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Report Extract

JP Morgan Outlook 2023 Report Extract

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Contents

Pharma Outlook 2023: The Rollercoaster Shows No Signs Of Slowing Down

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Executive Summary

What will 2023 bring as the industry faces one of the toughest periods in the last decade? In Vivo asked threeindustry experts for their views.

The biopharma train is riding into unfamiliar territory. An era shift to high-cost capital from low-cost capital, macro-economic considerations from the intense and unpredictable geopolitical situation in eastern Europe, worldwide inflation, and a continued flirt with global recession could push companies off course,while the swirling myriad of industry issues such as the competition for talent, the politicization of drug pricing in the US, leveling up diversity in clinical trials, and increasing pressure to prove commitment to ESG (Environmental, Social and Governance) issues could make the horizon difficult to see with the required clarity.

And how could we forget the patent cliff? Over the course of the next six years, the patent cliff looms ever closer, with 33 of the biggest selling therapies losing exclusivity. That is a lot of blockbuster drugs in a short period of time.

Fast Ride To The Patent Cliff

In 2023, the market exclusivity for Humira, Januvia/Janumet and Stelara, generators of 2021 US revenues of$17.30bn, $1.77bn, and $5.94bn, respectively, will be lost to its manufacturers. The following year, five drugs lose patent exclusivity, including Bristol Myers Squibb Company ’s Sprycel and Novartis AG ’s Gilenya. (Also see “The Next Big Patent Cliff Is Coming, And Time Is Running Out To Pad The Fall” - Scrip, 4 Apr, 2022.)

In the recent past, high patent exposures have triggered merger activity: BMS's Celgene Corporation buy in 2019 ahead of its Eliquis patent loss, for example, and AbbVie Inc.'s acquisition of Allergan, Inc. in 2020, several years ahead of its 2023 Humira exclusivity loss. Most of the companies facing the highest cliffs, such as BMS, Pfizer Inc. and Merck & Co., Inc., have a high capacity for M&A.

Fred Hassan, chairman of Caret Group and ex-CEO of Schering Plough and Pharmacia, who lobbied for the Part D drug benefit for US seniors as chairman of the industry organization The Pharmaceutical Research and Manufacturers of America (PhRMA) in 2002-2003, believes that the removal of the "government non-interference" clause in that original 2003 legislation, in the recent Inflation Reduction Act (IRA) will accelerate to cost reduction-driven industry consolidation.

Indeed, Pfizer had an acquisitive year in 2022, with its $6.7bn Arena Pharmaceuticals, Inc. buy, the $11.6bn deal to buy Biohaven Pharmaceutical Holding Company Ltd., the $525m ReViral Ltd. buy in April, and its most recent Global Blood Therapeutics, Inc. acquisition for $4.8bn. (Also see "Pfizer Leads Big Pharma M&A In 2022 – But Is There More To Come?" - Scrip, 12 Oct, 2022.)

With Pfizer active in the M&A market, dipping into its COVID-19 coffers from sales of its Comirnaty vaccine and the antiviral Paxlovid (nirmatrelvir), which are set to sell $32bn and $22bn, respectively, this year, other companies should be following the Big Pharma's lead.

However, this year it seems most companies have favored bolt-on acquisitions rather than large-scale M&A, as was the case in 2021. By the end of the Q3 2022, total M&A deal value reached $50.7bn compared to $118.1bn for the same period in 2021. Indeed, while Pfizer seems to have spent big in 2022, it emerged that Sanofi was the most active dealmaker, inking 20 deals, while Johnson & Johnson secured 16. (Also see "The Busiest Dealmakers Of 2022" - In Vivo, 1 Dec, 2022.)

These and many other companies chose to make partnerships in 2022, with the French pharma firm inking seven deals in the first three quarters of 2022 with a reported value of more than $1bn a piece.

Big Pharma is taking its time to pounce on good deals, to find the right asset at the right price. Inherent to this dynamic is good data and value. "They are taking their time, and that's understandable," Antoine Papiernik, chairman and managing partner at European venture capital firm Sofinnova Partners told *In Vivo*. "First and foremost, its data driven. Big Pharma is interested in deals, but the data must be there. Secondly,buying a company that is worth less than its cash is not as easy as it looks," he said.

Acquiring a company worth negative technology value, as many small and mid-size biotechs were in 2022, is a high risk and high reward activity. While this is a strategy that many Big Pharma companies opt for on a regular basis, the barriers to this are monetary as well as psychological. "Buying a company like this is complicated because you have to offer something close to the underlying value. And if that underlying value is worth $500m, and the company's worth $100m in the stock exchange, it's very difficult for a pharma company to buy a company at a multiple of its market cap that is above 2x," Papiernik explained. "The boards don't want to be seen overpaying, even though the value would be $500m. And they would find it difficult to pay five times the market cap. They would rather the company be worth $500m and buy it at $500m."

The fiduciary duty of the board, to obtain the best value for the shareholders, is difficult to follow when the large disconnect in decreased valuations is prevalent. However, if we fast

forward 12 months, when there is likely to more good data and the VIX Index (the measure of expected volatility in the US stock market) is more stable, prices may come back to a mean average to reflect the true value of companies. This is when the industry will start to make more transactions, said Papiernik.

"When deals happen, premiums are often going to be good because people are looking for quality assets. People are still willing to pay because they have the money, but it must be a quality asset," Hassan told *In Vivo*.

Hassan believes the current US administration's "sceptical view" of large mergers, which will continue for the next two years, is also reflected in the pharma industry's attitude to dealmaking, dampening enthusiasm for larger horizontal deals. "Nobody wants to get trapped in a very long review period, as you lose a lot of value. The US government has not been very successful with its legal challenges, but the delay in getting the deal done influences the valuations, this is not very conducive for big mergers, or even medium sized mergers," he said.

Political Twists And Turns

And financial influence is not only coming from the US government. The November mid-term elections brought to the fore the economic and cultural wars felt in the world's largest pharma market which created a more moderate result than many expected. With the US Congress divided after the mid-term elections,pharmaceutical companies that want to weaken the recent Inflation Reduction Act (IRA), signed into law by President Joe Biden in August, will have to wait a while longer.

With Congressional Democrats passing major legislation to control drug prices in Medicare in August, the US Health and Human Services Department is authorized to 'negotiate' drug prices in Medicare for the first time and will be releasing an initial list of drugs up for debate in September 2023. (Also see "Medicare Price 'Negotiation' Process Gets Broad Brush Treatment In New Law" - Pink Sheet, 16 Aug, 2022.)

At the time, PhRMA president and CEO Stephen J Ubl released a statement that read: "The President signed into law a partisan set of policies that will lead to fewer new treatments and doesn't do nearly enough to address the real affordability problems facing patients at the pharmacy. We will explore every opportunity to mitigate the harmful impacts from the unprecedented government price setting system being put in place by this law. We will continue to advocate for policies that give patients better and more affordable access to lifesaving treatments and for a system that supports innovation."

Now, with the Democrats in charge of the Senate, and the Republicans running the House of Representatives in January 2023, the pharmaceutical industry will have to regroup to impact the new law.

"The list prices in the US are probably the highest in the world, but they are [simply] 'list prices.' If you hear presentations from companies, they actually follow the net price they are able to realize after rebates and discounts. Biopharma has struggled to get net price increases over the last five years, because the rebates keep going up. Drug costs as a percent of total health care costs for the US, which are at 14%, are well within the 9 to 20% band of similar ratios among other advanced economies. But these are complicated things to explain to voters," said Hassan.

While he admits that some patients, the "relatively small minority of enrolees in Medicare," that do get hit with very high drug bills on a cost-sharing basis in any single year may feel financial "toxicity," the majority of the enrolees in insurance plans do not see such large out-of-pockets. For those who get individually impacted, more needs to be done on a selective

basis. “This across-the-board conversation about price controls is not a good idea,” Hassan said.

“IRA is meant to be cost-cutting legislation, yet inexplicably, here it incentivizes the typically more expensive biologics over small molecules, so this is the kind of thing that often happens when you push through a partisan legislation via the narrow reconciliation pathway.”
- Fred Hassan

“Price controls are not the reason that societies innovate and prosper. I think it is hard to know what this particular legislation is going to do because there are still the PBMs, the market price controllers. On top of this, there are some dysfunctionalities in the legislation, which may or may not get fixed,” he said. One“dysfunctionality” Hassan points to is that small molecule drugs become subject to government price interference in Medicare beginning nine years after approval, while single-source biologics are given 13years. “IRA is meant to be cost-cutting legislation, yet inexplicably, here it incentivizes the typically more expensive biologics over small molecules, so this is the kind of thing that often happens when you push through a partisan legislation via the narrow reconciliation pathway,” he said.

Non-visible decisions on R&D projects are already being made as a result of IRA. Some decisions are also becoming visible. Alkermes plc, for example, has spun off its oncology drugs unit, which is based on the biologics nemvaleukin alfa, an interleukin-2 drug, and two additional cytokine therapeutics. “The Inflation Reduction Act … fundamentally [shifted] the relative economic value of biologic medicines in cancer,”chairman and CEO Richard Pops said during the company’s earnings call on 2 November.

While many have come forward to criticize the law, saying it is particularly destructive to the development of small molecule drugs. (Also see “Cancer Drugs And Medicare: Range Of Impacts Expected From IRA Price Reforms” - Pink Sheet, 8 Nov, 2022.)

Hassan has individual concerns about the lost opportunity in CNS which is characterized by small molecules that can cross the blood-brain barrier, as opposed to large biotech molecules which typically have a difficult time doing this.

The next decade should be the years in which brain science flourishes, he said, because researchers have learned so much about targeting therapies for diseases such as Alzheimer’s, Parkinson’s, epilepsy, anxiety,and depression. These distressing diseases missed the biotech revolution in the last three decades and also the oncology-led precision medicine revolution in the past decade. A nine-year exclusivity period is not enough to learn much about a drug, he continued. He recalls his time at Wyeth. The company introduced the first of the SNRI-class antidepressant, Effexor (venlafaxine), in 1993. Originally the drug was administered twice a day, but some years later, this was improved to a more targeted delivery beyond the stomach and as a once-a-day form. Beyond its improved adherence benefit, this form also reduced the side effects of nausea and blood pressure. This enabled the company to bring in the anxiety indication on top of the depression indication. Effexor became a blockbuster several years after the drug launched. “That cycle of innovation is not easy to accommodate if you only have a nine-year window, and you can see why this would affect people’s investment decisions,” he said. Generic venlafaxine has been available since around 2008, and in2020 it was the 43 most prescribed drug around the globe.

Round And Round We Go

In 2021, investment in the life sciences sector, and biotech specifically, reached an all-time high. According to figures from McKinsey, venture capital firms invested in 2,200 biotech start-ups in 2016, and by 2021, that number had grown to 3,100. Biotech companies raised more than $34bn globally in 2021, more than doubling the 2020 total of $16bn.
2022, however, spoilt biotech's party. Companies endured a post-pandemic market correction, coupled with macro-economic pressures of inflation and rising interest rates, causing one of the worst years in many decades as market values sank below cash.

For those companies that went public in 2020 and 2021, the impact has been "brutal", said Robert Tansley, partner at Cambridge Innovation Capital. "There are a lot of a lot of companies suffering, but also there are a lot of companies who are trading under their cash." (Also see "After Cutting Back And Clinging On, Will Biotech Bounce Back In 2023? " - Scrip, 16 Nov, 2022.)

The biopharmaceutical stock performance has caused valuations to fall sharply throughout 2022. At the time of writing (December 2022), the Nasdaq Biotechnology Index is down by year-on-year by 11.9%. Falling valuations have made the path harder for companies to raise capital, both for privately - and publicly-held firms.

With limited fundraising options, those companies that need to extend their cash runways have restructured and actioned layoffs to protect shareholder value. Companies such as Mereo Biopharma have laid out plans to articulate how their cash will continue to fund lead assets. (Also see "Finance Watch: With Limited Fundraising Options, Biotechs Restructure To Extend Cash Runways" - Scrip, 19 Oct, 2022.).

"If you need money today, you could be in trouble. Even if you have a great company, if that company is in trouble, it may go under if its current investors don't support it" - Antoine Papiernik

Some biotech companies that need cash now, may not even survive, Sofinnova's Papiernik told *In Vivo*. "There are two types of biotech companies, and those that have two to three years of cash have a real chance to get to the other side of the chasm without too much trouble and meet milestones. If you need money today, you could be in trouble. Even if you have a great company, if that company is in trouble, it may go under if its current investors don't support it," he said.

At the time of writing, Acrivon Therapeutics, Inc. 's $99.4m IPO was only the 20 listing of 2022, while a record-breaking 2021 saw 107 biopharma listings. (Also see "Finance Watch: Acrivon Adjusts Expectations To Launch$99.4m IPO" - Scrip, 16 Nov, 2022.) (Also see "IPO Outlook: 2021 Saw Record Numbers But Poor Returns; 2022 Looks Muted" - Scrip, 7 Jan, 2022.)

The fall in valuations has caused companies to stay away from the public markets, but while these markets continue to confound, there have been some large follow-on financings on NASDAQ.

"Many of the founders or the entrepreneurs are not happy at the prospect of selling equity at discounted valuations, they're also concerned about the effect on the existing investors if they sell into the market with a discounted valuation," Hassan told *In Vivo*. "IPOs are going to remain pretty shut, there will be a few IPOs of companies which are higher quality with good assets,but much fewer, like this year. And I think it's likely to remain like that through 2023."

Because the IPO window is shut, and is likely to remain so throughout next year, the impact on those later-stage private companies that cannot list is significant. The US investment bank, Raymond James, estimates that between 50 to 70 companies have filed S-1 forms but cannot list; these companies represent a large number of later-stage companies that will have to do an extra round of private investment.

