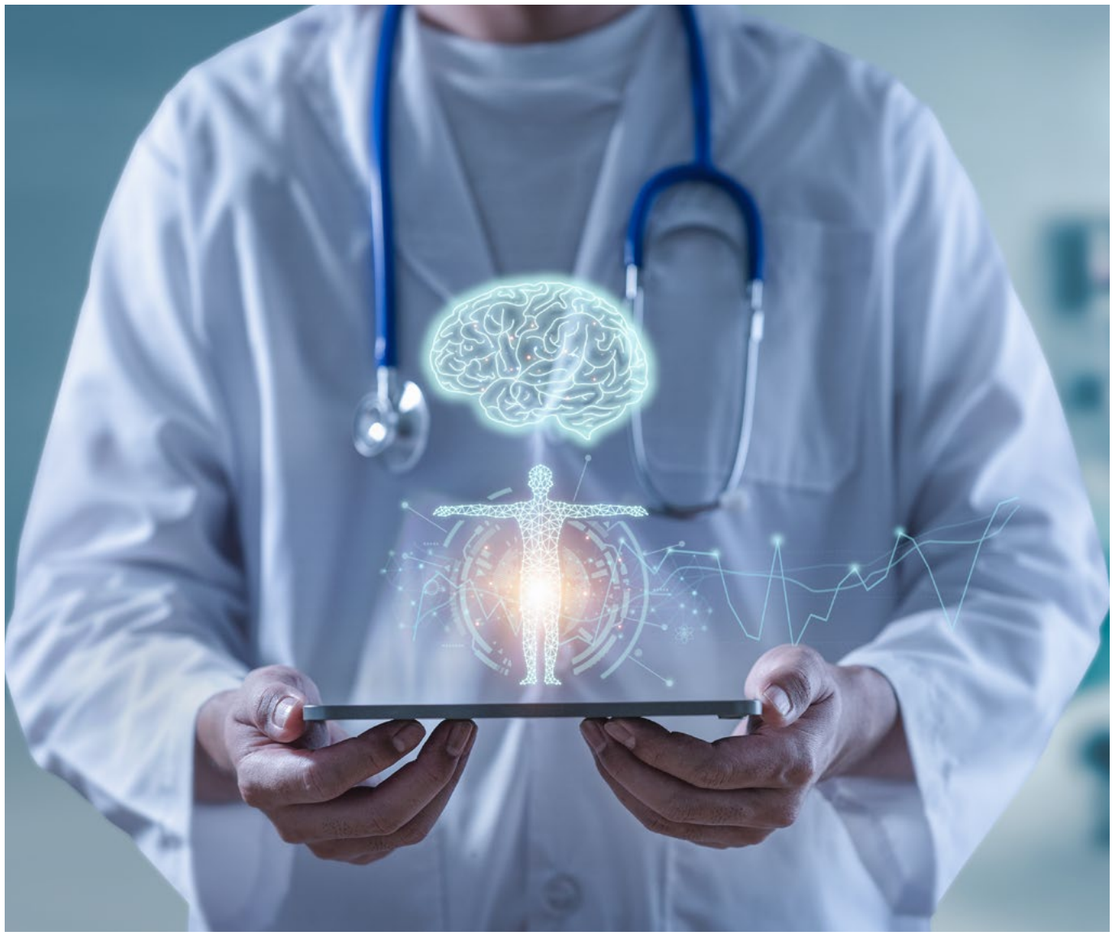
Source: Forbion

FIGURE 56: SNAPSHOT OF BIOGENERATION VENTURES PORTFOLIO

Source: BioGeneration Ventures

FIGURE 57: SNAPSHOT OF JEITO PORTFOLIO

Source: Jeito



CORPORATE AND PHARMA VENTURE ARMS

These are the strategic investment arms of large pharmaceutical companies. Their goal is dual-pronged: generate financial returns and provide the parent company with a window into external innovation. They are critical partners for startups seeking validation, expertise, and a potential future acquirer.

FIGURE 58: SNAPSHOT OF SUNSTONE PORTFOLIO

sunstone
LIFE SCIENCE VENTURES

Focuses on both private and public companies, recently raising a $1.3B fund to continue its strategy of backing innovative biotechs.

