General Market Overview

As we navigate the evolving landscape of the life science industry in the post-pandemic era, the biopharmaceutical industry has returned to pre-COVID-19 levels of investment, R&D, and approvals of novel medicines. Scientific and technological advances are filling an unprecedented pipeline of new treatments, and encouragingly life science investors have continued to raise large funds and invest in new opportunities.

Highlights

- For the first time since 2019, XBI ended the year with a 7.6 % gain driven by increased pharma M&A. ADCs, radiopharmaceuticals, immunology, and neurology were hot therapeutic areas for dealmaking.
- Big pharma has increasingly focused on large indications such as cardiometabolic diseases and neurology. Obesity leaders Novo Nordisk and Eli Lilly's stocks skyrocketed following groundbreaking data showing benefits of GLP1-class drugs beyond weight loss alone.
- A rebound was seen in FDA drug approvals with 55 new drugs and in addition several cell and gene therapies and vaccines.
- The IPO window continued to be closed but might be opening in 2024.

Public markets

Global stock markets exhibited their strongest year performance since 2019 following a two-month rally at the year's end, driven by a dramatic shift in interest rates expectations after a faster-than-expected fall in inflation. S&P 500 was up 24 % on an annual basis and traded just short of its record high in January 2022. The surge was mainly driven by big tech stocks, and the tech-dominated Nasdaq Composite index showed an impressive 43 % gain.

While the wider US stock market is approaching record levels, large drugmakers illustrated here by S&P 500 Pharmaceuticals index have underperformed relative to the S&P 500 with the exceptions of Eli Lilly (up 59 %) and Novo Nordisk (up 53 %). During the year, the biotechnology index XBI had several dips following macro events. XBI still remains almost 50 % lower than its all-time high in early 2021. However, the bet on interest rate-cuts and a surge in pharma deals the last months have raised hopes of a turnaround in the biotechnology sector, as the XBI rallied 39 % from its lowest point in October and ended with a 7.6 % increase on an annual basis. XBI was one of the biggest beneficiaries following the interest rate cuts in late 2023, as it had its best two-month stretch since 2019.

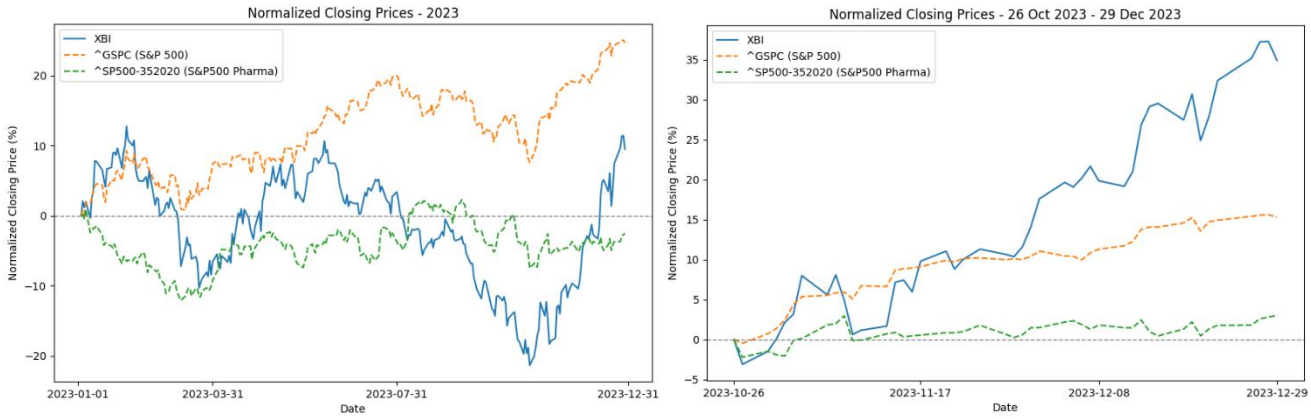
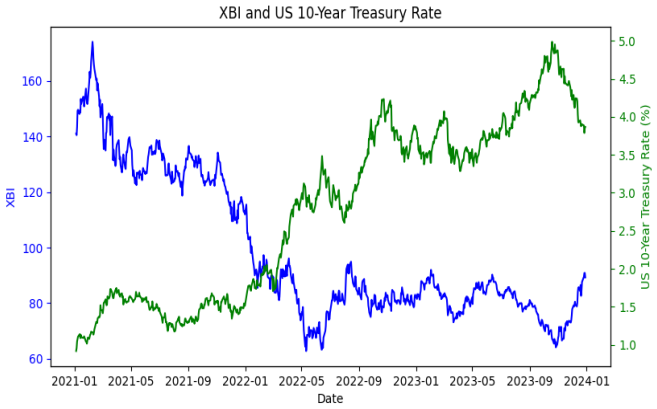


Figure 1: (Left) 2023 stock index performance for XBI (blue), S&P500 (orange) and S&P 500 Pharmaceuticals (green). (Right) Index performance from last week of October to end of year (right).