Private investors now need to back their portfolio companies for longer than they predicted, said CIC's Tansley. "But some large investors who can invest in both public and private are looking at the public markets and, given that valuations have come down so dramatically, are finding a lot of bargains," he explained. Where the investment syndicates are strong,they are doing internal rounds to bridge until at least 2024, and maybe even longer. Where an external investor is brought in, there have been decreases in valuation. The most recent report from the US banking firm, Wilson Sonsini, suggests that there has been around a 30% to 50% reduction in the late-stage valuations when an external investor was brought in.

Largest IPOs of 2022

1. Jiangsu Asieris $373m (STAR Market in China)
2. HilleVax $213.9m
3. Third Harmonic $198.1m
4. CinCor $180m
5. Amylyx Pharmaceuticals $176.7m (Upsized IPO)
6. Prime Medicine $162.8m
7. Arcellx $142.3m
8. Lepu Bio $103.9m (HKEX Market in Hong Kong)
9. PepGen $100.4m
10. Jiangsu Recbio $97.6m (HKEX Market in Hong Kong)

Leveling Out

Market volatility looks set to continue pharma's rollercoaster ride into 2023. Cell and gene therapy, however,is a market that is expected to have an exciting news flow in 2023, and venture capital remains the bedrock of funding for the sector. In 2023, there are expected to be 14 US, and three European regulatory decisions made. Among those are bluebird bio's lovo-cel gene therapy for sickle cell disease, BioMarin Pharmaceutical Inc.'s Roctavian gene therapy for hemophilia A, Orchard Therapeutics Limited's Libmeldy gene therapy formetachromatic leukodystrophy. Just over a decade after CRISPR was first discovered, the first CRISPR technology may reach the market, with Vertex Pharmaceuticals Incorporated/ CRISPR Therapeutics AG's CTX001gene editing therapy for sickle cell disease and beta thalassemia on the cards for US, EU and UK regulatory approval.

Venture capital was at 40% of full-year 2021 levels through the first half of 2022, according to figures from the Alliance for Regenerative Medicine (ARM). This indicates continued investor excitement about scientific breakthroughs and new treatment possibilities, despite investment headwinds, it says.

In 2022, sector financing reverted to pre-pandemic levels from the records set in 2020 and 2021 (see Exhibit1). While it was a difficult environment for public financing, ARM expects total 2022 investment to land somewhere between $9.8bn and $13.5bn, the sector's performances from 2019 and 2018, respectively.

Despite ongoing investment confidence, regenerative medicine remains a subset of the pharmaceutical industry that is stymied by market access issues and commercialization challenges, especially in Europe. bluebird bio exited Europe in 2021, after failing to achieve "value recognition" for its gene therapy product Zynteglo for beta thalassemia. In another example, in September 2022 Insmed stopped

supplies of Arikayceafter failing to agree a price with the German National Association of Statutory Health Insurance Funds (GKV). Indeed, according to ARM, seven of the 23 advanced therapy medicinal products (ATMPs) approved in the EU have been withdrawn from that market.

In the US, the latest wave of modernization efforts has been spearheaded by the director for the FDA's Center for Biologics Evaluation and Research, Peter Marks, and these should start to take effect in 2023. Approvalsaside, the wave of ATMP potentially coming to market in the next few years may be stymied by paymentsystems that are not equipped to allow patients the access to drugs that are desperately needed by the raredisease population.

The Big Dipper

Questioned on this theme by *In Vivo*, all three interviewees stated that fundraising will be the biggestchallenge for the next 12 months. "We've seen four or fi ve years of record amounts of money, I think we'll seea signifi cant decrease in 2023," said Tansley. "Those funds which have raised in the last two or three yearswill be well placed. And often in diffi cult times, that's when the best returns are had. Those looking to raisemay have to temper those ambitions. Fundraising for venture intervention is going to be tough next year."

"Those funds which have raised in the last two or three years will be well placed. And often in diffi cult times, that's when the best returns are had. Those looking to raise may have to temper those ambitions. Fundraising for ventureintervention is going to be tough next year."
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Sofinnova Partners has 100 portfolio companies and has completed 10 deals and 23 refinancings in the last12 months. It has been a very active fundraising environment caused by venture investors raising a lot ofmoney over the last two years, said Papiernik. "The coffers are relatively full which has created a 'positiveinertia' to the system. People have money and will defend the company when they can." In his view, there isno reason for this situation to change, and 2023 will be no different unless the IPO starts going up, anunrealistic situation. This "harsh environment" will remain the same for the 2023.

There will be a prolonged period of caution until the IPO window opens again, concurred Tansley. "Until wesee an uplift in the in the public markets, the later-stage investors will focus on the public markets ratherthan private," he said.

But, as far as sectors are concerned, the biopharma industry is well positioned as the predominant part of thehealth care sector. And health care is well positioned compared to the other 10 S&P sectors, said Hassan. "Itis a defensive sector, and there is a need for better health care. Populations are getting older. And innovationis helping improve the valuations in the market. I still see health care as a pretty good sector," he concluded.

The Busiest Dealmakers Of 2022

2022 Deal-Making Led By Sanofi, J&J And Roche

Joseph Haas

01 Dec 2022

Executive Summary

With only weeks to go in 2022, the three major pharmas each had inked between 16 and 20 deals. Meanwhile, Pfizer has been less busy with 12 deals, but those include M&A totaling $18.2bn.

As 2022 draws to a close, an unusually low number of marquee deals have been made in the biopharma sector. But it has been a hectic year nonetheless, with a high volume of deal-making and the lower valuations reflecting broader economic factors and continuing trends seen in recent years toward smaller, easier-to-manage deals.

Macroeconomic concerns stemming from inflation and rising interest rates, supply-chain uncertainty earlier in the year and the continuing war in Ukraine have imposed a dampening effect on the biopharma sector, creating a tailwind in the financing environment as well as the business development arena. (Also see "After Cutting Back And Clinging On, Will Biotech Bounce Back In 2023?" - Scrip, 16 Nov, 2022.) But while this has weighed especially hard on biotechs, big pharmas continue to face the perennial pressure of filling the R&D pipeline, underscored by a looming patent cliff for several players. (Also see "The Next Big Patent Cliff Is Coming, And Time Is Running Out To Pad The Fall" - Scrip, 4 Apr, 2022.)

That has helped to maintain a high volume of deal-making in the sector, although the biopharma industry continued a trend toward bolt-on acquisitions and away from major M&A deals this year, similar to the deal activity seen in 2021. (Also see "2021 Deal Snapshot: Continued Emphasis On Bolt-Ons, Alliances Up" - Scrip, 1 Apr, 2022.) As of mid-November, Biomedtracker recorded 16 biopharma M&A deals valued at $1bn or greater, with the Pfizer Inc./Biohaven Pharmaceutical Holding Company Ltd. $11.6bn takeout as the largest of

2022. That mirrors 2021, with 16 M&A deals of $1bn or greater through mid-November, with the largest being Merck & Co., Inc.'s acquisition of Acceleron Pharma, Inc. for slightly more than $11bn. But analysts had been hoping 2022 would mark the return of mega-mergers. (Also see "A Biopharma M&A Bonanza In 2022? Analysts Pick Top Targets And Likely Buyers" - Scrip, 2 Feb, 2022.)

Biopharma M&A was very constrained through the first three quarters of 2022 compared to the previous year. M&A transaction volume only declined slightly – from 116 deals in the first three quarters of 2021 compared to 104 deals during the same period in 2022 – but total M&A deal value in 2021 stood at $118.1bn through the first three quarters. In 2022, total M&A deal value was $50.7bn at the end of the third quarter.

Big pharma did its part, with seven companies making 10 or more merger-and-acquisition or alliance deals during this year. Twenty companies have made at least five deals, and that group includes some less familiar names, like NexImmune, Inc. and Twist Bioscience Corporation.

But large pharma is leading the charge, with Pfizer – although only sixth in deal volume – coming in second by total deal value, accounting for nearly 40% of reported M&A value in the biopharma sector so far this year as it emphasizes external R&D. (Also see "Pfizer's Dolsten On Finding Ways To "Accelerate External Science"" - Scrip, 4 Nov, 2022.)

On the other side of the M&A picture, four of the seven busiest deal-makers – Eli Lilly and Company, Roche Holding AG/Genentech, Inc., Johnson & Johnson, and Sanofi – combined for less than $1bn in M&A activity through 15 November. Sanofi reported no M&A spend for the year; J&J subsidiaryJanssen Pharmaceuticals Inc. purchased Anakuria Therapeutics, Inc in February but no financial terms were disclosed.

Meanwhile, J&J initiated the biggest health sciences M&A deal of the year, agreeing to buy heart, lung and kidney implantable device maker Abiomed, Inc. for $16.6bn on 1 November. That not-yet-closed deal, along with the Pfizer/Biohaven takeout, are the only $10bn-plus M&A transactions of 2022 to date. (Also see "Pfizer To Put Big Marketing Muscle Behind Migraine With Biohaven Purchase" - Scrip, 10 May, 2022.)

2022's Busiest Biopharma Deal-Makers At A Glance

Company	Number Of Deals[1]	Total Deal Value[2]	M&A Deal Value[3]
Sanofi	20	$21.3bn	$0
Johnson & Johnson	16	$2.3bn	$0
Roche/Genentech	16	$13.4bn	$250m
Eli Lilly	13	$5.6bn	$720m
Bristol Myers Squibb	13	$14.2bn	$4.1bn
Pfizer	12	$20.6bn	$18.2bn
Merck & Co.	11	$10.1bn	$1.4bn

Source: Biomedtracker, Scrip

1 - Includes M&A, R&D and commercial partnerships, and licensing agreements. Does not include clinical trial collaborations, financings or manufacturing and supply agreements.

2 - Total deal value includes contingent future payments, such as milestones and royalties, which may not be realized.

3 - Report figures - not all M&A transactions have publicly disclosed valuations.

Here are snapshots of the five busiest deal-makers of 2022 so far:

Sanofi

Through mid-November, Sanofi is the sector's busiest deal-maker by both volume and total value. Not typically a stranger to M&A activity – having made six acquisitions in 2021 with a total reported value of nearly $6.8bn – the French pharma has focused on partnerships in 2022, including seven with a reported total potential value of more than $1bn a piece. The company appears to be more focused on earlier-stage R&D collaborations at present, in areas such as artificial intelligence-driven drug discovery, monospecific/bispecific antibody R&D, RNA-based medicine and gene editing.

Sanofi inked AI technology platform alliances with Exscientia Ltd. in January, Atomwise, Inc. in August and Insilico Medicine on 8 November, with each deal valued at more than $1bn including potential milestones and royalties. Those follow an equity investment and collaboration Sanofi made with French AI specialist Owkin in November 2021; the biotech then poached Sanofi's global head of partnering Alban de La Sablière to serve as its initial chief business officer in October. (Also see "Ex-Sanofi Partnering Chief Wants AI Start-Up Owkin To Be Industry Leader" - Scrip, 4 Oct, 2022.)

Sanofi has remained an industry leader in harnessing AI to aid with discovery. In the tie-up with Oxford, UK-based Exscientia, Sanofi got potential license rights to small molecule candidates for oncology and immunology targets derived from patient samples. (Also see "Exscientia And Sanofi Will Search For 15 Novel Oncology, Immunology Drugs Under New Pact" - Scrip, 7 Jan, 2022.) The pharma paid $20m to San Francisco-based Atomwise for computational drug discovery and development against five targets, and made a $21.5m upfront payment to Hong Kong-based Insilico to advance candidates against up to six targets. (Also see "Sanofi Looks To Atomwise For More AI Help" - Scrip, 17 Aug, 2022.)

Sanofi/Exscientia Partnership

- Collaboration and license agreement to develop up to 15 novel small molecule candidates across oncology and immunology, leveraging Exscientia's AI-driven platform utilizing actual patient samples.
- Exscientia gets $100m up front.
- Each program could yield research, clinical development, regulatory and commercial earnout of up to approximately $343m, including up to $193 in the aggregate for R&D and regulatory milestones, and up to $150m in commercial milestones. Aggregate milestones could top $5bn.

Sanofi also signed several potential billion-dollar partnerships with antibody-focused biotechs during 2022, looking both east and west for innovative partners. (Also see "Sanofi Will Employ Adagene's Technology For Precision Targeting In Cancer" - Scrip, 2 Mar, 2022.) In January, it teamed with China's Adagene Inc. on masked monoclonal and bispecific antibodies for precision cancer therapy in a deal valued at $2.52bn and in March inked a potential $1.06bn partnership with ABL Bio Corp. to co-develop the South Korean firm's preclinical bispecific antibody targeting alpha-synuclein and IGF1R for Parkinson's disease. (Also see "ABL's Bispecific Antibody For Parkinson's Lands In Sanofi's Hands" - Scrip, 12 Jan, 2022.)

Cancer was the focus of most of the French pharma's business development activity. In March, Sanofi unveiled a potential $6.17bn collaboration with California's IGM Biosciences, Inc. on antibody agonists against three targets in cancer and three more in immunology/ inflammation indications. (Also see "Sanofi Bets Big On IgM 'Super Antibodies' In Potential $6bn Cancer and Immunology Deal" - Scrip, 29 Mar, 2022.) The pharma also paired up in March with antibody-drug conjugate specialist Seagen Inc. at undisclosed terms to design, develop and commercialize up to three ADCs for cancer. (Also see "Sanofi Dives Back Into ADCs With Seagen Pact" - Scrip, 17 Mar, 2022.)

In September, Sanofi paid $25m up front to Scribe Therapeutics, Inc. in a deal worth up to $1.02bn to use CRISPR gene-editing technology in an effort to develop natural killer (NK) cell therapies for cancer. (Also see "Sanofi ThiNKs Scribe's CRISPR Approach Can Advance Its NK Cell Therapy Goals" - Scrip, 27 Sep, 2022.)

The Paris-headquartered pharma also made four divestment transactions this year, with financial terms revealed for only one – it got $3m from Rallybio Corp. for rights to KY1066/ RLYB331, a matriptase-2 antibody thought to offer potential therapeutic benefit in forms of anemia. Sanofi also offloaded late-stage central nervous system candidates to Terran Biosciences, Inc.; a 17-product portfolio of CNS, pain and vascular products to Neuraxpharm Arzneimittel GmbH; and a small interfering RNA (siRNA) therapeutics portfolio to Rona Therapeutics.

