HEALTH CAPITAL GROUP

Health Capital Group White Paper

Rare Disease Companies in the Public Markets: Challenging Performance Against a Backdrop of Policy Uncertainty

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Executive Summary

- There are more than 10,000 known rare diseases affecting 30 million Americans, and half of those affected are children. Rare diseases are responsible for 35% of deaths that occur in the first year of life.[1]
- The 1983 Orphan Drug Act (ODA) – and policy initiatives in decades that followed – reflected policymakers' recognition that the investment case for rare disease faces challenges, including very small patient populations, difficult timelines, and unique scientific hurdles. These policies have spurred billions in investment resulting in hundreds of new treatments for rare disease patients with acute unmet needs.
- Despite great progress, 95% of orphan conditions do not yet have FDA-approved treatments.[2] Yet the policy environment that has encouraged investment into treatments appears to have reversed course in recent years. The Inflation Reduction Act (IRA) subjects orphan drugs to potential price controls; the Orphan Drug Tax Credit has been reduced and targeted for further reductions; the FDA's accelerated approval pathway has been subject to intense scrutiny and potentially reduced reimbursement; and many states are adopting prescription drug "affordability" boards (PDABs) using methods borrowed from European health technology assessment systems that systematically limit economic returns for rare disease drugs.
- Seemingly small changes like the single-indication limit for orphan drugs can have outsized consequences on investor expectations. We find that 18% of orphan drugs secured at least one additional approved orphan indication, with the average drug in that subset earning 1.8 additional approvals. Assuming each orphan indication treats the same number of patients, limiting the average drug in the clinic to just one orphan indication would reduce the number of expected patients treated by over 24%.
- Our research examines how rare disease investors have been impacted by the shift in the policy environment over the past five years. We find that rare disease companies have experienced significant funding and market performance challenges. Rare disease companies

[1] www.rarecoalition.com
[2] ibid

lost nearly 7% in market value per year versus an annual loss of 1.3% per year for non-rare companies. The lowest-performing group in our trading index was clinical stage rare disease companies – which exhibited nearly a 10% annual decline over the period.

- Only 1/3 of commercial-stage rare disease companies with significant revenues (over $100 million per year) were profitable in 2022, compared to more than half of comparable non-rare commercial stage companies. This reflects the fact that commercial-stage rare disease companies invested over 40% of their revenue into R&D in 2022 compared to 17% for non-rare companies. The select group of profitable commercial stage rare disease companies continued to invest almost 30% of their revenues in R&D (vs. under 20% for non-rare) in 2022.
- Clinical stage biopharmaceutical companies often de-risk ongoing R&D by signing licensing deals with more established companies, but rare disease companies are much less likely to rely on licensing revenue than non-rare counterparts. Our analysis shows that for every licensing dollar received, clinical stage rare disease companies invested $4.32 of their own funds into R&D, compared with $1.74 for non-rare clinical stage companies. This disparity is reflected in the market for licensing and partnership revenues, where in 2022, the average value of deals at signing was down 45% for rare disease (vs. 21% decline for other categories) and total potential deal value was down nearly 30% for rare disease but up nearly 7% for all therapeutics.[3]
- The serious challenges we have identified in the funding environment for rare disease R&D have coincided with five years of growing policy pressure and uncertainty. The relatively sudden shift away from the previously robust system of incentives that spawned a generation of treatments for rare disease patients appears to have placed rare disease investors under a cloud of doubt. There remains an extremely large unmet medical need for 30 million patients across thousands of rare diseases, even after several decades of the current level of policy encouragement. If policymakers wish to spur investment in rare disease innovation, they will need to reassure investors that further policy deterioration is off the table.

[3] Global Genes NEXT Report, July 2023.

Introduction

The economic premise of developing treatments for rare diseases is naturally challenging. About 30 million Americans have a rare disease (defined as a condition with less than 200,000 patients), spread out across more than 10,000 distinct diseases.[4] Despite significant progress in recent decades, roughly 95% of rare diseases do not yet have an FDA-approved treatment. The average development time for a rare disease treatment is over 15 years, compared with 10 years for non-rare treatments, and more than half of new rare disease treatments are first-in-class treatments (compared to less than 25% of new non-rare treatments).[5] Recruiting a sufficient number of patients for clinical trials in diseases with very small patient populations can be expensive and time consuming. More than 50% of identified rare disease patients are also children,[6] which presents special challenges in drug development. Often there is a lack of well-established endpoints and understanding of a rare disease's natural progression, and disease heterogeneity further complicates drug development and leads to an uncertain regulatory outcome. Given these challenges, investors considering the relative commercial prospects for rare disease must be realistic about the size of the potential market and the potential risks of failure.