REPRESENTATIVE PORTFOLIO COMPANIES

OxThera
TEITUR TROPHICS
step pharma

Source: Sunstone

FIGURE 59: SNAPSHOT OF HEALTHCAP PORTFOLIO

HealthCap

European, early-stage venture capital firm investing in novel therapeutics.

REPRESENTATIVE PORTFOLIO COMPANIES

adcendo
HEM:B
PRIOTHERA
Vivet THERAPEUTICS
vcore pharma

Source: HealthCap

FIGURE 60: SNAPSHOT OF SANOFI VENTURES PORTFOLIO

sanofi ventures

Strategic venture arm of Sanofi, recently recapitalised with $625M to invest in areas including rare diseases and neuro-innovation.

REPRESENTATIVE PORTFOLIO COMPANIES

SPLICEBIO
glycomine
NUVIG THERAPEUTICS
VERALOX THERAPEUTICS
Tisento THERAPEUTICS

Source: Sanofi Ventures

FIGURE 61: SNAPSHOT OF NOVO HOLDINGS PORTFOLIO

novo holdings

A leading international life sciences investor, managing the assets of the Novo Nordisk Foundation. It invests across all stages, from seed (via Novo Seeds) to large, publicly-traded companies.

REPRESENTATIVE PORTFOLIO COMPANIES

HEM:B
coave THERAPEUTICS
Alentis THERAPEUTICS
augustine therapeutics
NMD PHARMA NEUROMUSCULAR DISORDERS

Source: Novo Holdings

FIGURE 62: SNAPSHOT OF ROCHE VENTURE FUND PORTFOLIO

Roche

Roche Venture Fund

The strategic venture fund of Roche, investing globally in innovative biotech and diagnostic companies.

REPRESENTATIVE PORTFOLIO COMPANIES

NMD PHARMA NEUROMUSCULAR DISORDERS
Vivet THERAPEUTICS
Mironid
SAREPTA THERAPEUTICS
minoryx therapeutics

Source: Roche Venture Fund

FIGURE 63: SNAPSHOT OF UCB VENTURES PORTFOLIO

UCB Ventures

A €150M strategic corporate venture fund that invests in innovative science and technology with the potential to transform the lives of patients with severe diseases.

REPRESENTATIVE PORTFOLIO COMPANIES

code bio
SPLICEBIO
IRIS MEDICINE
seamless THERAPEUTICS

Source: UCB Ventures

CROSSOVER AND PUBLIC-PRIVATE INVESTORS

This category includes large, multi-stage investors and hedge funds that invest across the private-public continuum. They are known for leading large mezzanine rounds (Series B/C) and participating in IPOs and follow-on financings, providing crucial scale-up capital.

FIGURE 64: SNAPSHOT OF ORBIMED PORTFOLIO

Source: Orbimed

FIGURE 65: SNAPSHOT OF RA CAPITAL PORTFOLIO

Source: RA Capital

FIGURE 66: SNAPSHOT OF BAIN CAPITAL LIFE SCIENCE PORTFOLIO

Source: Bain Capital Life Science

FIGURE 67: SNAPSHOT OF TCG CROSSOVER PORTFOLIO

Source: TCG Crossover

OUTLOOK: A DECADE AHEAD

The past four decades have transformed the landscape for rare diseases, moving from diagnostic odysseys to the dawn of targeted, hopefully curative, therapies. The next ten years promise an even greater acceleration, driven by a confluence of maturing platform technologies and a deeper biological understanding of disease pathways. While commercial and access hurdles remain critical points, the sheer momentum of innovation suggests a future where previously untreatable conditions become manageable.

Amongst the many challenges yet to overcome, we see two frontiers which will likely define this new era: conquering the brain's last line of defence and mastering the complexities of gene therapy.