Johnson & Johnson

Johnson & Johnson and its Janssen subsidiaries have been busy deal-makers this year with 16 biopharma transactions in total, but only one M&A deal, for which no financial terms have been disclosed – the acquisition of Navitor Pharmaceuticals, Inc. subsidiary Anakuria on 2 February. The deal brings J&J a portfolio of selective rapamycin analog mTORC1 inhibitors, including Phase I AT-20494, a first-in-class opportunity in autosomal dominant polycystic kidney disease. (Also see "Deal Watch: Amgen Taps Plexium's Expertise In Targeted Protein Degradation" - Scrip, 8 Feb, 2022.)

Otherwise, J&J's business development activity this year – amounting so far to $2.3bn in announced valuation – reflects its broad range of therapeutic focus and modalities. On 3 February, it paid Mersana Therapeutics, Inc. $40m up front under a collaboration to develop cancer ADCs against three specific targets. The Cambridge, MA-based firm can realize more than $1bn in earnouts under the agreement, bringing the aggregate potential value to about $1.07bn.

Two weeks later, the pharma committed $45m in upfront cash to another Cambridge biotech, Remix Therapeutics, to team up on discovery and development of small molecule therapeutics that modulate RNA processing using the latter's REMaster drug discovery platform. (Also see "J&J Jumps On RNA-Based Small Molecules Train In Pact With Remix" - Scrip, 17 Feb, 2022.) J&J gets rights to oncology and immunology candidates under the agreement, which could yield more than $1bn in total for Remix.

Evotec's Busy Partnering Year

In addition to its R&D alliance with J&J, Evotec also:

- Signed partnerships with Lilly in metabolic disease; with Boehringer Ingelheim GmbH in stem-cell research for ophthalmology; with Sernova Corp in diabetes; and with Almirall SA in dermatology.
- Acquired Italy's RigeneranD Srl to expand its cell therapy production and capabilities and launched antimicrobial resistance-focused Aurobac Therapeutics SAS in a joint venture with BI and bioMeriuex Inc.

On 14 June, J&J announced a collaboration with Germany's Evotec SE – itself one of 2022's busiest deal-makers, with seven transactions to date – using the latter's Target AlloMod platform technology to screen specified targets and then partner on hit identification and lead optimization of promising candidates. Therapeutic focus areas were not disclosed and financial details were vague, with Evotec getting research funding and potential research and commercial milestones of up to $220m per program. (Also see "Deal Watch: Organon Obtains Rights To Perjeta, Prolia/Xgeva Biosimilars From Shanghai Henlius" - Scrip, 15 Jun, 2022.)

Roche/Genentech

The Swiss conglomerate comprising Roche, Genentech and Chugai Pharmaceutical Co., Ltd. also made 16 deals to date in 2022, including the acquisition on 7 September of privately held Good Therapeutics, Inc. for $250m at closing with potential for development, regulatory and commercial milestone payments to the Seattle biotech's shareholders. (Also see "Roche Buys IL-2 Technology From Good, Which Forms New Firm Bonum" - Scrip, 7 Sep, 2022.) Despite a relatively low M&A total, Roche has made upfront and downstream commitments of more than $13bn this year.

Roche's focus in buying Good is on a conditionally active PD-1-regulated interleukin-2 receptor agonist candidate for immuno-oncology, but the smaller firm's overall focus is on regulated, context-dependent molecules that combine an antibody sensor directed against a specific marker and a therapeutic component active only when the sensor has bound its target. Under the sale agreement, which closed on 30 September, Good's personnel and non-IL-2 programs will spin out into new company Bonum Therapeutics.

Much of Roche's deal-making this year has centered on cancer, with an emphasis on immuno-oncology and cell therapy. The pharma's potentially biggest deal of the year came on 3 August when it paid Poseida Therapeutics, Inc. $110m up front with another $110m in near-term milestones to partner on allogeneic CAR-T cell therapies for hematologic cancers. All told, the San Diego biotech could realize more than $6bn under the deal, which gives Roche global licensing rights to the Phase I P-BCMA-ALLO1 for multiple myeloma, and three preclinical CAR-T candidates, including P-CD19CD20-ALLO1, an allogeneic dual CAR-T for the treatment of B-cell malignancies. (Also see "Deal Watch: Gemini Goes Through Second Re-Invention Via Reverse Merger With Disc Medicine" - Scrip, 10 Aug, 2022.)

In other cancer-related deals with high earnout potential, Roche obtained license rights to HOOKIPA Pharma Inc.'s HB-700 for KRAS-mutated cancers and an option for a second undisclosed novel arenaviral immunotherapy. (Also see "Roche Goes Big On KRAS-Mutated Cancers In Hookipa Pact" - Scrip, 20 Oct, 2022.) The 20 October agreement brought the Austrian firm $25m up front, a $15m option-exercise fee for the second candidate and total potential value of $958m.

Roche/Good Buyout At A Glance

- Acquisition closed on 30 September for $250m in cash plus potential milestones to Good shareholders tied to predetermined regulatory, development and commercial achievements.
- Founded in 2016, Good Therapeutics focuses on generation of a new class of drugs that offer potent activity only where needed.
- After closing, Good management spun out Bonum Therapeutics to focus on design of conditionally active therapeutics in immuno-oncology, autoimmune diseases, metabolic disease and pain management.

Meanwhile, Roche subsidiary Chugai inked a licensing agreement on 22 August for rights to fellow Japanese firm Noile-Immune

Biotech, Inc.'s PRIME (Proliferation-Inducing and Migration-Enhancing) CAR-T technology, intended to enhance immune cell function through the expression of the cytokine IL-7 and the chemokine CCL19 from CAR-T cells. (Also see "Deal Watch: Ovid Teams With Gensaic On Phage-Derived, Gene-Delivered Therapies" - Scrip, 25 Aug, 2022.) Although the financial terms weren't disclosed in detail, Noile-Immune can realize more than $146m under the agreement including upfront cash and earnouts.

Across all of its life sciences interests, the Roche conglomerate has made more than 20 deals this year, including four diagnostics tie-ups by its subsidiary Foundation Medicine, Inc..

Eli Lilly

Eli Lilly's 13 deals so far in 2022, with a total reported potential value of $5.6bn, are highlighted by its most recent transaction, the $610m takeout of the genetic medicine firm Akouos. Lilly has agreed to pay $12 per share for the Boston biotech, estimated at $487m, with another $123m in contingent value payments possible for Akouos, Inc. shareholders. (Also see "Lilly Builds On Gene Therapy Focus With Akouos Takeout" - Scrip, 18 Oct, 2022.) Founded in 2016, Akouos is developing a portfolio of first-in-class adeno-associated viral gene therapies for the treatment of inner ear conditions, including sensorineural hearing loss.

The Indianapolis pharma's deal-making to date also includes seven alliances with potential value of greater than $200m apiece. It began the year in January with a pair of partnerships – teaming with Canada's Entos Pharmaceuticals, Inc. on its nucleic acid delivery technology to develop products targeting the central and peripheral nervous system, and with China's Abbisko Therapeutics Co., Ltd. to develop novel molecules addressing an undisclosed target for cardiometabolic diseases of unmet medical need. (Also see "Deal Watch: J&J Begins 2022 With Trio Of Technology Alliances" - Scrip, 7 Jan, 2022.) Lilly ended the month with a third collaboration, with Evotec in a deal centered on diabetes and kidney disease that could yield the German firm more than $1bn. (Also see "Evotec Adds To Spate Of Metabolic Deals With Lilly Collaboration" - Scrip, 18 Jan, 2022.)

As the year went on, Lilly began signing alliances with US biotechs, including two Boston-area firms. In February, it paid $13m up front to ImmunoGen, Inc. for rights to cancer antibody-drug conjugate therapies by applying the biotech's camptothecin technology to targets selected by Lilly. (Also see "Deal Watch: AbbVie Adds Neuroscience Heft With Syndesi Acquisition" - Scrip, 1 Mar, 2022.) ImmunoGen ultimately could realize up to $1.75bn under the partnership.

Lilly's Tie-Up With Nimbus

- Focused on activating isoforms of 5' adenosine monophosphate-activated protein kinase (AMPK) for metabolic disease.
- Nimbus to conduct initial research; Lilly will assume development and commercialization responsibilities.
- Nimbus can earn up to $496m in upfront cash and milestone payments plus tiered, double-digit sales royalties.

In October, Lilly signed on with Nimbus Therapeutics, Inc. to deploy that company's computational drug discovery platform for novel targeted metabolic disease therapies that target an isoform of AMPK. Nimbus can earn up to $496m under the pact. (Also see "Deal Watch: Aging-Focused Calico Taps Start-Up Terray For Discovery" - Scrip, 13 Oct, 2022.)

The pharma also partnered in May with San Francisco's Genesis Therapeutics in an AI-driven discovery and development pact for up to five targets across a range of therapeutic areas. (Also see "Deal Watch: Novo Nordisk Links With Flagship To Create Cardiometabolic, Rare Disease Portfolio" - Scrip, 12 May, 2022.) Genesis got $20m up front tied to the first three Lilly-

selected targets and could realize up to $670m in earnouts under the agreement.

Bristol Myers Squibb

With a financial commitment of more than $14bn (including potential downstream payments), BMS is big pharma's third-largest spender so far in 2022, trailing Sanofi and Pfizer. It inked one of the year's largest M&A transactions, paying $4.1bn in June to acquire Turning Point Therapeutics Inc., while also negotiating five collaborations with total valuations of $1bn or greater.

The Turning Point deal closed in August, bringing BMS a pipeline of cancer medicines intended to target the most common mutations associated with oncogenesis. (Also see "BMS Hopes Turning Point Buyout Will Fare Better Than Roche's Ignyta Acquisition" - Scrip, 3 Jun, 2022.) Lead asset repotrectinib is a next-generation, potential best-in-class tyrosine kinase inhibitor targeting the ROS1 and NTRK oncogenic drivers of non-small cell lung cancer (NSCLC) and other advanced solid tumors. Repotrectinib has been granted three breakthrough therapy designations from the US Food and Drug Administration.

BMS's total of 13 deals through 15 November also incorporates a licensing agreement Turning Point signed in May with China's LaNova Medicinesto pick up rights to LM-302, a novel antibody-drug conjugate targeting Claudin18.2. (Also see "China Deal Watch: Four Biotechs Kick Off May With Multiple In/Out Deals" - Scrip, 10 May, 2022.)

To date, BMS has signed four cancer-focused alliances that each could top the billion-dollar mark. In January, the pharma paid $100m up front and made a $50m equity investment in Century Therapeutics, Inc. to license rights to up to four induced pluripotent stem cell (iPSC)-derived, engineered natural killer cell and or T-cell programs for hematologic malignancies and solid tumors. (Also see "Deal Watch: Bristol, Pfizer Lead Off J.P. Morgan Week With Two Deals Apiece" - Scrip, 11 Jan, 2022.)

BMS/Century Partnership

- Research and licensing collaboration centered on up to four induced pluripotent stem cell-derived, engineered natural killer cell (NK) and or T-cell programs.
- Focused on both hematologic cancer and solid tumors, with initial programs in acute myeloid leukemia and multiple myeloma.
- Century has a co-promotion option under the agreement and also received a $50m equity investment from BMS under the deal, priced at 57% premium.

In March, BMS placed a wager on synthetic lethality, paying $30m up front in a potential $1.13bn tie-up with Volastra Therapeutics, Inc. to combine its oncology expertise with the latter's understanding of chromosomal instability. (Also see "BMS Is Latest To Join Synthetic Lethality Bandwagon With Volastra Deal" - Scrip, 21 Mar, 2022.)

During Q2, BMS aligned with Scotland's Amphista Therapeutics to discover, develop and license small molecule protein degraders derived from the biotech's Eclipsys platform and with Immatics N.V. to develop autologous T-cell receptor (TCR) therapeutics. (Also see "Ups And Downs In Protein Degraders: Big Deals For BMS, Merck KGaA, Safety Worries For Kymera" - Scrip, 5 May, 2022.) Amphista got $30m up front in a deal that could total $1.25bn, while Immatics got $60m up front with potential for up to $700m per program in its alliance with BMS, for a total potential value of $4.26bn. (Also see "Deal Watch: Organon Obtains Rights To Perjeta, Prolia/Xgeva Biosimilars From Shanghai Henlius" - Scrip, 15 Jun, 2022.) That deal built upon an existing relationship between Immatics and Celgene Corporation, which was furthered by a license agreement between BMS and the German biotech in December, which brought Immatics $150m up front. (Also see "Deal Watch: BMS Licenses Bispecific TCR Candidate

From Immatics" - Scrip, 17 Dec, 2021.)

Pfizer, Merck Busy As Well

Beyond the five busiest biopharmas in deal-making this year, Pfizer and Merck both have hit the double-digit mark for deals already. Although our analysis does not include clinical trial collaborations without licensing or financial commitments as deals, if it did, the continued hectic pace of collaborations to test novel cancer drugs with Merck's anti-PD-1 stalwart Keytruda (pembrolizumab) would make the New Jersey pharma the busiest deal-maker of all.

Pfizer's 12 deals this year have been among the most impactful in the biopharma space given that the New York-based firm has spent more than $18.2bn on M&A due to its Biohaven and Global Blood Therapeutics, Inc. acquisitions in May and August, respectively. (Also see "Pfizer's Buying Spree Continues With GBT, Gaining A Sickle Cell Disease Franchise" - Scrip, 8 Aug, 2022.) Pfizer's business development activity this year also includes a potential $1.65bn in vivo base-editing tie-up focused on rare diseases with Beam Therapeutics Inc. and a cancer-focused antibody discovery and development partnership valued at $1.02bn with Dren Bio, Inc. . (Also see "Beam Anticipates Pfizer Deal Will Lead To Additional Partnerships" - Scrip, 12 Jan, 2022.)