Investors and policymakers have recognized the significant unmet medical need presented by rare disease patients and their families. Billions of dollars are invested annually through a funding ecosystem that includes venture capital, privately funded companies, public firms, tax credits, NIH grants, charitable foundations, and other sources. Private (non-governmental) sources account for 2/3 of all biopharmaceutical R&D.[7] US public policy has been a key element of supporting such investments since the 1983 Orphan Drug Act (ODA), which provided enhanced exclusivity and tax credits for developing rare disease treatments. That policy environment has been changing over the past few years, leading some investors to question the long-term viability of the rare disease commercial model. This white paper examines how rare

[4] See www.rarecoalition.com.
[5] Ibid.
[6] Ibid.
[7] See Congressional Budget Office, "Research and Development in the Drug Industry," May 2021. Available at https://www.cbo.gov/system/files/2021-04/57025-Rx-RnD.pdf.

disease investments have fared over the past five years and illustrates some of the potential risks inherent in the policy changes that are now in motion.

Growing Policy Uncertainty for Rare Disease

For decades, US public policy has been geared toward strengthening incentives for rare disease drug development. The ODA introduced the Orphan Drug Tax Credit (ODTC) and added market exclusivity incentives for orphan approvals; the FDA's accelerated approval pathway was created in 1992[8] and reinforced by Congress in 2012 specifically for use in rare disease; the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 created the Breakthrough Therapy designation and extended the priority review voucher program to include rare pediatric indications;[9] the 21st Century Cures Act of 2016 included several provisions to encourage additional rare disease investment, and so on. These incentives – and the expectations that they would continue – sparked private-sector investments of billions of dollars annually in rare disease R&D. The result has been a steady flow of innovation and hundreds of new drugs targeting very small patient populations with acute unmet needs.

Despite this progress, 95% of all orphan conditions do not yet have FDA-approved treatments; the policy imperative for supporting rare disease research has not changed.[10] In recent years, however, many of these policies have been weakened or threatened, including a significant reduction in the ODTC from covering 50% to 25% of clinical development costs, which was adopted in 2017 (after a proposal to eliminate it entirely was rejected in final negotiations). The Inflation Reduction Act of 2022 (PL #117-169) subjects orphan drugs with more than one designation to potential price controls beginning in 2026, and there have been numerous proposals to impose a one-designation limit on the ODTC (or eliminate it). There are current proposals to curtail or eliminate the intent of the accelerated approval pathway, which was created to make promising treatments available earlier for patients who are often in immediate need. For example, in 2022, the Center for Medicare and Medicaid Innovation announced that they were exploring a model targeting accelerated approval drugs in Medicare Part B, proposing

[8] https://rarediseases.org/wp-content/uploads/2021/06/NRD-2182-Policy-Report_Accelerated-Approval_FNL.pdf
[9] https://www.govinfo.gov/content/pkg/COMPS-9932/uslm/COMPS-9932.xml
[10] See www.rarecoaltion.com

a special mandatory rebate on such drugs. A growing number of states have begun implementing or exploring the use of prescription drug "affordability" boards (PDABs), employing methods borrowed from European health technology assessment systems that would introduce additional uncertainty specifically into investments in rare disease, for example, by adopting price limits based on Quality-Adjusted Life Years (QALYs).[11] Such methods systematically ignore key elements of patient and societal value without accounting for disease severity, inherently undervaluing potential gains for rare disease patients (as well as their lives).[12] In addition, CMS recently proposed a Medicaid drug price "verification" survey, which would set the stage for further mandated price reductions.[13]

The recent focus on additional orphan designations for the same product provides a useful illustration of how investor expectations might change because of policy uncertainty even if a potential product is years away from launch. Companies face long, well-known odds in achieving a first orphan drug approval. A first approval is no guarantee of profitability; as we show below, most commercial-stage rare disease companies remain unprofitable. A second approved indication can significantly increase the number of treatment-eligible patients for an approved product, giving companies a good reason to keep investing in R&D after the first approval. However, under the new IRA rules and previously-proposed ODTC changes, a second orphan designation can also come with obvious costs if it would make a drug eligible for Medicare price limits or potentially ineligible for a tax credit. Some companies have already declared publicly that pursuing a second designation for already-approved products is no longer feasible given the IRA rules.[14]