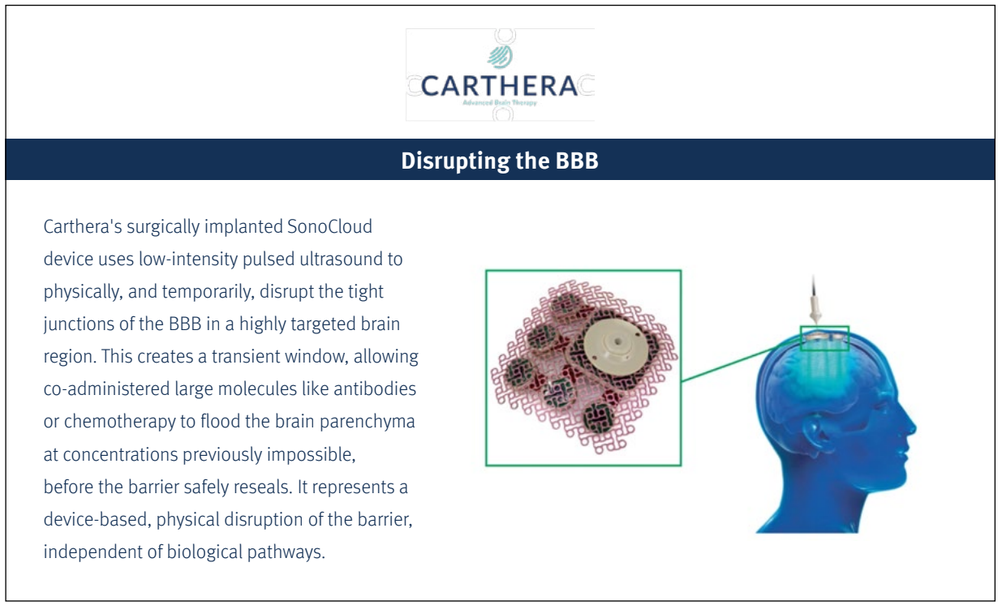
BREACHING THE BLOOD-BRAIN BARRIER

For centuries, the brain remained a therapeutic black box, stubbornly resistant to systemic medicines that proved effective elsewhere in the body. Only in the late 19th century did science begin to understand why, giving a name to this physiological fortress: the blood-brain barrier (BBB). As a complex, tightly regulated cellular shield, it has protected the CNS but has simultaneously locked out countless promising therapies for hundreds of devastating neurological rare diseases. The challenge is not so much a lack of potent drugs, but the inability to deliver them. The coming decade will be defined by the clinical and commercial validation of a diverse array of technologies designed to systematically breach this barrier. This is moving from a theoretical challenge to an engineering reality, with multiple distinct strategies now advancing in human trials.

The field is not relying on a single approach. A rich ecosystem of technologies is advancing in parallel, a clear sign of a maturing and competitive landscape where different strategies will be tailored to specific payloads and diseases.