Merck's deal-making to date is highlighted by the potential $1.41bn it has agreed to pay China's Sichuan Kelun Pharmaceutical Co Ltd. for rights to an undisclosed macromolecule cancer project. The two firms inked a second licensing pact – giving Merck rights to an ADC candidate for solid tumors – in July. (Also see "Asia Deal Watch: Taiho Brings Cullinan Pearl Back In House" - Scrip, 17 May, 2022.)

The most notable action by Merck in 2022 might be the failure to complete a hotly rumored acquisition of Seagen. Already partnered with the ADC specialist on ladiratuzumab vedotin, in September 2020 Merck acquired $1bn worth of Seagen shares. The combination of Merck's need to reboot ahead of the Keytruda loss of exclusivity and the tumultuous exit of Seagen founder and CEO Clay Siegall raised expectations of a pending announcement. (Also see "Merck & Co Closing In On Seagen Acquisition" - Scrip, 8 Jul, 2022.)

However, Seagen's hiring of a high-profile CEO – David Epstein, most recently a partner at the venture capital firm Flagship Pioneering and previously president of Novartis AG's Pharmaceuticals division – seems to be a signal the company is intent on determining its own strategic path rather than a merger. (Also see "Seagen Taps Epstein As New CEO After A Tumultuous Year" - Scrip, 10 Nov, 2022.)

A Merck-Seagen merger would have been valued at upwards of $30bn and become the clear bright spot in a rather drab year of deal-making. But even in a year without flashy mega-mergers, the business end of business development continues – this year's crop of the busiest players shows the type of transactions that keep the biopharma engines running.

Pfizer Leads An Unusual Year For The Scrip 100

Jessica Merrill
30 Dec 2022

Executive Summary

Pfizer catapulted back into the lead in the pharmaceutical rankings on the strength of COVID-19 revenues while BioNTech and Moderna both made the list for the first time.

It was an unusual year for the Scrip 100 rankings as revenues from the sale of vaccines and treatments forCOVID-19 skewed the leaderboard in ways that could not have been anticipated before the virus emerged in2020 and sparked a global health crisis.

Pfizer Inc. reclaimed the number one spot in the drug company rankings based on 2021 pharmaceutical revenues, while two young biotechs – BioNTech SE and Moderna, Inc. – debuted in the rankings for the first time, with BioNTech breaking the top 20 ranking number 15 and Moderna breaking in at number 21.

Demand for COVID-19 vaccines in 2021 and a global mass vaccination campaign resulted in two new brands – Pfizer/BioNTech's Comirnaty and Moderna's Spikevax – that are larger by revenue than most pharmaceutical companies included in the Scrip 100. Industry's response to COVID-19, which also resulted in monoclonal antibody drugs and antivirals, contributed to higher revenue growth for the Scrip 100 companies overall.

Pharmaceutical revenues for the 100 companies in the Scrip 100 combined grew 20.5% in 2021 to reach $1.1tn.

While the successful commercialization of vaccines against COVID-19 were a boost, particularly for Pfizer, BioNTech and Moderna, maintaining those positions long term will be challenging as the COVID-19 market transitions to a commercial one driven by regular boosters and demand for vaccines tapers off.

Pfizer and BioNTech are partnered on the commercialization of Comirnaty, which

generated $36.78bn in 2021, while Moderna is commercializing Spikevax, which generated $17.7bn. Both products contributed to another year of strong financials for their developers in 2022, though Pfizer, in particular, is poised for an unprecedented year driven by sales of Comiranty as well as the antiviral Paxlovid (nirmatrelvir/ritonavir), which was authorized in late 2021 and Pfizer owns sole rights to. (Also see "Pfizer Is Changed 'Forever' By COVID-19; Revenue Forecast Hits Triple Digits" - Scrip, 8 Feb, 2022.)

Smaller, Then Bigger

For Pfizer, returning to the top of the Scrip 100 was unexpected, coming after a multi-year strategic initiative to scale back the size and scope of the company. That effort involved narrowing the focus of the diversified big pharma primarily to innovative pharmaceuticals, culminating with the spin out of Pfizer's Upjohn established products business in 2020 into a new company. (Also see "Mylan Reveals First Steps For Viatris As Key Date Approaches" - Generics Bulletin, 9 Nov, 2020.)

Upjohn was merged with Mylan to form Viatris Inc., which ranked number 20 in the Scrip 100 rankings. Viatris is now in the midst of its own reshaping that will change the size and focus of the company as it looks to exit biosimilars and certain other businesses like women's health so that it can invest more into innovative pharmaceuticals in areas like ophthalmology and dermatology. (Also see "Viatris Buys Two Eye Specialists, Setting The Stage For 'Phase Two' Of Its Growth Plan" - Scrip, 7 Nov, 2022.)

As a result of the Upjohn spinout and the spin out of consumer healthcare as well, Pfizer became a substantially smaller company by revenue, and last year Pfizer relinquished the number one spot it had long held in the Scrip 100 rankings, dropping to number seven. (Also see "Novartis Slips Into Pfizer Number One Pharma Slot Amid Leaderboard Shakeup" - In Vivo, 6 Dec, 2021.)

Now, on the strength of Comirnaty, Pfizer catapulted back up to the number one spot – and by a staggering margin. The company's 2021 pharmaceutical revenues of $79.56bn were more than $20bn more than that of Pfizer's next big pharma peer – AbbVie Inc. – and more than $10bn more than Pfizer's prior peak revenue in 2010 of $67.81bn, the year after Pfizer merged with Wyeth and while it still retained patent protection for Lipitor.

BioNTech and Moderna – the mRNA developers behind the two vaccines – were also financially rewarded for their pandemic response.

Both companies joined the Scrip 100 in unprecedented positions for young biotechs having never previously generated revenue from the sale of commercial drugs. BioNTech made a debut at number 15 and Moderna at number 21, with those newcomers, along with the Chinese drug maker Sinovac Biotech Ltd. and Viatris,displacing Teva Pharmaceutical Industries Ltd., Biogen, Inc. and Astellas Pharma, Inc. in the top 20.

Regeneron Among Other Big Movers

Regeneron Pharmaceuticals, Inc.'s growth in the Scrip 100 was also notable, with the biotech jumping 10 spots in the rankings to number 22, driven in part by COVID-19. The company's 2021 pharmaceutical revenues increased 89% to $16.07bn, driven by solid growth of core brands Eylea (afl ibercept) and Dupixent(dupilumab) and turbo-charged by the addition of monoclonal antibody treatments for COVID-19, which added $5.83bn to the top-line. Regeneron ranked number 32 in the Scrip 100 in 2020.

Eli Lilly and Company lso benefi ted from the sale of COVID-19 antibody therapeutics in 2021, and rose in theScrip 100 rankings to number 12 in 2021, from number 14 the year before. The company's 2021 revenue grew15% to $28.32bn, but excluding the antibodies for COVID-19, revenue grew 10%.

Pfizer Leads An Unusual Year For The Scrip 100

Changes at the top of the leader board, including Pfizer's return to the top spot and strong growth by AbbViein the number two position and Johnson & Johnson in third resulted in Novartis AG and Roche HoldingAG slipping in the rankings. Novartis led the leader board in 2020 but fell to the number four spot in 2021,while Roche dropped from number three to number five.

While Novartis and Roche both experienced pharmaceutical revenue growth in 2021, that growth was outpaced by that of AbbVie, which grew 22.7% in 2021, and J&J's pharmaceutical business, which grew14.3%. Both of the US companies have been on solid fi nancial footing, but are approaching more challenging periods heading into 2023, when they are both poised to lose their top-selling drugs to biosimilar competition.

AbbVie's Humira (adalimumab) is set to face biosimilar competition beginning in January 2023, positioning the company directly into a strong headwind, given that Humira accounted for 37% of AbbVie's 2021revenues. J&J's Stelara (ustekinumab) is also the company's top-seller, and the loss of exclusivity in thesecond half of 2023 will also be hard for the company to navigate, though to a lesser extent.

J&J is less reliant on any single drug; Stelara made up 17% of J&J's 2021 pharmaceutical revenues. Thecompany has vowed to investors that the pharma business will grow through 2025 despite the loss of Stelaraand has set a goal to reach $60bn in pharmaceutical sales by then. (Also see "With Stelara's Star Set To Fade, J&J Assures Investors It Will Grow Anyway" - Scrip, 18 Oct, 2022.) The diversified healthcare company is also in the midst of a big transition, with the goal of becoming a leaner pharmaceutical and medical device-focused organization. The company is targeting a spin out of its consumer healthcare organization next year into anew company called Kenvue.

RNA Medicines: Advancements Leading To Investments

Amanda Micklus

19 Sep 2022

Executive Summary

Improvements in generating, purifying, and delivering RNA material, as well as addressing challenges with degradation by enzymes, have made the RNA class more attractive to drug developers.

The concept of RNA as a medicine is not new. The act of using ribonucleic acid molecules to treat or prevent diseases by affecting biological pathways has been pursued for almost 50 years. Antisense oligonucleotides were first synthesized in the 1970s; aptamers first described in the 1990s; the first use of exogenous mRNA to induce the expression of a protein in vivo occurred in the 1990s; and microRNA was discovered in 1993.

These efforts and proofs of concept have been translated into actual commercial products. Since 2004, 18 RNA therapeutics or vaccines have been launched, mainly antisense and RNAi therapies. The latest approval, in September 2022, saw the EMA authorize Alnylam Pharmaceuticals Inc.'s RNAi product Amvuttra (vutrisiran) for adult patients with stage 1 or 2 polyneuropathy caused by hereditary transthyretin-mediated (hATTR) amyloidosis. FDA approval came a few months before, in June 2022. (Also see "Alnylam's Amvuttra To Take Off From Onpattro's Runway" - Scrip, 14 Jun, 2022.)

Approved RNA medicines have been around for almost 20 years. But what has changed more recently are improvements in generating RNA material, as well as purifying and delivering it, and addressing challenges with degradation by enzymes. All together, these improvements have made the RNA class more attractive to drug developers. Their relatively simpler manufacturing leading to lower cost of goods, and ability to reach drug targets not previously accessed by small molecules make RNA especially attractive. According to a 2022

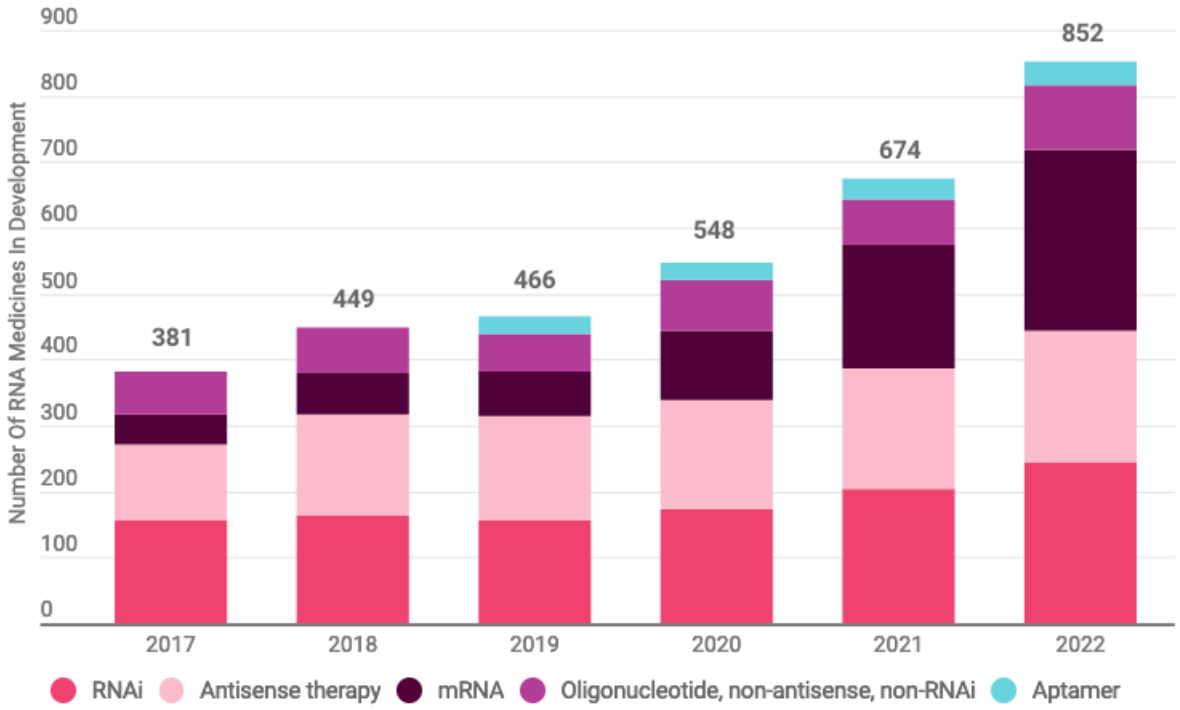
survey by consulting firm CRB Horizons, industry respondents say they are either planning or have already made significant investment in the short term in new RNA manufacturing capacity, and intend to dedicate a substantial proportion of investment toward large-scale production of RNA products.

Moreover, within the last two years, the investment in RNA has accelerated thanks to the rapid development and success of preventative mRNA vaccines for the COVID-19 pandemic. Effectiveness of the COVID-19 vaccines has paved the way for companies to step up resources not only toward development of mRNA, but for RNA medicines as a whole.

RNA Pipeline Is Growing

The number of RNA medicines in the pipeline across all modalities – RNAi, antisense therapies, mRNA vaccines and therapeutics, oligonucleotides (non-antisense and non-RNAi), and aptamers – has more than doubled since 2017, growing from 381 to 852 therapies in preclinical testing through pre-registration as of May 2022. RNA clinical trial starts have also been trending upward, including a nearly doubling of actual trial starts from 104 in 2020 to 197 trials in 2021, and 2022 seeing a healthy number of 136 trial starts as of 31 October. Companies leading the charge and most active in the pipeline include Moderna, Inc., Ionis Pharmaceuticals, Inc., and BioNTech SE.