The positive return on XBI was driven by acquisitions of small- and midcap biotechnology companies. Moreover, an analysis by RA Capital found that biotechnology companies with at least one specialist investor performed significantly better on the public markets than companies with only generalist investors. As for M&A in the public sector, the same analysis showed that 99 % of the cash flowed to companies with at least one specialist investor. Companies with at least three specialist investors (about a third of all companies analyzed) attracted >90 % of all cash and equity in M&A, generating a +15 % return on investment for the investor-base.



Generally, high interest rates tend to have a larger negative impact on biotechnology sector performance, as the inherent uncertainty in biotech investments causes generalist investors to sell or not invest further into these companies. Interestingly, in the last three years XBI displayed a significant inverse correlation with US 10-year interest rates (Figure 2). For specialist investors, however, this has limited impact as investments are based on the idea that innovation will always be necessary in this sector.

Figure 2: XBI (blue) and US 10-year treasury rate (green) 2021-2023.

Something worth noting in 2023 was how companies specializing in anti-obesity drugs have managed to attract generalist investors despite the market sentiment. This may show as an example of how certain areas of innovation in the biotechnology sector are more attractive than others for generalist investors, due to their prevalence and visibility in society. Data readouts in such indications are also of a more comprehensive nature for the general public, and therefore perceived as less risky investments. As larger indications such as obesity, cardiometabolic diseases, and neurology are moving more into focus and cost of capital is decreasing, biotech stocks might become more attractive for generalist investors the coming years.

As for drivers in 2024, we expect that pharma M&A will continue to be the main driver as big pharmaceutical companies are in need to fill their pipelines with later-stage assets in light of the upcoming patent cliffs. Public biotechnology companies mainly constitute matured, well-capitalized, de-risked companies fit for this purpose.

IPOs

The IPO window remained relatively closed during 2023, as expected from the market conditions. Both the number of IPO listings and total amount raised were in line with 2022. During the last few years, however, a growing number of private companies with strong data packages have matured and built a backlog of companies waiting for the IPO window to open back up. With a recovery in biotech stocks, an abundance of good private companies and increased confidence among investors, the conditions are good for a rebound in IPOs to pre-pandemic levels in 2024. The market will likely remain focused on themes like cardiometabolic diseases, precision oncology including ADCs and radiopharmaceuticals, neurological disorders, and immunology. We expect to see platform IPOs as well in key areas like AI and RNA therapeutics.

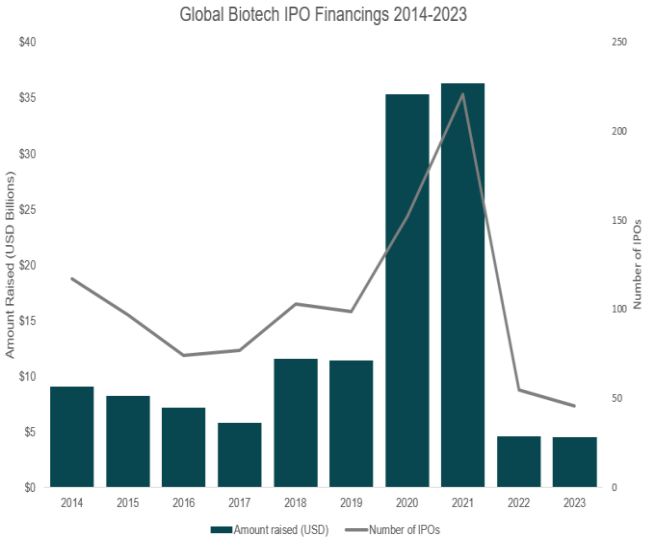


Figure 3: Global IPO financings 2014-2023 (source: BCIQ)

M&A and Licensing

The importance of small- and midsize biotechnology companies to drug development has grown over the past decades. An analysis of the role of external innovation in the 20 largest pharmaceutical companies showed that 65 % of new drugs between 2011-2021 originated from external sources through in-licensing (38 %) and M&A (62 %). According to an EY analysis, larger pharmaceutical companies sat on approximately USD 1.4 trillion in dealmaking firepower at the start of 2023. Despite a slight drop in total number of M&A deals compared to last year, the total deal value rose with 58 % to USD 173 billion. The last quarter saw an increased pace of > USD 1 billion deals with almost half of the total number of deals happening the last three months. Five of the > 1 USD billion deals were announced in December, including the USD 14 billion acquisition of Karuna Therapeutics (neurology) which was the year's second largest, and the notable 100 % premium acquisition of

radiopharmaceutical Rayze Bio. Both companies were acquired by BMS. Data-driven, later-stage deals were in focus as nine of the > USD 1 billion deals were of acquisitions of companies with at least one marketed product and eight companies had a lead candidate under review or in phase III (data from BCIQ). Oncology was the top therapeutic area by deal value, followed by rare diseases and immunology.