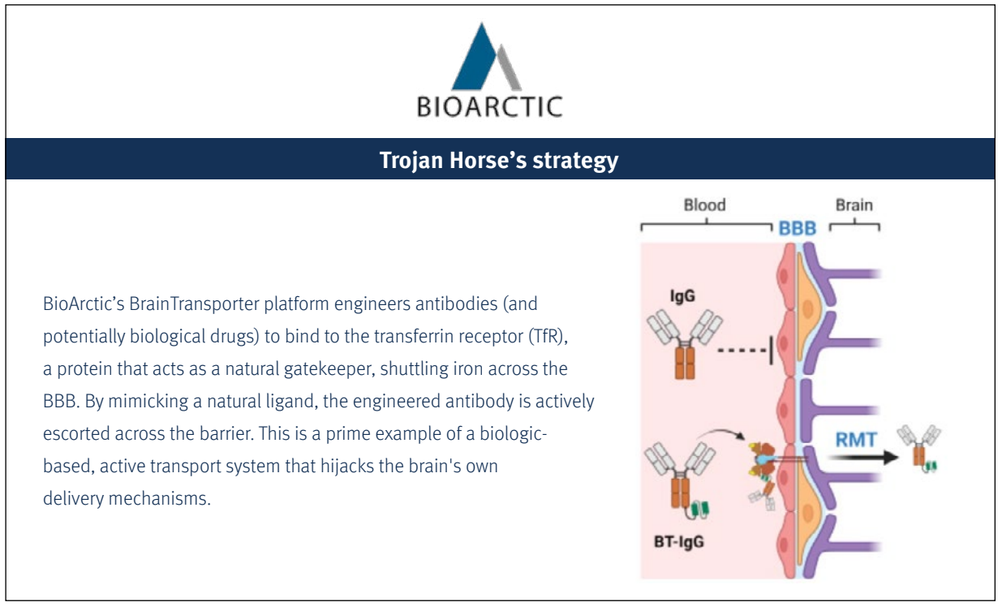
- **Receptor-mediated “Trojan Horses”:** This is perhaps the most elegant biological solution, tricking the brain’s natural defences into granting access. Companies like Denali Therapeutics and Japan's JCR Pharma are pioneering sophisticated “Transport Vehicle” platforms that disguise their therapeutic payloads by fusing them to molecules that bind to the transferrin receptor (TfR). Since the brain requires iron, it actively pulls transferrin across the barrier, unwittingly carrying the drug along with it. The technology licensed by Chiesi from Key2Brain employs this same principle, using engineered single-domain VHH antibodies to target TfR1 and shuttle therapies across the BBB. Taking a broader view, France’s Vect-Horus has developed its VECTrans platform not to target a single receptor, but to screen vast libraries of peptides to discover novel vectors that can hijack a wide variety of the brain’s natural import pathways.
- **Next-generation gene therapy vectors:** This is a more advanced application of the same Trojan Horse principle, where the gene therapy vector itself is engineered to be the key. This has spurred a new generation of AAV capsid engineering. Companies like Shape Therapeutics and Apertura Gene Therapy are using directed evolution and machine learning to design entirely new AAV capsids (the protein shell of the virus) that are purpose-built to cross the BBB after a simple intravenous injection. Apertura's capsids have shown high efficiency at doses 40-fold lower than current CNS-targeted vectors, a potential game-changer for safety and efficacy. The considerable value of this approach is highlighted by Eli Lilly's blockbuster deal to license Sangamo's novel STAC-BBB capsid for use across five CNS targets, a major vote of confidence from Big Pharma.
- **Bypassing or disrupting the barrier:** Some companies are choosing not to “pick the lock”, but to find another door. CERES BRAIN Therapeutics is pioneering a clever "nose-to-brain" pathway for its lead candidate, CBT101. Administered as a simple nasal spray, the drug is designed to travel along the olfactory and trigeminal nerves, which provide a direct anatomical connection to the CNS, thereby completely circumventing the BBB to treat conditions like creatine transporter deficiency. A more physical way of disrupting the barrier is being developed by Carthera with SonoCloud, an implantable ultrasound device that temporarily increases the permeability of the barrier, allowing co-administered drugs to enter.
- **Novel small molecules:** The classic approach of designing small molecules that are inherently brain-penetrant continues to evolve. Companies like Minoryx Therapeutics, with its brain-penetrant candidate leriglitazone, and Augustine Therapeutics, which is developing a new class of brain-penetrant small molecule inhibitors are good examples of this more classic CNS drug development model.

FIGURE 68: CASE STUDY - CARTHERA



Source: Company reports

FIGURE 69: CASE STUDY – BIOARCTIC

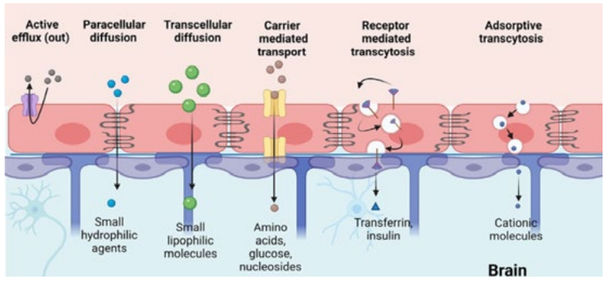


Source: Company reports

FIGURE 70: CASE STUDY – MINORYX THERAPEUTICS

Inherently brain-penetrant molecule

Rather than building a delivery vehicle, Minoryx's strategy is to design a molecule that does not need one. Their lead candidate, leriglitazone, is an inherently brain-penetrant small molecule, a novel agonist of the PPAR-gamma receptor. This approach relies on meticulous medicinal chemistry to optimise the drug's intrinsic properties (size, charge, and lipophilicity) allowing it to passively diffuse across the BBB and engage its CNS target directly.

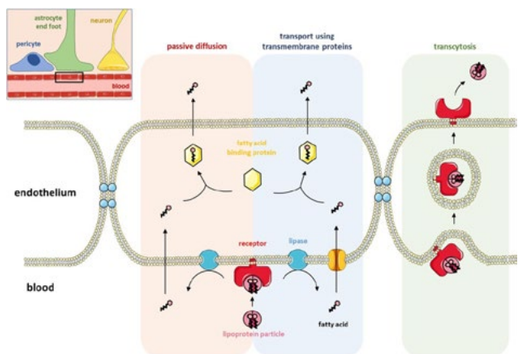


Source: Company reports

FIGURE 71: CASE STUDY – ARTHEX BIOTECH

Fatty acid conjugation

Arthex solves the delivery puzzle for nucleic acid therapies by giving them a "greasy" passport. The company conjugates its antisense oligonucleotide with oleic acid, a fatty acid. This lipid modification dramatically alters the molecule's biodistribution, enabling it to cross the BBB after a standard intravenous injection and achieve broad, homogeneous CNS penetration, a feat that has long plagued "naked" oligonucleotide therapies.