Exhibit 1: Growth In RNA Pipeline Has Doubled Since 2017



Notes: Chart includes candidates in development from preclinical through pre-registration. Annual snapshots taken in May.

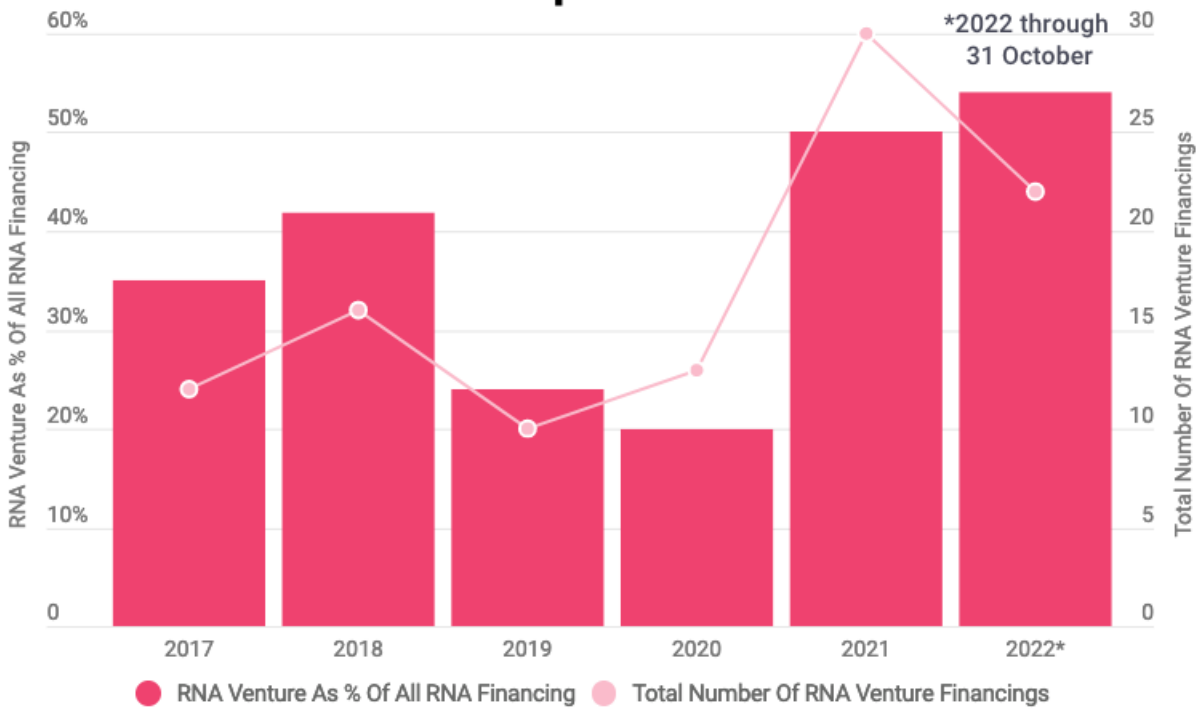
Source: Pharmaprojects

Biopharma companies and venture capitalists have taken notice and increased investments in the RNA field through financing and dealmaking. This increased attention is expected to continue over the upcoming years, with potentials for breakthroughs emerging in the process.

Venture Investment In RNA Has Increased In Recent Years

RNA technologies have been a big driver of venture capital investment over the past five years, as VC firms look to get involved earlier in companies' lifecycles and hope for bigger returns as these companies exit. The number of RNA company venture rounds nearly tripled in 2021 compared with the levels in previous years, reaching a total of 33 financings. And 2022 is on its way to another strong year for RNA venture financing with 22 completed through the end of October, and only needing another 11 to match 2021's full-year total. Further, venture financing as a proportion of total RNA fundraising (including all financing types) is rising, accounting for more than half (54%) of the funding in 2022 so far, a slight increase over the 50% proportion seen in 2021.

Exhibit 2: RNA Technologies: Source Of Increasing Venture Capital Investment



Source: Biomedtracker

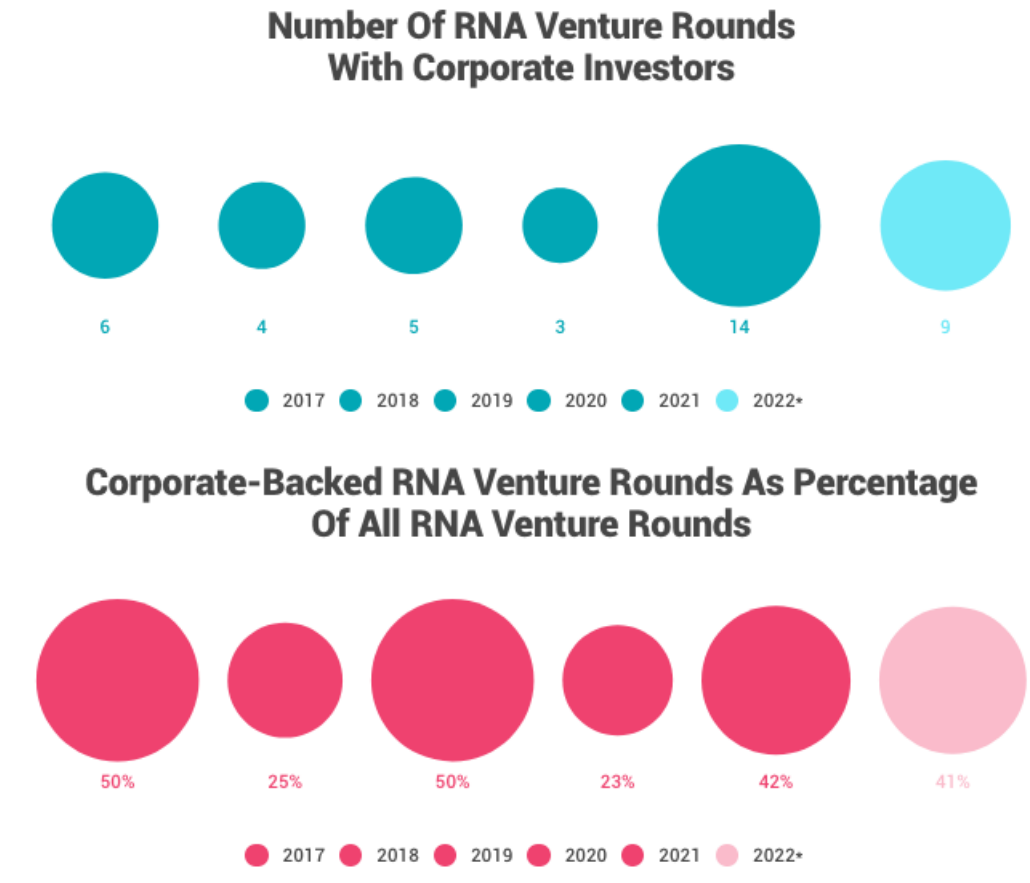
In the last few years, some of the biggest venture rounds have gone to mRNA vaccines developers. These players were drawing attention well before the COVID-19 pandemic, a strong indication of the promise of this technology. Notably, Moderna brought in $560m in its Series G round in 2017, while BioNTech raised a combined $595m in Series A and B financings during 2018–19. That excitement has continued through the pandemic era: In 2021,

Chinese mRNA vaccine start-up Suzhou Abogen Biosciences closed over $700m in its Series C financing led by Temasek Holdings and GL Ventures.

Corporate Investors Are Taking Note Of RNA

An important metric in venture financing is participation from corporate venture arms, or direct investments by pharma or biotech companies themselves, as this is another way to take a pulse of the investment interest by key industry players. RNA venture activity including corporate or biopharma investors had not fluctuated much since 2017; in fact, it was trending slightly downward through 2020. But in 2021, the number of corporate-backed RNA venture financing increased substantially with 14 rounds announced, and accounting for almost half (42%) of the venture rounds done that year. 2022 also looks to be on its way to a strong year in which nine RNA financings through October have included corporate backers. At 41%, this volume has nearly already reached full-year 2021's proportion of RNA corporate venture rounds as a percent of all RNA venture financings.

Exhibit 3: Corporate-Backed RNA Financing On The Rise



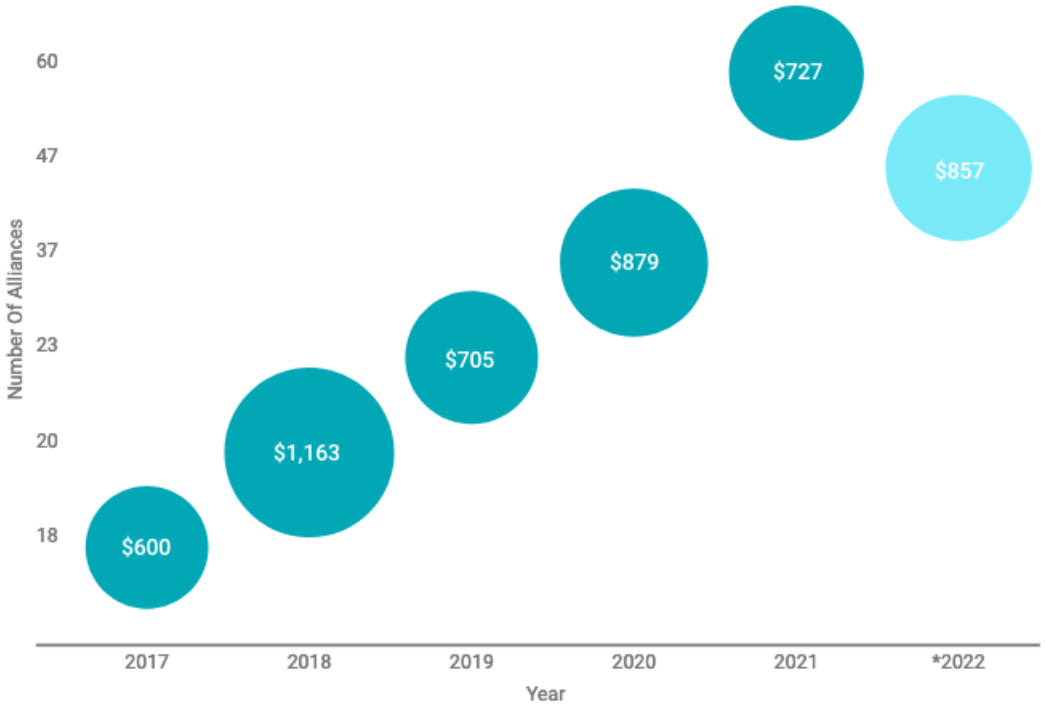
*2022 through 31 October

Source: Biomedtracker

Eli Lilly and Company has been the most active corporate/biopharma company investor over the past five years, participating in six RNA venture rounds. Alongside its corporate venture arm Lilly Asia Ventures, the combined entity has been involved in a total of 10 financings. Eli Lilly is no stranger to RNA, having signed five partnerships each worth at least $1bn since 2017. Its partners have included CureVac NV, Evox Therapeutics Limited, MiNA Therapeutics, ProQR Therapeutics N.V., and Dicerna Pharmaceuticals, Inc. (now owned by Novo Nordisk A/S), whose 2018 RNAi agreement in the areas of cardio-metabolic and neurodegenerative diseases could be worth almost $4bn if all milestones are met.

To date, Eli Lilly has joined in with investors to back three $100m-plus venture rounds. In 2019, the big pharma put in $15m toward Avidity Biosciences, Inc.' $100m Series C financing to support the start-up's work on antibody-oligonucleotide conjugates for myotonic dystrophy type I. Avidity went on to IPO a year later. In 2021, Lilly was part of the investor syndicate for DTx Pharma's $100m Series B round, helping to advance the biotech's work around the FALCON (Fatty Acid Ligand Conjugated OligoNucleotide) platform. And the big pharma joined many other corporate investors to back Capstan Therapeutics Inc.'s $102m Series A financing in 2022. Capstan is looking to address multiple therapy areas, including oncology, inflammation, fibrosis, and blood diseases, with mRNA-encoded CARs and gene editing.

Exhibit 5: RNA Partnerships Are Growing With Average Values >$500M



Note: Size of bubble represents average deal value for that year

* 2022 through 31 October

Source: Biomedtracker

Partnering RNA Assets Gaining Steam

Licensing and collaborations to enable progression in RNA development is another form of investment that industry players have leveraged. RNA partnerships have steadily gained traction, reaching a high of 60 deals in 2020 after steadily increasing in volume since 2017. Annually, average deal values for most years has fallen in the $600–800m range, but in 2018 the average ballooned to over $1bn thanks to the aforementioned Lilly/Dicerna deal, as well as a potential $4bn agreement between Janssen Pharmaceuticals Inc. and Arrowhead Pharmaceuticals, Inc. around ARO-HBV, an RNAi therapy (now called JNJ-3989) for HBV. (Also see "RNAi Partners Vie To Lead Race To Cure Hepatitis B" - Scrip, 4 Sep, 2020.)