We analyzed data provided by Chambers et al[15] listing every approved indication for every drug originally approved as an orphan drug to test whether the additional indication issue

[11] See https://nashp.org/state-strategies-to-lower-drug-prices-new-legislative-and-medicaid-models/

[12] See https://www.nopatientleftbehind.org/getting-the-math-right-when-valuing-new-medicines

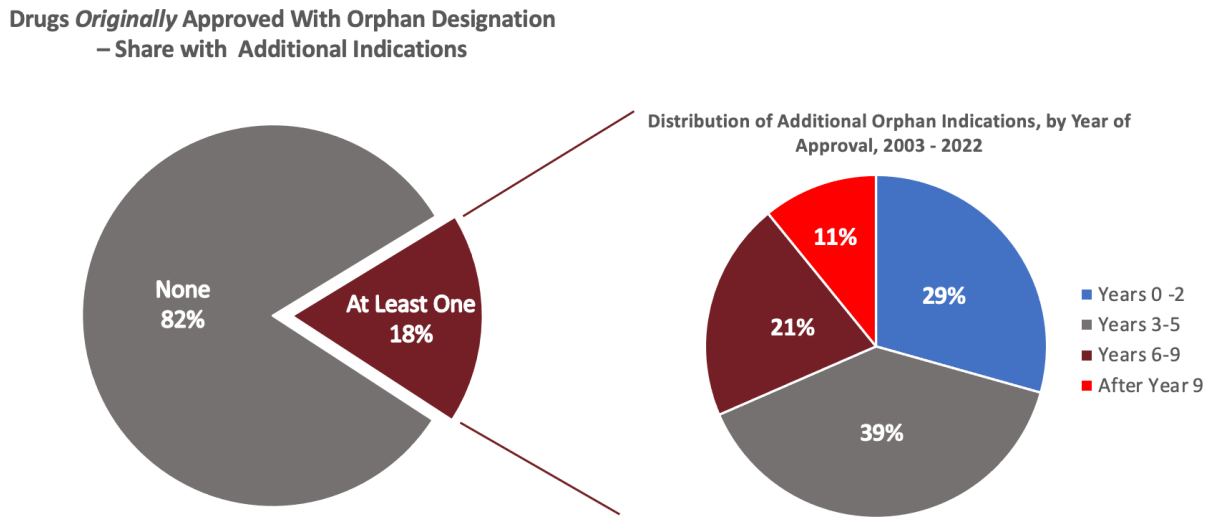
[13] www.federalregister.gov/documents/2023/05/26/2023-10934/medicaid-program-mislassification-of-durgs-program-administration-and-program-integrity-updates

[14] See https://healthpolicy.usc.edu/article/the-inflation-reduction-act-is-already-killing-potential-cures/

[15] Chambers JD, Clifford KA, Enright DE, Neumann PJ. Follow-On Indications for Orphan Drugs Related to the Inflation Reduction Act. *JAMA Network Open.* 2023;6(8):e2329006. We thank the authors for providing their data.

is likely to matter to investors broadly. The FDA approved 372 orphan indications between 2003 and 2022 for the 280 drugs that were first approved as orphan drugs (out of over 900 total approved indications over that time). Of the 372 orphan indications, 92 were additional indications for drugs originally approved as orphan drugs, with the mean additional approval occurring 4.6 years after original orphan approval. Figure 1 shows the distribution of the timing of when those additional orphan indications were approved.

Figure 1. Distribution and Timing of Additional Orphan Approvals for Drugs First Approved as Orphan Drugs, 2003-2022



Source: Health Capital Group analysis of data provided by Chambers et al

We find that 50 of the 280 approved orphan drugs (18%) secured at least one second approved orphan indication, with the average drug in that group getting 1.8 additional approvals. Roughly 1/3 of all subsequent approvals occurred at least six years after the initial orphan approval. Later approved additional indications included treatments for rare heart conditions, multiple rare cancers, graft vs. host disease, mesothelioma, generalized myasthenia gravis, and many other conditions without prior treatments. In some cases, the additional indications have doubled or tripled the number of rare-disease patients who could potentially benefit from treatment – or increased it from a few hundred per year to a few thousand.

