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

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ANALYSIS

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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 three industry 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 enrollees 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 enrollees 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.

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“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 13 years. “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 in 2020 it was the 43rd 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.”

Sidebar: (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.).

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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 20th 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.

**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)

“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.

**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 for metachromatic 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 CTX001 gene 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 Exhibit 1). 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 Arikayce after 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. Approvals aside, the wave of ATMP potentially coming to market in the next few years may be stymied by payment systems that are not equipped to allow patients the access to drugs that are desperately needed by the rare disease population.

**The Big Dipper**

Questioned on this theme by *In Vivo*, all three interviewees stated that fundraising will be the biggest challenge for the next 12 months. “We’ve seen four or five years of record amounts of money, I think we’ll see a significant decrease in 2023,” said Tansley. “Those funds which have raised in the last two or three years will be well placed. And often in difficult times, that’s when the best returns are had. Those looking to raise may have to temper those ambitions. Fundraising for venture intervention 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 last 12 months. It has been a very active fundraising environment caused by venture investors raising a lot of money over the last two years, said Papiernik. “The coffers are relatively full which has created a ‘positive inertia’ to the system. People have money and will defend the company when they can.” In his view, there is no reason for this situation to change, and 2023 will be no different unless the
IPO starts going up, an unrealistic 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 we see an uplift in the in the public markets, the later-stage investors will focus on the public markets rather than private,” he said.

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