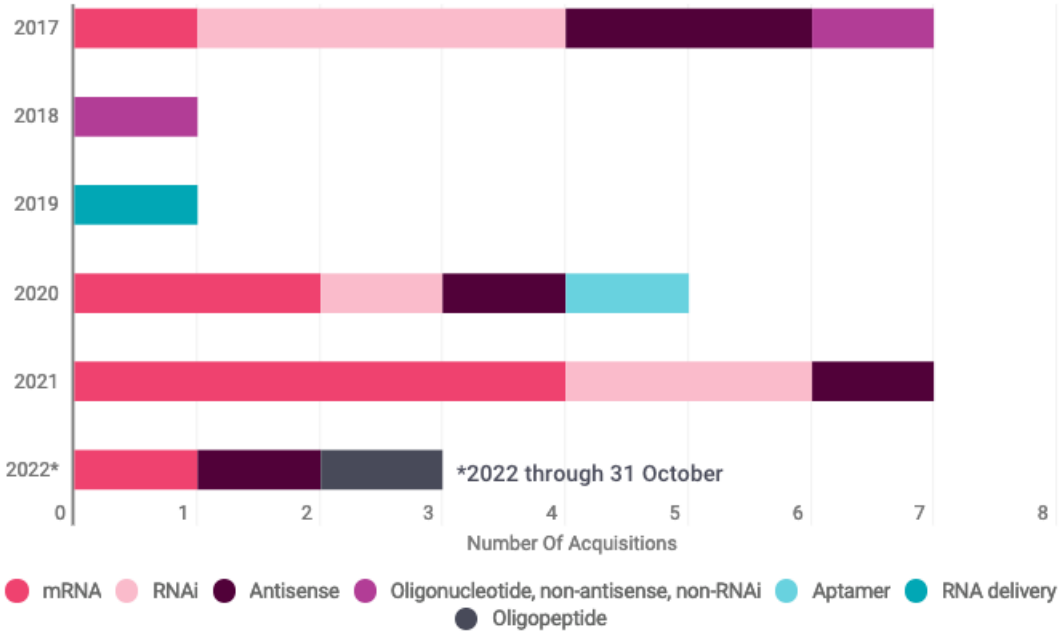
Notably in 2022 so far, the average partnership value is trending on the higher side, at $857m. Looking ahead to the rest of 2022 and beyond, some of the biggest investments may go into novel RNA technologies if the latest partnerships are any indication. The most expensive deal of 2022 to date focuses on circular RNA (circRNA). Merck & Co., Inc. may pay Orna Therapeutics, Inc. up to $3.65bn in up-front and milestone fees for development of circRNA-based vaccines and therapeutics in infectious disease and oncology. Orna has been well funded by venture investors as well, raising over $300m from its Series A and B rounds. CircRNA may have many advantages over linear RNA, including resistance to exconuclease degradation and better stability. Even so, circRNA is very much a nascent field, with only eight therapies in the pipeline. All of the drug candidates are currently in preclinical studies, with CirCode being the most active at four therapies in development.

In another big money deal in 2022, Beam Therapeutics Inc. will use its mRNA and lipid nanoparticle technologies to deliver in vivo based editors to treat rare liver, muscular, and genetic diseases. That agreement resulted in partner Pfizer Inc. paying $300m up front and potentially another $1bn in milestones.

An additional area of excitement in the RNA field are self-amplifying mRNAs, which have the potential for reduced dosing and longer protein expression. In early November 2022 (just past In Vivo's data cut off), Arcturus Therapeutics Ltd. signed a deal worth up to $4.5bn granting CSL Seqirus rights to use its self-amplifying mRNA technology for development of COVID-19, influenza, and respiratory infectious disease vaccines. (Also see "CSL Licenses Arcturus mRNA Technology, But COVID-19 Vaccine Remains Uncertain" - Scrip, 2 Nov, 2022.)

Volume is generally low in RNA-focused acquisitions – only a total of 21 have been done since 2017, making it difficult to understand trends over time. Even with the small numbers, it is worth noting a shift: A greater number of companies in the mRNA space – including mRNA vaccines and therapeutics, and mRNA cell-based therapy – have been targeted for acquisitions, while fewer companies involved in RNAi have been bought recently. This increased concentration on mRNA acquisitions is yet another result of the success that the industry has seen with mRNA vaccine development, which has trickled into investment in mRNA therapies.

Exhibit 6: Shift From RNAi To mRNA: RNA Acquisitions By Modality



Notes: mRNA category includes vaccines, therapeutics, or cell therapies. Deals that include >1 RNA modality were counted more than once.

Source: Biomedtracker

Looking Ahead In RNA Investment

There is strong reason to believe that the momentum gained in recent years with investment in RNA medicines will continue for the foreseeable future, as advances are made drawing increased venture funding. Peer-to-peer dealmaking between smaller biotechs in RNA has been the norm, but many multinational players have already signed deals, and the expectation is for the trend to increase. The current environment is encouraging, but similar to other advanced therapies like cell and gene therapies, the question still remains how commercially viable the RNA market will be, considering the investment in research, development, and manufacturing while ensuring that patients eventually have access to these life-saving medications.

Flight Of The Navigator: Bluebird bio's Andrew Obenshain

The gene therapy firm is transitioning to a commercial organization

Jo Shorthouse

07 Dec 2022

Executive Summary

For 12 years, bluebird bio has been developing gene therapies for rare genetic disease and now, with two approvals under its belt, the company is continuing to explore uncharted territory as it brings forward innovative new treatments. Holding the map is CEO Andrew Obenshain.

When deciding on its company moniker in 2010, bluebird bio said the name exemplified its intent to set a bold new course for the future. The Eastern Bluebird is known to be a symbol of transition and renewal as well as a competitive and disciplined bird, it said at the time, traits that were reflected in the company's passion for transforming the lives of patients and their families.

Twelve years down the line and two therapy approvals later, the company continues to set its stall by the characteristics of transition and renewal. The last two years have been punctuated by an evolution of what the company looks like, develops, and how it works with major stakeholders. The organization has changed shape by spinning out its oncology arm, restructuring to extend its cash runway, exiting commercial activities in Europe after failing to secure reimbursement for gene therapy Zynteglo (betibeglogene autotemcel), and debuting an innovative outcomes-based contracting strategy in the US.

The other major change has been a new leader, Andrew Obenshain, who became CEO in January 2021 when predecessor Nick Leschly

became CEO of the company's oncology spinoff. Not that Obenshain is a new bird in the nest, he has worked with the company since 2016 as head of Europe, and then as president of its Severe Genetic Diseases division. Having previously worked for Shire Pharmaceuticals Group PLC as general manager for France and Benelux, responsible for a portfolio that included seven rare disease products, and prior to that for Sanofi Genzyme, Obenshain has spent his career working alongside researchers, developers, regulators, and payers have pushed forward new strategies for cell and gene therapy.

His career path took him further, to becoming the leader of a pioneering company during yet another transition, this time at a fully commercial company. 2023 is set to be a huge year for bluebird, with two newly approved therapies to commercialize and a third on the horizon.

Following the August 2022 FDA approval of Zynteglo for the treatment of children and adults with beta-thalassemia who require regular red blood cell transfusions, the company is progressing through launch plans and is on track for first apheresis (cell collection). It has also completed the activation of its first wave of qualified treatment centers, expecting to scale these to 40 to 50 by the end of 2023. At the time of writing, the company had signed outcomes-based agreements with pharmacy benefit managers (PBMs) representing more than 40 national and regional plans.

The company will not see revenue from Zynteglo until it is infused into patients, which will take months due to the ex vivo gene therapy's complex manufacturing and quality control process. The list price for Zynteglo is $2.8m, with an 80% payback option for patients who do not achieve and maintain transfusion independence in the two years following treatment. The investment bank Raymond James estimates that peak sales of the gene therapy should reach around $206m in 2027. (Also see "Bluebird's Zynteglo Launch Under Way, But First Revenue Will Take Months" - Scrip, 18 Aug, 2022.)

In September 2022, the FDA granted accelerated approval for Skysona (elivaldogene autotemcel) to slow the progression of neurologic dysfunction in boys 4 to 17 years of age with early, active cerebral adrenoleukodystrophy (CALD). Three QTCs have been activated for this therapy, and the company anticipates commercial readiness for Skysona, with a list price of $3m, by the end of 2022. Unlike Zynteglo, Skysona is not subject to a outcomes-based payment scheme.

Bluebird plans to submit the sickle cell gene therapy lovotibeglogene autotemcel (lovo-cel) to the FDA in the first quarter of 2023 and could potentially be launched by the end of the year. Could bluebird be looking at three commercialized products by the end of 2023? "I'll leave that to the FDA," Obenshain diplomatically tells In Vivo.

Whether 2023 brings two successfully launched therapies, or three, the grooves made by commercialization of Zynteglo and Skysona will ultimately benefit the launch of lovo-cel. It will be the same physicians using Zynteglo that will be using lovo-cel at the same transplant centers.

Obenshain is especially excited about the potential for lovo-cel's use in the US Black community, which has been "significantly underserved" and "under invested in". He said: "The potential to bring a solution to this patient community is incredibly gratifying."

Ruffling Feathers

Bold commercial decisions taken by Obenshain, and the wider bluebird team have led to this point of transition, taking the company from nest builder to fully fledged trailblazer. But those decisions have not been taken without a huge amount of consideration. "I'm a big believer

that you don't make decisions in a silo, you make them with your team," Obenshain said. "I believe in sweating the details of the decision because it's the decision that matters. You can't always control the outcome, even if you make a good decision."

"I believe in sweating the details of the decision because it's the decision that matters. You can't always control the outcome, even if you make a good decision."

The company has two principles that it follows universally for making those big decisions: taking the long-term view and keeping focus on its mission. Obenshain and his team consider not just what is best for bluebird and the patients that it serves, but also for the whole gene therapy industry. While these types of commercial decisions are never easy, he says, these two principles help to clarify and points the organization toward its "true north."

Having now brought forward two of the five approved therapies in the US, those decisions have come to bear in a positive way, both for the company, and for the gene therapy industry. Some strategic choices are easier to make than others; bluebird's innovative outcomes-based contracting strategy with payers for Zynteglo was made based on insights from the payers themselves. (Also see "Zynteglo Could Be Gene Therapy Test Case For Viability Of Outcomes-Based Contracts – UHC Exec" - Pink Sheet, 21 Jun, 2022.)

With Zynteglo, bluebird has a therapy with a high efficacy rate but a small risk of failure in its clinical data (in clinical studies 89% of patients achieved transfusion independence). However, having an endpoint that was easily measurable – transfusion independence – made the reimbursement strategy simpler, explained Obenshain. "What we learned from the payers, which actually surprised us a little bit, is they don't want to look for more than a year or two out, they want something they can measure quickly and easily, and they want to mitigate the risks," he said.

Rationalization aside, some decisions cut deeper than others. "The decision to leave Europe was heartbreaking," said Obenshain when discussing bluebird's 2021 exit from the continent to prioritize the US market when European payers did not recognize the value in the $3m therapy. As a child Obenshain lived in London, before moving to Belgium, then France, and finally Switzerland before moving to the US. Despite the American accent his cultural identity hangs somewhere over the Atlantic, he explains. (Also see "Bluebird Exits Europe, Casting Clouds Over Gene Therapy Commercial Effort" - Scrip, 9 Aug, 2021.)

"The decision to leave Europe was heartbreaking"

Despite bluebird's commitment to clinical sites, patient communities, regulators, and even governments and payers at first, there "really wasn't a decision," the CEO said. "There was only one path forward that we could have taken. So as much as we sweated, I really think that there was no other option to us. Looking on that today, the fact that we're around as a company and able to bring these therapies forward, at the very least in one geography, it owes in large part to the fact that we made those really difficult decisions then."

The value of Zynteglo has been recognized in the US, with an ICER report validating that the cost is justified up to $3m. (Also see "Zynteglo Is Cost Effective At $2.1M, ICER Proposes; Validation For Bluebird's Pivot To US?" - Pink Sheet, 15 Apr, 2022.)

Bluebird is fully focused on the US, said Obenshain, to show that it can commercially scale the therapy, and take some risk and uncertainty out of the system for payers. The

hope is that this, in turn, will help the gene therapy industry—and maybe, someday, bluebird—move forward not just in one country, but many markets.

A Hard 12 Months

The organization has had a particularly hard 12 months of decision making. In April, it had to lay off 30% of its workforce and deprioritize some investments to free up capital for upcoming launches, aiming to deliver up to $160m in cost savings over the next two years. (Also see "Bluebird Bio Restructures Amid Financial Woes, But Will It Fly?" - Scrip, 5 Apr, 2022.)

Two years of taking tough decisions mean that the firm is now ahead of the curve, said Obenshain, and prepared for the macroeconomic headwinds that have been battering the biopharma industry since February 2022 when the biotech bubble burst and valuations floored.

Remember that the Eastern Bluebird is a competitive and disciplined creature? That still stands to this day, he said. The company has it's spend under control, it is operationally sound, and has hit all its milestones this year, said Obenshain. It is also producing therapies that offer clinical value. "That amalgamation of an internal company that can really make hard decisions and has discipline, combined with therapies that bring value to the healthcare system, means that we're in a good position to get through this tough time," he opined.

The tough times over the last year have been eclipsed by the first approvals in the company's 12-year history, and Obenshain's reaction to these events is visceral. He described the emotion when Zynteglo got approved, "I thought it'd be difficult to top that, then Syksona got approved," he recalls.

"I tell my team, 'You're writing a chapter in the history of medicine'. The approval of Zynteglo and Skysona are key moments in that chapter."

Having been involved in the biotech industry for over 20 years, the weight of bluebird's accomplishments to date are not lost on him. Its place in the history of medicine has now been secured and Obenshain is well aware of that. "I tell my team, 'You're writing a chapter in the history of medicine'. The approval of Zynteglo and Skysona are key moments in that chapter."

Leading The Flock

Obenshain has been involved in the gene therapy industry since he studied genetics, cell, and developmental biology at Dartmouth College, before receiving his MBA from Northwestern's Kellogg School of Management. He has worked as a consultant, a venture capitalist, and then pursued a career in pharma by joining Genzyme and Sanofi in commercial roles before leaving to work in rare disease at Shire.

Having been a bluebird for many years, Obenshain – like his company - is indicative of the firm's phenotype. He describes himself as non-hierarchical, collaborative, and mission driven. As a leader, he is clear on direction, adding that "people don't generally doubt what my opinion is on something."

A visiting CEO once advised a younger Obenshain to plant himself where he would grow. Having planted himself at bluebird in 2016, his roots are now intertwined with the success of the company, as it continues to develop budding gene therapies. As an organization, those roots have created a company that is stronger than it was 18 months ago, and it is Obenshain's leadership that will determine whether this plant now bears fruit.

Pharma Innovation: Europe Is Being Edged Into Third Place

Daniel Chancellor

24 Oct 2022

Executive Summary

With a declining share of global R&D and investment, Europe risks the pharmaceutical industry being increasingly molded in the image of others.