Source: Company reports

THE VOLATILE TRAJECTORY OF GENE THERAPY: RISE, FALL, AND RISE AGAIN?

Gene therapy has lived through a full cycle of hope, backlash, and recalibration. The early breakthroughs created expectations that the field could not yet sustain: approvals like Roctavian opened the door, but durability concerns quickly tempered the excitement; Bluebird carried the weight of multiple clinical holds and heavy commercial pressure; and several high-dose AAV programmes were halted after severe toxicities, including fatal outcomes.

By the time these setbacks accumulated, the perception had settled into something close to resignation: the science was astonishing, but the practical path looked too narrow, too fragile, and too risky for meaningful scale. In the meantime, it has shaped the strategic decisions of several large companies. In 2025, both Vertex and Biogen dismantled their internal AAV research programmes, signalling a strategic pivot away from the high-risk, capital-intensive modality. Roche undertook a deep organisational reset at Spark Therapeutics, absorbing a US$2.4 billion impairment charge and tightening the unit's integration into its core R&D structure.

Compounding the sector's cautious mood, the FDA's recent feedback on uniQure's Huntington's programme raised concerns within the gene therapy field. By ruling that uniQure's external-control data was inadequate for a BLA filing, the agency disrupted a regulatory strategy that the company believed was already in place. This unexpected reversal signalled a potentially stricter FDA stance, challenging the assumption that the agency was becoming more accommodating to innovative trial designs. It is too early to know whether this is specific to the uniQure dataset or a broader inflection in the agency's expectations, but it is not the most reassuring signal for the field.

Despite this, capital and industrial interest have not disappeared, but are maybe more shifted toward repairing the foundations. Investors are increasingly backing companies that focus on the mechanics of delivery, dose, and manufacturability.

- In January 2026, Beacon Therapeutics closed an oversubscribed Series C, raising over US$75m to prepare for the potential launch laru-zova (in P3 in X-Linked Retinitis Pigmentosa, data expected in 2H26)
- In November 2025, AAVantgarde Bio raised US$141m for its dual-hybrid AAV platform.
- In June 2025, SpliceBio raised US$135m to advance its protein-splicing platform, explicitly designed to address AAV's packaging limits without escalating dose.
- In April 2025, Atsena Therapeutics closed a US$150m Series C to progress its AAV.SPR "lateral-spreading" capsid for retinal diseases, a vector designed to improve coverage and reduce reliance on high local dosing.

Fuse Vectors' US$5.2m pre-seed round in February 2025 shows that even at the inception stage, investors are concentrating on vector redesign. Meanwhile, companies like Vivet Therapeutics continue to work on enabling treatment for patients with pre-existing neutralising antibodies, a practical barrier that has quietly excluded a large fraction of otherwise eligible patients.

On the pharma side, renewed activity is similarly selective and disciplined. In April 2025, Eli Lilly licensed Sangamo's STAC-BBB capsid, an improved vector engineered for CNS delivery, acknowledging that existing AAV architectures are not sufficient for reliable brain targeting. This deal sits alongside the expanded Lilly–MeiraGTx ophthalmology agreement from November 2025, which focuses heavily on manufacturing and expression control. Even companies

that have pared back their own gene therapy pipelines, like Roche and Astellas, have retained core capabilities and strategic interest rather than exiting entirely, signalling a belief in the modality's long-term potential. The common thread is not unbridled enthusiasm but a focus on discipline: the sector is being rebuilt around delivery science rather than headline-driven therapeutic ambition.

This sharper focus also clarifies where the next milestone lies. The first decade of AAV proved feasibility in ultra-rare, genetically defined populations. The next decade will test whether those same tools can be applied to larger, more heterogeneous indications with tighter dose constraints and far higher expectations on durability and safety. Several companies are already positioning themselves for that transition: programmes in rare ophthalmic diseases (like Beacon Tx or Spur Tx) are being used as controlled proving grounds before attempting to generalise these delivery principles to much broader retinal or even systemic populations.