Given the long odds of getting a first indication, a potential 18% chance of getting 1.8 additional indications can significantly bolster the investment case and the number of treated

patients. Assuming each indication is for roughly the same number of rare disease patients, limiting orphan drugs to just one approved indication before subjecting them to price controls would reduce the expected number of treated patients by over 24%. While most orphan drugs have not received more than one approved orphan indication historically, the *ex-ante* prospect that additional indications *might* happen is enough to provide substantial additional motivation for investors, especially when they are contemplating additional investments for products that have already met key safety hurdles.

New Evidence on Rare Disease Company Financial Performance

To examine the degree to which such concerns are weighing on investors in existing companies, we assembled a data set of 698 biopharmaceutical firms that traded on a US public exchange anytime over the past five years (September 2018 through September 2023). We included companies with a starting price of at least $2 per share either at the beginning of the period or whenever they started trading during the period. We assigned each company to one of four groups: commercial stage rare disease, commercial stage non-rare, clinical stage rare disease and clinical stage non-rare.

We defined clinical stage companies as those without an FDA-approved product or those with only one product approved within the prior 12 months. We defined "rare" companies to include clinical stage companies where the lead indication or compound has been designated with orphan status or where the target disease is clearly a rare disease. For commercial stage companies, we define "rare" companies as those with at least 80% of their revenues from rare disease drugs. Table 1 summarizes the key characteristics of our sample.

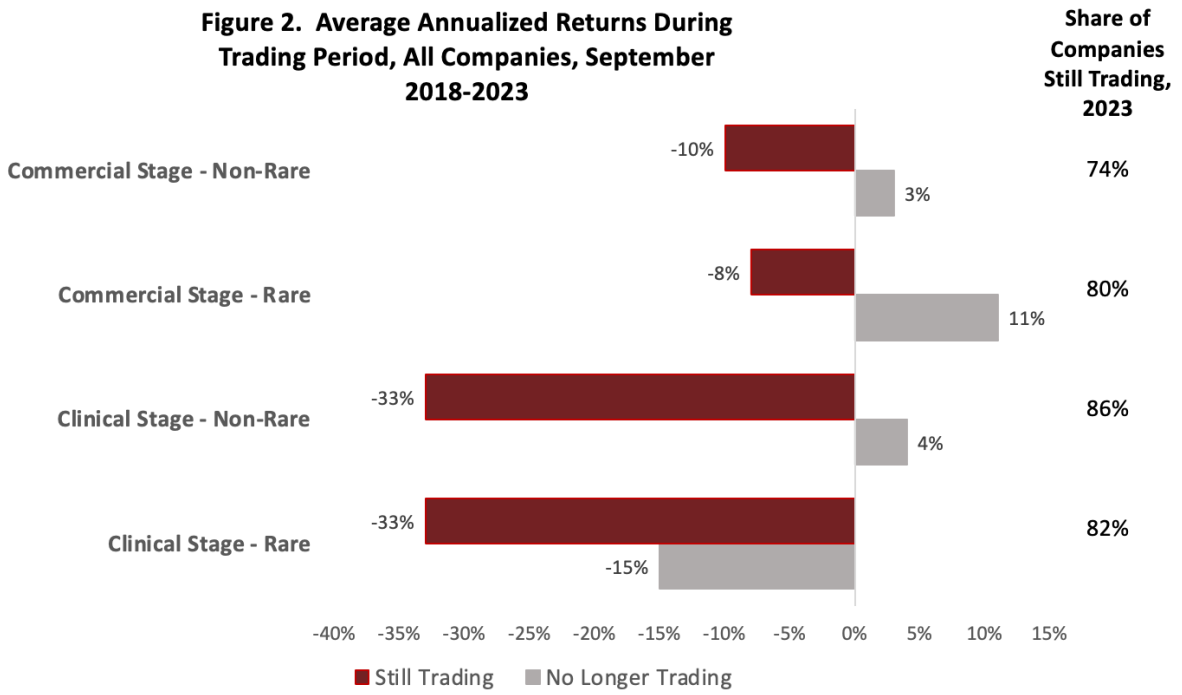
Table 1. Characteristics of Public Biopharmaceutical Companies, September 2018 – September 2023