Each year, the European Federation of Pharmaceutical Industries and Associations (EFPIA) publishes an annual factbook to emphasize the tremendous strategic importance of the pharmaceutical industry to the continent. Among the key figures, European companies collectively invest approximately €40bn in R&D annually, rising at a compound annual growth rate (CAGR) of 4.0% since 2017. An impressive figure at face value, although one that the US eclipses with more than €70bn spent, with an equivalent growth rate of 8.5%.

While the trans-Atlantic equilibrium continues to tilt away from Europe and to the US, a new powerhouse in China is emerging. The local drug market has been growing at a double-digit rate for many years, and this has been accompanied by intense domestic R&D activity. EFPIA estimates that R&D growth in China is running at an impressive 12.9% CAGR. If the current trajectory is maintained, China is on course to overtake Europe within the next 10–15 years purely in terms of spend, although other indicators point towards the crossover point being reached much earlier.

This rebalancing in Europe's position on the global stage has been a gradual process, beginning perhaps as early as the 1990s, but certainly accelerating in more recent years, as In Vivo's analysis shows. While this is by no means an existential threat, biopharmaceutical industry stakeholders must be mindful of the current state of innovation within Europe. Past successes alone will not sustain the industry, and innovation is an essential component to protect Europe's future.

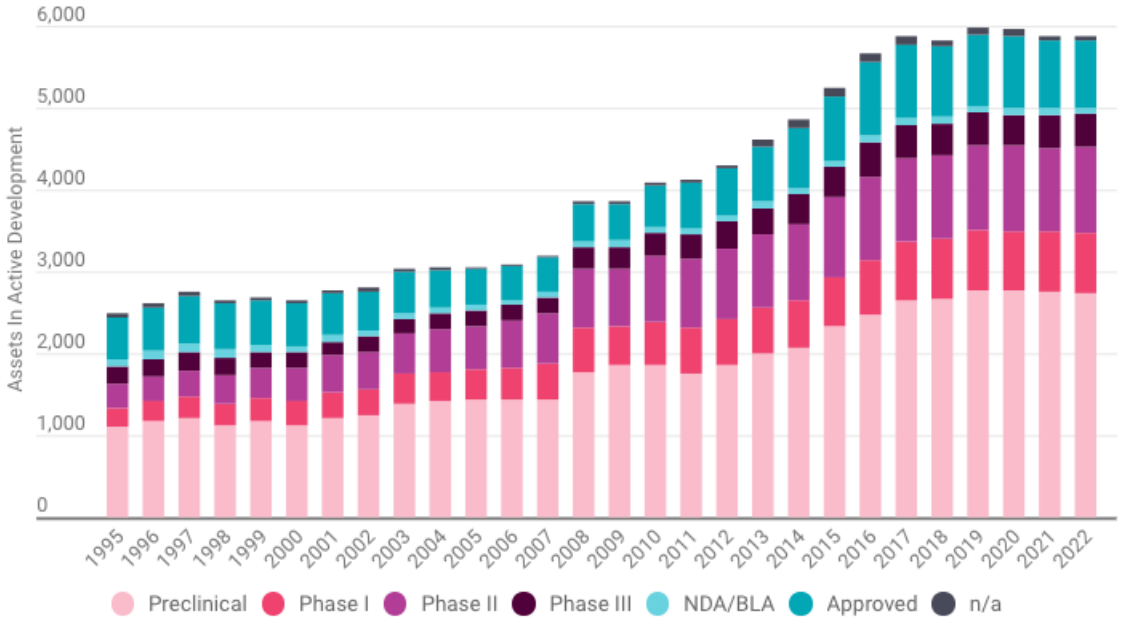
Pharma Innovation: Europe Is Being Edged Into Third Place

Pharma Pipelines Have Reached A Ceiling

In line with its rich heritage, European biopharmaceutical companies have discovered or developed many of the medicines that have had most impact on global health. Buoyed by successes, drug developers have continued to increase R&D spending to produce the medicines of the future. This can be viewed through the lens of Citeline's drug development database, Pharmaprojects, which has tracked industry R&D over several decades. Annual snapshots are available going back to 1995, when European biopharmaceutical companies had a combined pipeline containing 2,500 assets under active development. This number has grown steadily year-on-year, before accelerating rapidly between 2012 and 2017 to reach almost 6,000 pipeline drugs.

However, rather than continue the ascent, European drug developers have reached a ceiling at this level, whereby current levels of investment cannot sustain any further expansion. Within this pipeline, 47% of drugs are in preclinical development, while 39% are at the various clinical stages from Phase I through to pre-registration. The remaining 14% are drugs that have already been approved and are being further developed in additional indications, patient subpopulations, or new geographies.

Exhibit 1. Evolution Of European Biopharma R&D Pipeline By Highest Stage Of Development



Source: Pharmaprojects, September 2022

Pharma Innovation: Europe Is Being Edged Into Third Place

In the years following 2017, the global pipeline has seen a notable shift. While Europe has remained stuck at around 5,900 assets, the global pipeline has expanded from 15,000 to exceed 20,000 drugs in 2022 with a CAGR of 6%. Europe's share of global R&D has plummeted from 39% to 28% in just five years.

A large proportion of the global growth has come from China, which has seen a remarkable 35% CAGR over the last five years. Starting from a small base, Chinese companies have surged from 800 R&D projects to almost 3,800 during this time. The US biopharmaceutical pipeline has maintained its upward trajectory, adding further distance to Europe in second place with a 4% CAGR. Japan, which for a long time has been a major R&D hotspot, has declined in recent years and now finds itself comfortably behind China.

Exhibit 2. Drug Pipeline Growth By Company Headquarter Location, 2017–22

	2017	2018	2019	2020	2021	2022	CAGR 2017–22
Europe	5,877	5,824	5,981	5,962	5,884	5,873	0.0%
US	7,737	7,832	8,341	8,535	9,113	9,481	4.1%
Japan	1,553	1,532	1,568	1,552	1,513	1,453	-1.3%
China	843	1,069	1,637	2,170	2,865	3,743	34.7%
Global	14,926	15,264	16,690	17,717	19,012	20,384	6.4%

Note, drugs will be counted across more than one region if a licensee in a different geography is also pursuing development, so the totals will not sum. Snapshots are taken annually in May.

Source: Pharmaprojects, September 2022

Underweight In Oncology, Cell And Gene Therapy

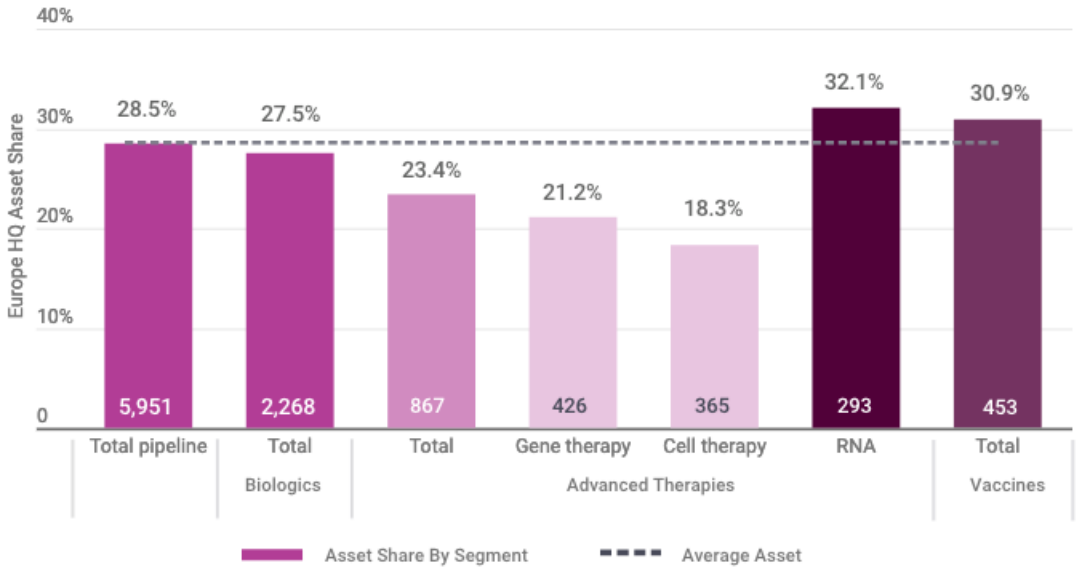
Europe's exposure to emerging science will also have long-lasting implications for its future prospects. As the industry pivoted towards biological drugs in previous decades, European companies have been well positioned with strong capabilities in antibody drug discovery. Pioneers include Cambridge Antibody Technology and Genmab A/S, while large European pharmaceutical companies have made strategic acquisitions to bolster their capabilities, such as Roche Holding AG (Genentech, Inc.) and AstraZeneca PLC (MedImmune LLC). This biotechnology revolution has also extended beyond the design of drugs, also modernizing the way vaccines can be manufactured. Europe has a long-established leadership position in the vaccines space through companies such as Sanofi and GlaxoSmithKline Pharmaceuticals Ltd..

The next wave of evolution within the pipeline is well underway, as drug developers are seeking to capitalize on new genomics technologies to create drugs and vaccines based on cell, gene and RNA scaffolds.

As shown in Exhibit 3, Europe is part of this transition, but with varying levels of exposure. With 5,951 drugs in active development as of September 2022, European biopharma has a 28% share of the total global pipeline. The proportion of biologics under development (2,268, 27%) is on par, while vaccines remain a strength (31%), although the subset of advanced therapies is notably below average. Europe possesses just 23% of the global pipeline

for advanced therapies, with 867 gene, cell or RNA-based drugs in development as of September 2022. Within this, Europe is well positioned in RNA drug development (32%), thanks to innovators such as BioNTech SE and CureVac NV, in addition to acquisitive larger companies like Novo Nordisk A/S and Sanofi. Counterbalancing this, Europe is trailing rivals from the US and China in gene (21%) and cell therapy (18%), with much smaller domestic pipelines. While these are not yet mainstream drug modalities, European innovators are already giving away a large head start, which will be difficult to overturn through acquisitions alone as the technologies gain further clinical validation.

Exhibit 3. European Exposure To R&D Growth Segments By Modality



Source: Pharmaprojects, September 2022

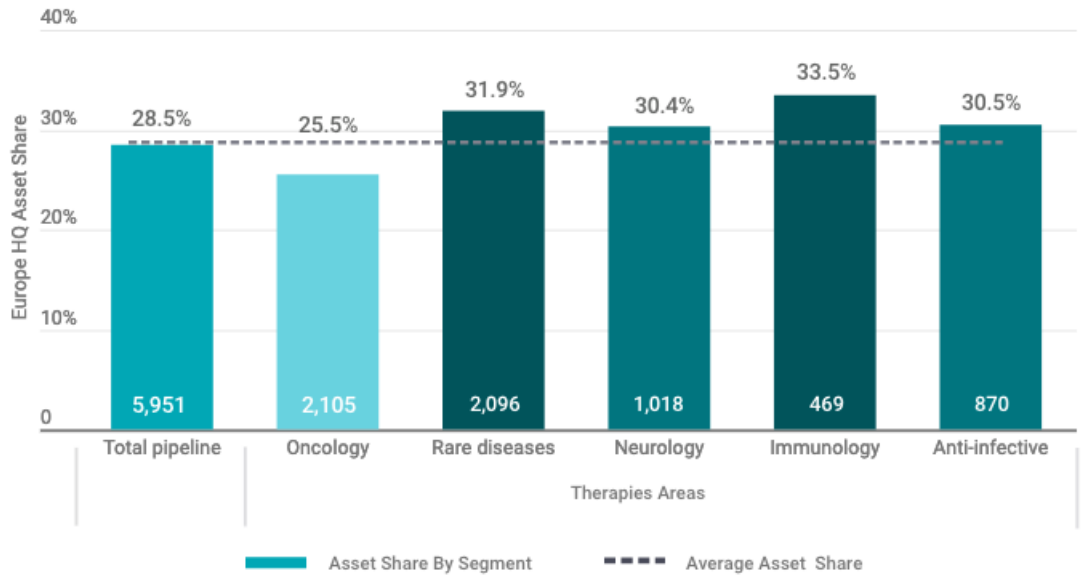
A similar analysis by therapy area shows an analogous trend, whereby Europe as a collective is underexposed to the single largest growth driver in R&D trends – oncology – but has pockets of strength in other growth drivers. Europe's share of global oncology drug development is just 25%, which leaves it underexposed to a therapy area that accounts for approximately 40% of active pipeline assets, new clinical trial starts and partnering activities globally.

By contrast, Europe is a global leader in rare diseases R&D. Thirty two percent of global rare disease drug development is taking place within European-headquartered biopharmaceutical companies, even despite the international acquisitions of former standalone companies such as Actelion Pharmaceuticals Ltd., Shire Pharmaceuticals Group PLC and GW Pharmaceuticals plc. This position is supported by the R&D legacy of such companies, plus the strategic emphasis that larger players place on rare diseases. AstraZeneca and Sanofi are two such big pharma companies that have placed large bets on Alexion Pharmaceuticals Inc. ($39bn) and Genzyme ($20bn), respectively.

Besides oncology and rare diseases, the other prominent segments of the pipeline are neurology, immunology and anti-infectives. Europe carries an above-average share of the global pipeline in each of these areas, ranging from 30–34%, as shown in Exhibit 4.

It could be argued that the European pipeline has better overall balance across the major therapeutic challenges. By limiting exposure to the hyper-competitive oncology drug landscape, eventual success rates and patient access may counterbalance any slower growth rates.