The direction of travel is clear: resolve immunogenicity, durability and delivery at the small scale, and the path opens towards indications that look very different in size and complexity from the ultra-rare disorders that defined gene therapy's first commercial era.

Obviously, innovation will not stop at BBB-crossing technologies or gene therapy, these are simply some of the clearest areas where delivery and biology are forcing the sector forward right now. The next wave will extend beyond both. But they capture the same underlying theme: the tools are starting to catch up with the ambition.

MAPPING THE COMPANIES

An extensive part of our work was to identify and reach-out to relevant actors in the rare-disease space, with a core focus on Europe. While we tried to provide a curated mapping of the orphan disease landscape, we do not expect this list to be exhaustive. Moreover, the US section serves as a strategic cross-section of the market leaders and high-impact biotechs, not a complete census.

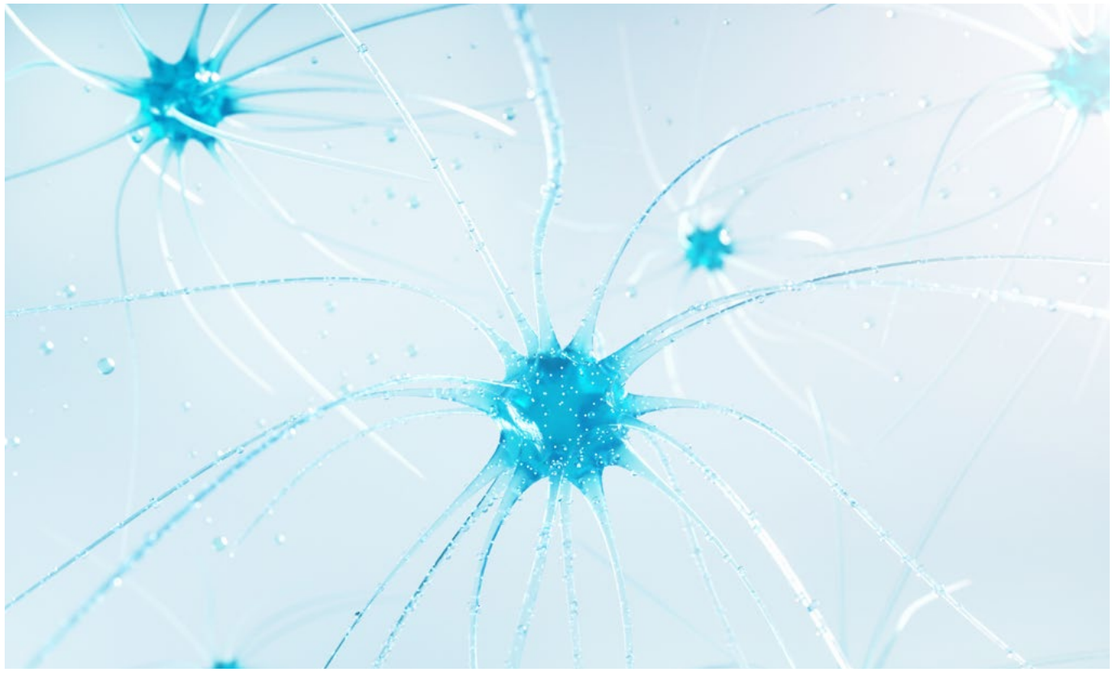


FIGURE 72: THE PRIVATE RARE-DISEASE ECOSYSTEM OF NORTHERN EUROPE

Source: Company reports and Stifel IRIS

FIGURE 73: THE PUBLIC RARE-DISEASE ECOSYSTEM OF NORTHERN EUROPE

Source: Company reports and Stifel IRIS

FIGURE 74: THE PRIVATE RARE-DISEASE ECOSYSTEM OF WESTERN/SOUTHERN EUROPE

Source: Company reports and Stifel IRIS

FIGURE 75: THE PUBLIC RARE-DISEASE ECOSYSTEM OF WESTERN/SOUTHERN EUROPE

Source: Company reports and Stifel IRIS

FIGURE 76: THE US PRIVATE RARE-DISEASE ECOSYSTEM

Source: Company reports and Stifel IRIS

FIGURE 77: THE US PUBLIC RARE-DISEASE ECOSYSTEM

Source: Company reports and Stifel IRIS

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