	Total Companies	Average 2022 Revenue	Average 2022 R&D	Avg R&D/Avg Revenue	Average Market Cap, Sept 2023
Non-Rare Clinical	279	$ 37,729,680	$ 65,647,718	174%	$ 602,750,749
Non-Rare Commercial	125	$ 6,222,142,504	$ 1,047,437,117	17%	$ 21,066,806,607
Rare Clinical	239	$ 18,954,240	$ 81,950,184	432%	$ 605,868,672
Rare Commercial	55	$ 771,900,244	$ 367,506,556	48%	$ 5,698,142,613
All Companies	**698**	**$ 1,097,084,861**	**$ 256,325,424**	**23%**	**$ 4,646,205,383**

Source: Stock data from Yahoo Finance; Health Capital Group LLC analysis

Table 1 shows that rare disease companies in our sample invested much more in R&D relative to revenue than their non-rare counterparts. As a group, commercial stage rare companies in our sample invested nearly 50% of their revenues into R&D in 2022 vs. 17% of revenue for non-rare commercial stage firms. While clinical stage companies do not have significant product revenues, they earn revenue through licensing and partnership deals. One way to measure the intensity and risk of R&D spending for clinical stage companies is to examine how much of their own investors' money they are putting at risk, as opposed to their partners' money. Clinical stage rare disease companies in our sample invested $4.32 for every licensing/partnership dollar, compared with $1.74 for non-rare companies, a significant difference highlighting the relative risks of rare disease investment.

Our objective is to understand how investors view rare disease relative to non-rare in the context of the policy changes experienced in recent years and forecasted to follow. We examined the stock market performance of each of our company categories over the past five years, taking two distinct approaches. The first approach, summarized in Figure 2, calculated the annualized return for each stock in our universe during the time it was actively traded. Many companies entered the market over our trading period, and many exited – sometimes because of an acquisition, and sometimes due to bankruptcy or delisting.

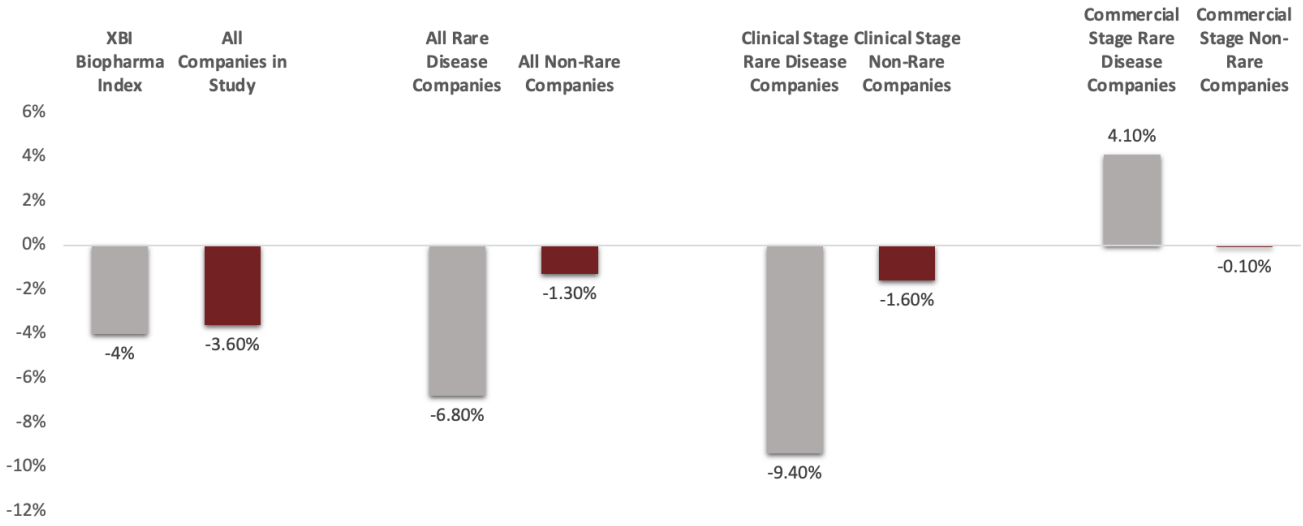


As shown in Figure 2, companies that are still trading have, on average, lost money for investors over the period in each of the four categories. For three of the four categories, these losses were offset to varying degrees by positive returns for companies that exited. For example, the 74% of "remaining" commercial stage non-rare companies from our company universe have lost, on average, 10% per year over the period. But companies in that category that have disappeared have, on average, provided investors a 3% annualized gain. Commercial stage rare companies that remain show similar losses of roughly 8% per year but had better (though fewer) "exits," gaining 11% per year on average. Clinical stage rare disease companies and non-rare companies that remain have both shown substantial losses, but those losses were significantly compounded for rare disease companies, because nearly 20% of them have exited trading, on average at a large loss as well. While the other three categories each have some degree of offsetting gains upon exit, clinical stage rare disease companies have been the most challenged because the companies that "exit" also generated significant investor losses.