Exhibit 4. European Exposure To R&D Growth Segments By Therapy Area



Source: Pharmaprojects, September 2022

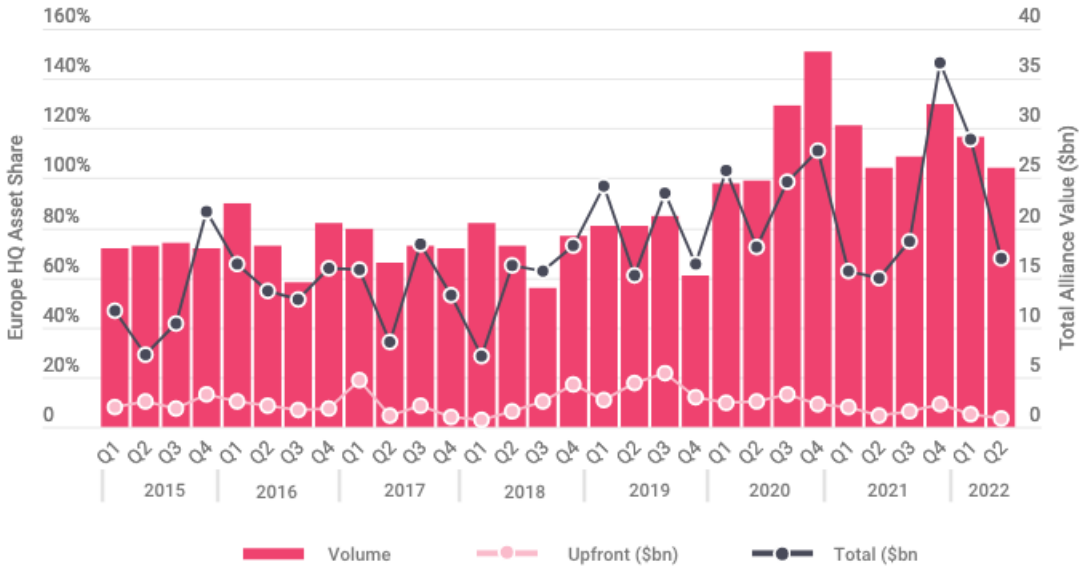
Healthy And Growing Appetite For Partnering Deals

European companies continue to play an active and prominent role in the global partnering landscape. Almost half (43%) of all alliances since 2015 involved at least one European company as either the licensee or licensor, which trails only the US (69%) and is a long way ahead of the nearest rival (China and Japan, both 12%).

As can be seen in Exhibit 5, the general trend within Europe is one of increasing partnering activity, measured either as the number of deals or their value. In the most recent period, there are an average of 115 alliances involving European biopharmaceutical companies each quarter, with combined upfront payments of $1.5bn and a total potential value in excess of $25bn. The number of deals has expanded at a compound annual growth rate (CAGR) of 8% between 2015 and 2021, which the total potential deal value slightly exceeds with a 9% CAGR.

Few deals will realize all the milestones required to hit this limit, so it is noteworthy that total upfront payments have declined at a CAGR of -4% over the same period. Set against the increase in the number of alliances, this reflects the growing tendencies of pharmaceutical companies to license assets at earlier stages of development and adapt typical deal structures to reflect this risk.

Exhibit 5. Europe Biopharma Alliance Trends, 2015–22

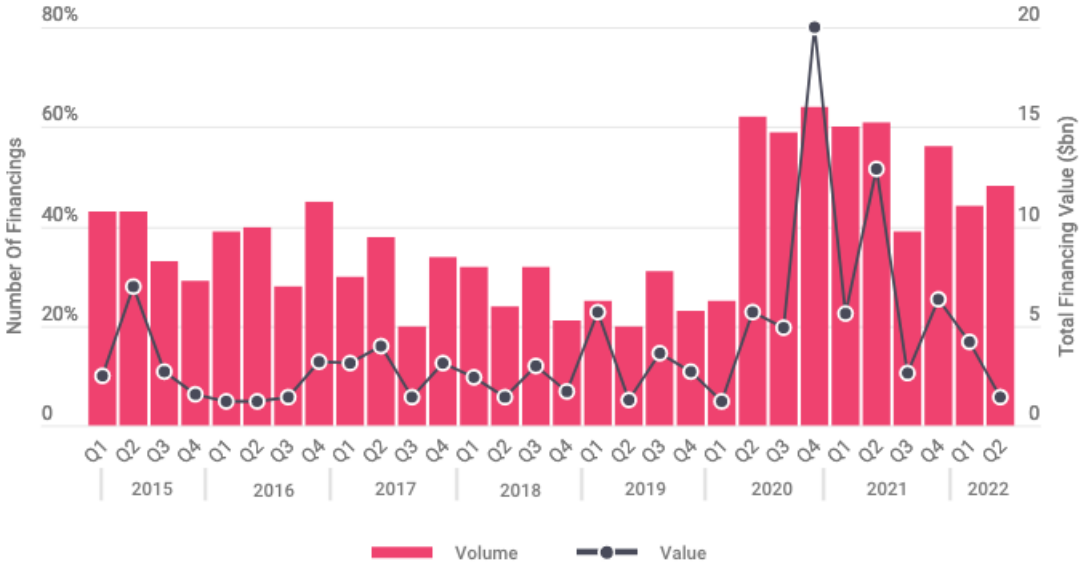


Source: Biomedtracker, September 2022

Despite Pandemic-Related Capital Influx, Europe Is Gradually Losing Global Share

European companies seeking to raise capital were among the beneficiaries of the pandemic, in line with broader investor interest in the biopharmaceutical sector. After several years of relatively stable levels of financing deals, 2020 saw a remarkable uptick in both the number and potential value of fundraising activities. This peaked in Q4 2020 with 64 separate financings tracked by Biomedtracker for a total value of $22bn, before gradually regressing back towards the mean. Some degree of fluctuation is inevitable, although the last full four quarters show an average run rate of approximately $4bn raised across 50 deals per quarter. It is not yet clear whether this is a new baseline level of fundraising activity, as activity is still approximately 40% higher than in the years prior to the pandemic.

Exhibit 6. Europe Biopharma Financing Trends, 2015–22



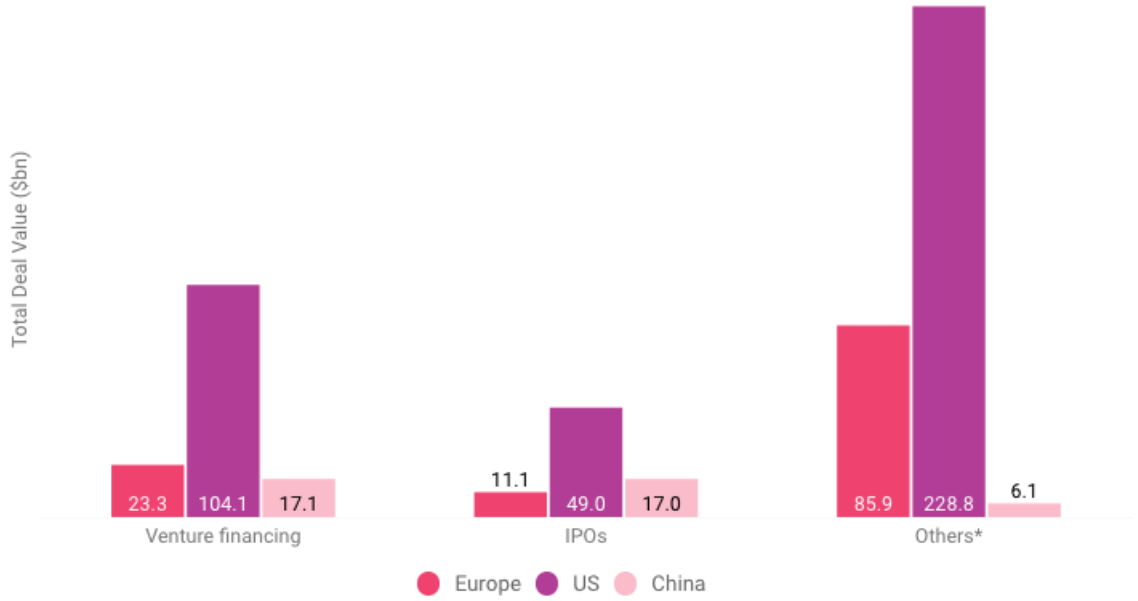
Source: Biomedtracker, September 2022

However, measuring the proportion of global fundraising activities conducted by European-headquartered biopharma companies shows a gradually diminishing share. In terms of deal volumes, European-headquartered companies had a one quarter share in 2015, although this has ticked down to one in five financings on average by the mid-point of 2022. Assessing by the value of these financings, the ratio declined from one third to one quarter of all activity over the same time period.

The chief beneficiary – or cause – of Europe's decline on this metric has been the rising attractiveness of Asian markets. China is capturing an ever-increasing portion of investment as both the domestic drug market increases in size and volume, and China-headquartered pharma companies expand their R&D capabilities to include innovative drug discovery as well as generics and manufacturing. In the meantime, the US has retained its standing as the leader in life sciences innovation and entrepreneurship.

Furthermore, investment into new companies in Europe has lagged international comparators. The balance of investment in Europe has largely been toward older companies, rather than venture financing or initial public offerings (IPOs) for companies in their earlier years. Since 2015, companies in Europe have raised a combined $34bn via these methods, accounting for just 15% of global start-up activities. This is overshadowed by the $153bn in new company financing that originates in the US, which possesses a two-thirds share of the global total. Rather than competing with the US, China is now a much more appropriate comparator, where companies have also raised $34bn via venture financing or IPOs since 2015 (see Exhibit 7).

Exhibit 7. Biopharma Financing In Europe, US, And China By Deal Type Since 2015



*includes debt, FOPOs, PIPEs, priority review vouchers and royalty sales

Source: Biomedtracker, September 2022

In Summary

Europe may no longer be the force it once was on the global stage. While humbling to admit, the axis between the US and Europe has tilted, such that Europe now occupies less than a 30% share of the global market across various measures. This includes the scale of innovation, from pipeline size to the number of therapeutic breakthroughs, as well as commercial indicators such as prescription pharmaceutical sales and financial investment.

Europe's current position is still one of strength, although the rate at which its stake is declining is a concern. It is incumbent on the full range of stakeholders – drug developers, academia, investors, payers, regulators, policymakers – to set about a strategy to halt any further decline and protect Europe's standing in the global innovation ecosystem. On the part of industry players, this involves an impartial assessment of scientific strengths and technological shortcomings, prioritizing investment at the cutting edge of innovation and unmet patient needs.

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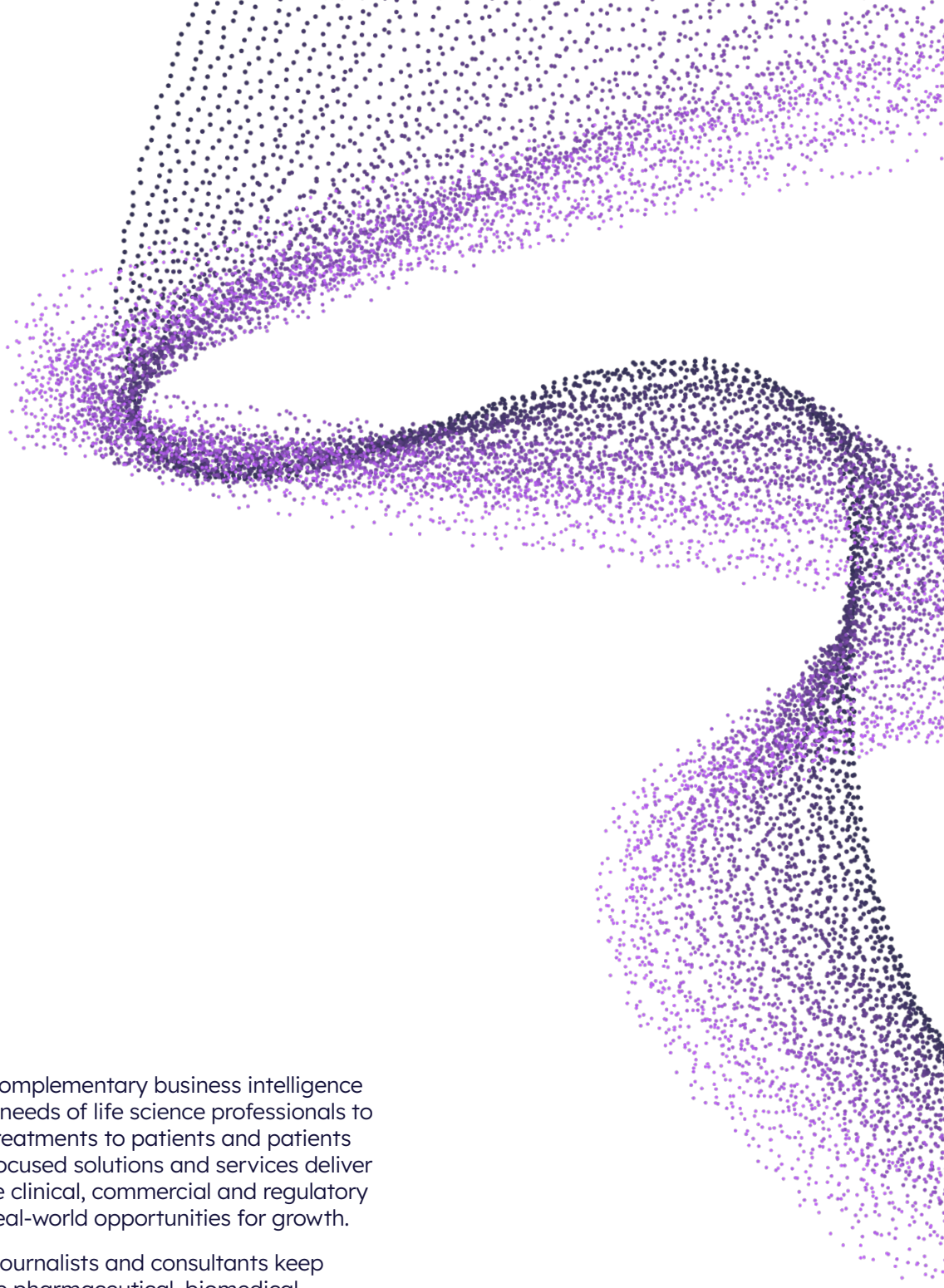

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