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Investment And Acquisition In Rare Diseases

by Jo Shorthouse

In Vivo talks to investors, analysts and companies in rare disease about the challenges they face to innovate and to grow.

Coming off the back of a challenging 2021 and 2022, many industry analysts cautiously forecast a bigger 2023, more deals, mergers and IPOs. While this has not happened, bar a few delicious morsels such as *Pfizer Inc.*'s $43bn *Seagen Inc.* buyout, the year did see a humbled pharma industry cherry pick mid-sized deals to fill pipelines in readiness of the dreaded patent cliff in the coming decade.

Industry and the markets are still grappling with the idea of value. What does a good deal look like? What does value look like, for all parties, with omnipresent rising interest rates, inflation, regulatory changes, macro-economic trends plus geopolitical uncertainty? These challenging conditions make navigating the growth landscape as tough as it has been for the past few years. The XBI Biotech Index has fallen by more than 10% this year while other generalist indexes, such as the S&P 500 have grown by around 13%.

Health Capital Group has created a rare disease trading index which declined by nearly 7% per year over the past five years versus an annual decline of 1.3% per year for its non-rare index. The worse performing companies within that index were clinical-stage rare disease companies, which declined by 9% per year over the period, compared to a less than 2% decline for clinical-stage companies in non-rare diseases, see *Exhibit 1*.

"Rare disease companies have been more profoundly impacted [than other types of biotech company] partly because their usual means of accessing capital – the IPO market and/or acquisition by bigger companies – have been severely depressed. This is partly a function of interest rates and general risk aversion on the part of investors, but because rare disease companies are more specifically dependent on the confidence of such investors, they have had a harder time than the average company," Neal Masia, Health Capital's CEO, and Pfizer's former

chief economist, told *In Vivo*.

Exhibit 1:

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Investment: A Slow Turn In The Road

Whether it is downgraded legislative incentives, macro-economic conditions or both, the reality is that rare disease companies have been hit both in the public markets as seen above, but also with venture capital and private equity investments.

Certain companies are still successfully financed, however. "If a company can find a novel innovation that tackles a very defined high unmet need with a de-risked mode of action that is highly attractive to VCs," said Søren Møller, Novo Holding's managing director of seed investments.

Novo Holdings was one of four investment funds that took part in the $80m series B financing of rare neuromuscular firm *NMD Pharma* in November 2023. The proceeds of which will be used to complete three Phase II studies with NMD670, the company's lead ClC-1 inhibitor. The three studies will evaluate the novel mechanism of ClC-1 inhibition in myasthenia gravis, spinal muscular atrophy and Charcot-Marie-Tooth disease, respectively.

"The market rewards outstanding clinical data. It is very tough on programs that are not designed to deliver an outstanding clinical study, maybe they were designed as a de-risking study towards the big trial, and then the market suddenly expects that you should have done a big study," explained Møller.

Anecdotally, people within rare disease companies had become a lot more optimistic about financing than they were three to six months ago, said Matthew Wood, director of Oxford Harrington Rare Disease Centre, a transatlantic accelerator.

Wood has founded several rare disease companies: *Evox Therapeutics Limited* and *PepGen*, which went public in May 2022, using the $124m it earned to fund clinical development programs in its Duchenne muscular dystrophy pipeline. Orfonyx was formed in late 2022, and Isogenix in 2023, both Oxford University spinouts earned UK funding in the last 12 months. (Also see "*Finance Watch: Bausch + Lomb Completes Split From Bausch Health Via IPO*" - Scrip, 6 May, 2022.)

In Wood's recent firsthand experience, it is seasoned and knowledgeable investors that are coming back to biotech investing. He references the pandemic as a time when generalist

investors were "throwing their money into health care" as the people that have retracted their attention in the last 18 months. "The people who are coming back in now are the people who are more knowledgeable about the sector, about rare diseases and about genetic drugs, rather than the non-specialist investor," he said.

David Meeker, CEO of *Rhythm Pharmaceuticals, Inc.* and ex-longtime CEO of *Sanofi Genzyme*, agrees that VC investment will return to biotech and rare disease, specifically, with the caveat of size. "The question, which has been there for decades, is what is too small in terms of patient numbers. I think that question is going to come back," he said.

Another question of clarity for investors will be the best business model for cell and gene therapy. As the number of approved therapies continue to rise (the US FDA has approved 22 to date) costing an average of $500k and $1m per treatment course for cell therapies and gene therapies, respectively, it is crucial to understand the constraints associated with these emerging modalities. Investors may have many questions about how companies plan to overcome limitations with payers, insurers and health care systems to ensure a successful market launch and a profitable return on investment.