We also examined how the general premise of investing in rare disease has changed over the past five years. We constructed a monthly trading index for each of our four categories, averaging the monthly performance for all active stocks in each category for each month over

the five-year period to provide a "portfolio" view of what an investor in each category experienced over the five-year period. These results are summarized in Figure 3:

Figure 3. Annualized Market Basket Returns, Sept 2018-Sept 2023



Source: Stock data from Yahoo Finance; Health Capital Group LLC analysis

Key results from this analysis include:

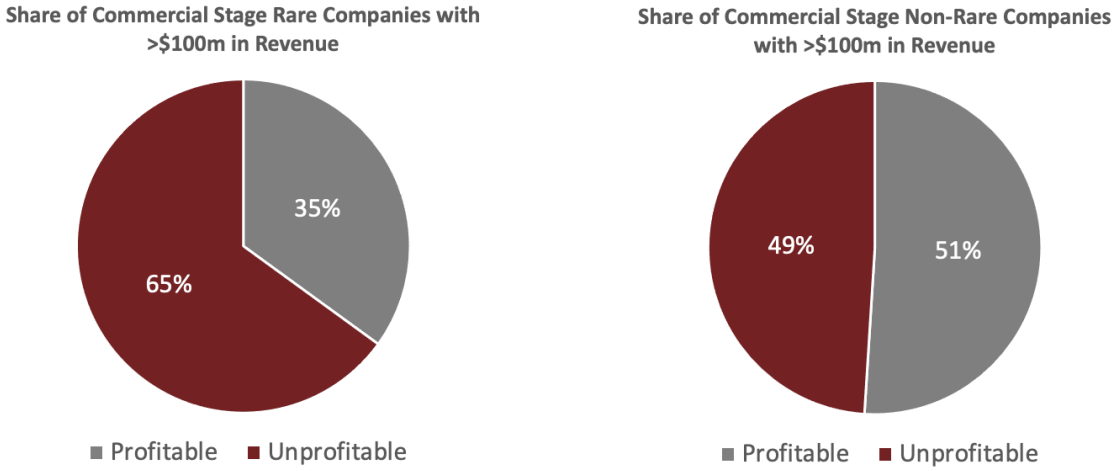
- Our overall sample tracks closely with the XBI index (the most common index tracking the broad biopharmaceutical company universe). Both indices lost about 4% annually.
- Our rare disease trading index declined by nearly 7% per year over the past five years versus an annual decline of 1.3% per year for our non-rare index.
- Our index for commercial stage rare firms fared best, gaining over 4% annually (vs. a flat market for non-rare commercial stage companies). As noted in Figure 2, these gains are driven by a handful of acquisitions in the space.
- The lowest-performing index was the clinical stage rare companies, which declined by over 9% per year over the period, compared to a less than a 2% annual decline for our clinical stage non-rare index.

Commercial Stage Rare Disease Companies – Ongoing R&D Highlights Policy Sensitivity

Our data show that commercial stage rare disease companies – which are most immediately impacted by potential policy pressure – operate differently than commercial stage

non-rare companies. We examined net income for companies that have reached a threshold of $100 million in revenue. The results are shown in Figure 4.