"I don't see a big turn around the corner," Møller told *In Vivo* about biotech investment in 2024. "I don't think we will get back to the pre-pandemic heyday, there's more conservatism in the market overall, which is good. It puts more onus on our investment decisions and focuses on high quality, which is good for the industry."

IRA Impact

Biopharma companies have been incentivized to develop therapies for the 10,000 known rare conditions – 95% of which still do not have treatments– since the Orphan Drug Act of 1983. Policy initiatives in the decades that followed spurred investment dollars and resulted in many new medicines.

However, certain policy decisions in the last five years have made rare disease drug development more challenging, and as such have spooked the generalist investor. The Orphan Drug Tax Credit has been reduced, the FDA accelerate approval pathway has been scrutinized more closely, certain US states are borrowing European-style health technology assessment prescription drug affordability boards, and more recently there was the introduction of the Inflation Reduction Act.

"For rare disease investors it can seem like policymakers are stepping on the gas and the brakes at the same time," said Masia. "There are some obvious, simple changes that policymakers could implement in the IRA – for instance,

Deals In 2023: Partnerships And Modest M&A

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encouraging rather than discouraging additional indications for orphan drugs – that would help restore confidence."

The Inflation Reduction Act, brought in by President Biden to lower drug prices, has been controversial in its application to orphan drugs. While the Act exempts drugs for rare diseases from Medicare price negotiations, this exemption only applies to those orphan drugs with a single approved indication. Consequently, drug companies have reduced financial incentive to pursue additional uses for their product and may lead to pharma manufacturers to develop single indication orphan drugs. This, coupled with increased scrutiny from the Federal Trade Commission, threatens drug development in the rare disease space.

By Melanie Senior

06 Feb 2023
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Arda Ural, EY's Americas industry markets leader for health sciences and wellness, told *In Vivo* that companies will begin paring down development of, or making deals for, assets that cannot garner a favorable price point in the marketplace or that require significant upfront investment if there is no guarantee that pharma companies can make a profit once approved. "There is a one-time rare disease exception but for molecules with multiple indications it is not sufficient protection," he said.

Figures published by Tufts University in a recent *JAMA* paper show that the FDA approved approximately 25% of orphan drugs from 2003 to 2022 for at least one follow-on indication, with most of these indications in expedited review programs. Such potential losses should be considered against the gains to consumers and society that come with lower drug prices, the authors opined.

Companies such as *Eli Lilly and Company* and *Alnylam Pharmaceuticals Inc.* have laid direct blame on the IRA for not pursuing potential treatments. Alnylam is not pursuing a Phase III trial of its hereditary transthyretin-mediated amyloidosis drug Amvuttra (vutrisiran) in a second indication of Stargardt Disease. If approved, it would trigger the price negotiation mechanism and would not be financially viable for the company.

The picture for 2024 may not be so bleak, however. Bipartisan federal legislation, The Optimizing Research Progress Hope and New Cures (ORPHAN Cure) Act, sponsored by Representatives John Joyce and Wiley Nickel, would allow orphan products to remain exempt from Medicare negotiations as long as approved uses are exclusively for rare disease. It would also clarify that

the negotiation clock starts for an orphan product only once it loses its exemption.

The loss of investment was not all down to policymaking, said Meeker. "The reality is that orphan disease legislation, as a pure business driver, is not why people started investing in rare diseases," he told *In Vivo*. "People started investing in rare diseases when Genzyme founder Henri Termeer set the price for Gaucher," he said, referring to the annual $150,000 price tag for alglucerase, set in 1991, with Termeer convincing insurers and government it was a price worth paying. In 2022, Cerezyme (imiglucerase), alglucerase's successor made parent company Sanofi $707m, growing by 2.6%.

Dealmaking: Controlling The Table

At the time of writing, there had been 17 rare disease M&A deals in 2023, with only six billion-dollar-deals on that list. Historically, biotech has been accused of selling its crown jewels too cheaply. Large pharma currently has the challenge of losing about $300bn of revenue through patent expiries in the coming years, but equally has the balance sheet strength to afford purchasing late-stage assets.

"Rare diseases continue to be attractive but not at the valuations we have seen recently," Ural said. "Niche orphan indications without any competition can be attractive if there is strong patient advocacy support to overcome market access and pricing challenges," he explained.

"Big pharma has over a $1trn in firepower and biotechs are starved for cash – whoever holds the money controls the table," he continued. While pharma companies need to replenish their topline and fuel their pipelines, they do have other means to control their financial prospects including their own internal innovation engines.

No pharma company, however, can maintain innovation at a pace that is required to feed the beast of a big company where growth is expected. "The demands of the markets will always outstrip what you can do just in your labs. There will always be a need for big pharma companies to partner with biotech. No company can afford to cover the entire waterfront of gene therapy, cell therapy, protein engineering, small molecules and rare disease oncology, and do it well," said Steve Uden, CEO of RallyBio and previously head of research at Alexion, Wyeth and Novartis Oncology.

The value of late-stage assets will become even higher, believes Ural. "We are already seeing companies competing to access the smaller number of viable compounds. The multiples of these deals are not small as they are already de-risked and ready to reach the patients through the established commercial infrastructure of the buyers."

Accessing and commercializing a rare disease compound was the driving strategy behind the standout rare disease acquisition of this year, and the third largest in 2023 biotech M&A at the

time of writing. *Biogen, Inc.*'s $7.3bn buyout of Plano, Texas-based *Reata Pharmaceuticals, Inc.* adds the only approved therapy for Friedreich ataxia, Skyclarys (omaveloxolone), to Biogen's pipeline, which earned $43m in the third quarter of 2023, its first full quarter within its new parent company. The deal enables Biogen to grow despite the disappointment of Alzheimer's disease drug Aduhelm (aducanumab) and the patent cliff of multiple sclerosis drug Tecfidera (dimethyl fumurate). (Also see "*Biogen Buys Time For Leqembi Ramp-Up With Reata Acquisition*" - Scrip, 28 Jul, 2023.)

In an investment note, Salim Syed, managing director at Mizhuo Group, praised the new proactive tone of M&A philosophy at Biogen under Adam Keeney, the recently appointed head of corporate development. This is the largest deal Biogen has undertaken and will please investors who have long wanted the company to be more aggressive in its deal-making. On the Reata acquisition call to investors, Biogen noted that it was likely to do more collaborations and licensing for the medium to long term.

In a similar vein, Ipsen's $925m acquisition of *AstraZeneca PLC* spin out *Albireo Pharma Inc.* brought in Bylavy (odevixibat), the first approved treatment in progressive familial intrahepatic cholestasis. This deal fits in with Ipsen's desire to be known as a rare liver disease company, said Jennifer Schranz, Ipsen's head of rare disease.

Schranz told *In Vivo* that the company wants to be known as a rare disease company specializing in bone and endocrine conditions, and leaders in rare liver diseases. To do this, it needs additional external innovation. "We are always looking for assets that address a high unmet medical need for indications. We're always looking in the background to supplement rare liver. That is our current strategy." Schranz confirmed the company is looking at partnering and acquiring companies with assets from pipeline to marketed products.

Looking earlier in development, Rhythm Pharmaceuticals bought *Xinvento*for $211m in February 2023, a move triggered by the natural fit of both firms which focus on rare endocrinology. Xinvento, a Dutch preclinical start-up founded by a parent of a child with congenital hyperinsulinism, will now form the CHI arm of Rhythm.

"We're open to rare disease opportunities. But because we have so much to do, we're not out there actively with a business development group looking to buy something," said David Meeker. He had been an advisor to Xinvento and was impressed with founder Claudine van der Sande. "For six to nine months, I was regularly talking with them and following their progress, so I got to know them. That's huge," he told *In Vivo*.

While clinical-stage biopharmaceutical companies commonly de-risk ongoing R&D by signing licensing deals with more established companies, rare disease companies are much less likely to rely on licensing revenue than non-rare counterparts.

An analysis from Health Capital 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.

The disparity is reflected in the market for licensing and partnership revenues. According to Health Capital, 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.

2024 And Beyond

In November, the UK became the first territory to approve a CRISPR-based gene therapy, *Vertex Pharmaceuticals Incorporated*'s Casgevy (exagamglogene autotemcel) for sickle cell disease and beta-thalassemia. While the price in the UK is not known, it is thought Vertex may price Casgevy between $2-$3m per treatment in the US. Bernstein analysts believe peak sales could reach $2.7bn, making it a rare disease blockbuster. (Also see "*Vertex Achieves Gene-Editing Milestone With First Ever CRISPR Therapy Approval*" - Scrip, 16 Nov, 2023.)

This approval paves the way for more gene-editing platforms and therapies, and with the promise of blockbuster rare disease medicines, it could spur on investment in this space. There are relatively few billion-dollar opportunities in rare disease, with Vertex already holding this accolade with its trio of therapies in cystic fibrosis.

An uncertain regulatory landscape in rare disease drug development is countered by the hope of cell and gene therapy in the curative therapies for patients but also the dollars it can drive for pharma. With 95% of all rare diseases still without treatment, the march toward finding novel treatments will continue, but the speed at which those treatments are developed is in the hands of investors and big pharma.