Figure 4. Share of Profitable and Unprofitable Rare and Non-Rare Commercial Stage Firms with at Least $100m in Revenue, 2022

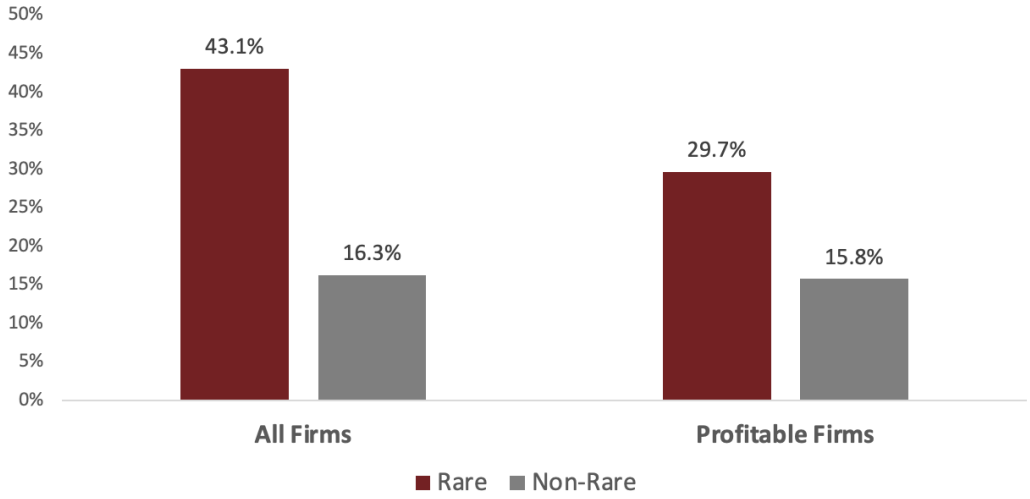


Source: Stock data from Yahoo Finance; Health Capital Group LLC analysis

Despite their relatively strong stock market performance, commercial stage rare disease companies with significant revenues (over $100m per year) are still, as a rule, unprofitable. Only about 1/3 of such companies were profitable in 2022, while over half of non-rare commercial stage companies with over $100m in revenue were profitable. The median commercial stage rare disease company in our sample requires more than twice as much revenue to become profitable compared to the median commercial stage non-rare company.

One reason why commercial stage rare disease companies remain unprofitable is their significant ongoing investment into R&D. Figure 5 shows the average R&D as a share of revenue for commercial stage rare and non-rare companies with at least $100m in revenue in 2022.

Figure 5. Share of Revenue Invested in R&D, Commercial Stage Firms With >$100 Million in Revenue, 2022



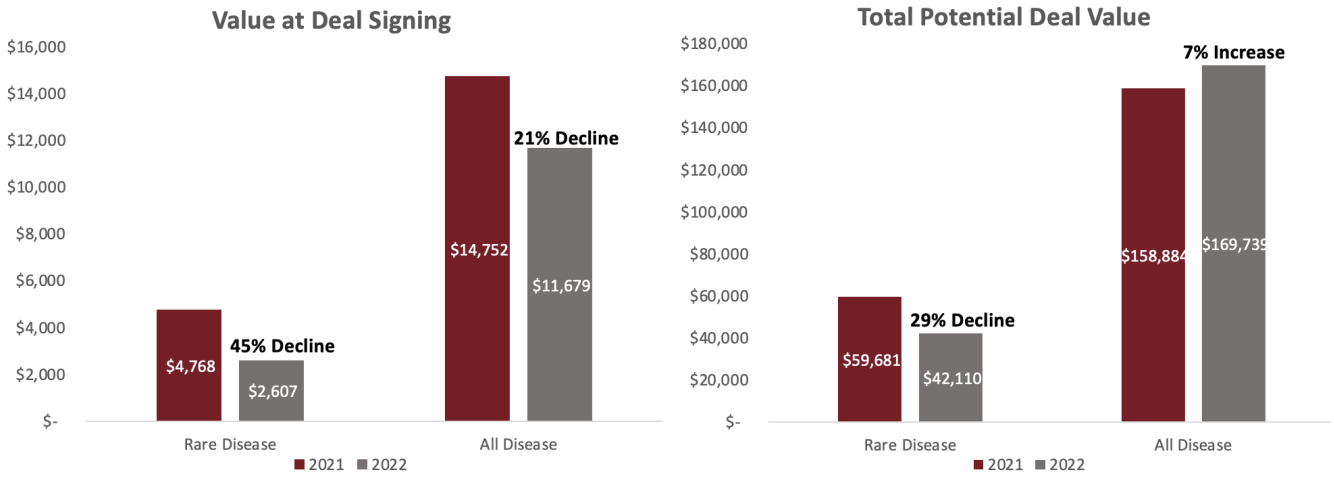
Source: Stock data from Yahoo Finance; Health Capital Group LLC analysis

Commercial stage rare disease firms continue to invest over 40% of their revenue into R&D, and even profitable firms continue to invest roughly 30% into R&D. Profitable rare and non-rare firms achieved similar profit margins (roughly 24%) despite the higher R&D investment levels of commercial stage rare disease firms. These high levels of investment make commercial stage rare disease companies particularly susceptible to concerns about the policy environment.

Clinical Stage Rare Disease Companies – Significantly More Reliant on Capital Markets

Major investments in rare disease come from venture capital, public markets (equity and debt), and through partnership deals with larger biopharma or private equity sources. Clinical stage companies often turn to more established biopharma companies to de-risk and fund R&D investments. Such deals may come with a significant payment upon signing that can help fund clinical trials and the regulatory process, and often provide much more potential value in the event of success. Clinical stage firms may also be acquired in full, providing returns to earlier investors. As shown in Figures 2 and 3, the public capital markets have not been kind to early-stage biopharmaceutical investments. The licensing and partnership market has been similarly challenging, especially for rare disease companies. The significant decline in the partnership and licensing market in 2022 is illustrated in Figure 6.

Figure 6. Changes in Dollar Value of Licensing/Partnership Deals for Rare and Non-Rare Companies, 2021 - 2022



Source: Global Genes *NEXT* Report, July 2023

Rare disease companies saw a nearly 50% decline in the cash available to them in the form of partnership deals in just one year and saw a nearly 30% decline in total potential deal value. The non-rare market experienced a much smaller decline in near term value, and an *increase* in total potential deal value.

We used our dataset to evaluate the licensing revenue picture over a longer time horizon. We identified over $55 billion invested in rare disease research over the past five years in our universe of publicly traded clinical stage rare disease companies. We then evaluated the share of R&D expenses during the five years that were "covered" by licensing/partnership revenue for clinical stage companies and compared those ratios based on the companies' overall stock performance over the period. The results are shown in Table 2.

Table 2. Share of R&D Investment Covered by Licensing Revenue, Clinical Stage Companies, by Stock Market Performance Category, 2018-2023

	Rare	Non-Rare
Lost >80% of Value	18.8%	44.4%
Lost 50% - 80%	39.3%	67.8%
Lost Under 50%	36.5%	86.6%
Gained Up to 25%	33.5%	31.5%
Gained 25% - 100%	11.4%	32.4%
Gained > 100%	45.0%	53.3%
Total	**28.8%**	**51.0%**

Clinical stage rare disease firms have significantly less coverage from licensing revenue to support their ongoing R&D. Overall, clinical stage rare disease companies cover less than 30% of their R&D investment through partnerships, while non-rare firms cover more than 50% of their investments. This difference is even larger for struggling companies. This means that rare disease companies must be more reliant on the private and public markets for their funding. Clinical stage rare disease companies are "working without a net" more often than non-rare companies, leaving them especially sensitive to investor perceptions about the ongoing commercial model for rare disease products.

Conclusions

Our analysis shows that rare disease companies have faced acute funding and valuation challenges over the past few years. Clinical stage rare disease companies have experienced very large annual declines in value over the past five years, reflecting a lack of investor confidence in the business model. Clinical stage rare disease companies also face a shortage in the supply of ready capital from potential long-range development partnerships. Commercial stage rare disease companies continue to invest heavily into R&D, but most remain unprofitable even when they have significant revenue, meaning that they too are vulnerable to ongoing capital market skepticism. Rare disease policy uncertainty creates additional pressure in this already fragile funding environment. Seemingly minor changes like the Inflation Reduction Act's limits on multiple orphan indications for the same product can have disproportionate consequences on the rare disease investment thesis.

The prospect of strong, long-lived returns for approved orphan drugs is a crucial motivation for continued investment in R&D, and the policy environment has been a cornerstone of those expectations since 1983. The serious challenges we have identified in the funding environment for rare disease R&D have coincided with five years of growing policy pressure and uncertainty. The relatively sudden shift away from the previously robust system of incentives that spawned a generation of treatments for rare disease patients appears to have placed rare disease investment under a cloud of doubt. There remains an extremely large unmet medical need for 30 million patients across thousands of rare diseases, even after several decades of the current level of policy encouragement. If policymakers wish to support the market for investing

in rare disease innovation and ensure the steady supply of rare disease treatments to address the deep reservoir of unmet medical need for the nearly 10% of the US population living with a rare disease, they will need to reassure investors that further policy deterioration is off the table.