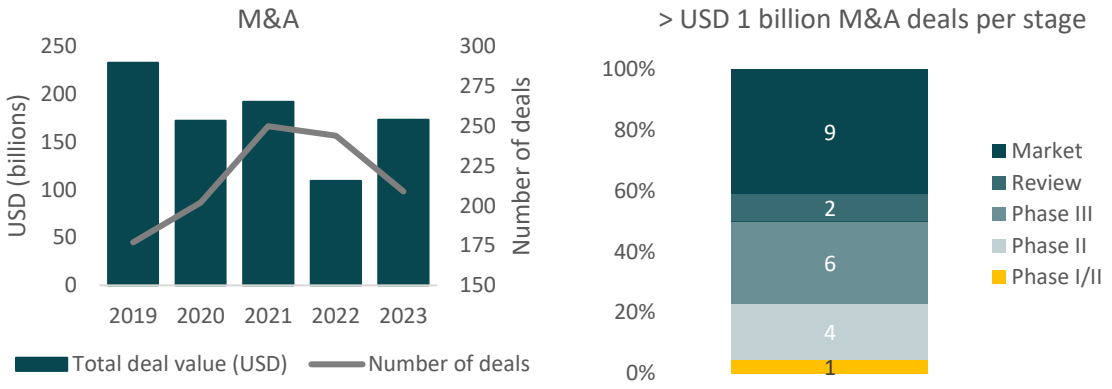


Figure 4: (Left) Total deal value (USD) and number of M&A deals the last five years (source BCIQ). (Right) Company stage of the 22 M&A deals with a total deal value > USD 1 billion in 2023 (source: BCIQ).

Pfizer's acquisition of ADC-specialist Seagen for USD 43 billion was the largest M&A transaction in the biopharma industry since 2019. Other noteworthy deals in the ADC space includes AbbVie's acquisition of Immunogen for USD 10.1 billion (fourth largest this year), Merck's licensing deal for three ADC drugs from Daiichi Sankyo for USD 4 billion, and BMS's deal with SystImmune for USD 800 million for a promising first-in-class phase 2 ADC.

In the pharmaceutical industry, dealmaking has been a way of filling pipelines with assets to compensate for potential loss of revenue following patent expirations. Between now and 2030, pharma sales of about USD 230 billion are at risk as loss of exclusivity for around 200 drugs is approaching. In later years, big pharma M&A and in-licensing has shifted focus from preclinical to clinical-stage deals (Figure 5), also indicating the need to mitigate some development risk and fill pipelines considering the upcoming patent cliff. In 2023, the median upfront cash and equity payments from big pharma for in-licensing of phase I and II assets increased with 42 % to USD 100 million and 400 % to USD 405 million, respectively. Oncology dominated deal activity, and cardiometabolic and neurological diseases were also frequent therapeutic areas of interest.

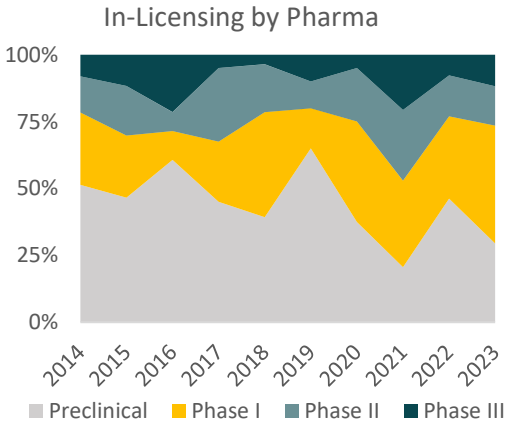


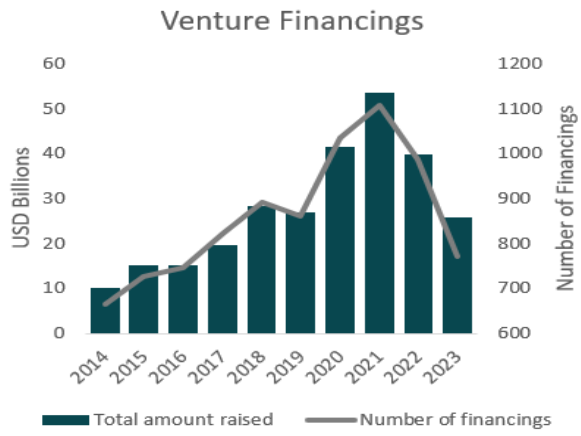
Figure 5: Stage of pharma licensing deals (source: JP Morgan Annual Biopharma Licensing and Venture report).

Predictions on what to expect in M&A and licensing in 2024:

Areas such as targeted oncology (ADC, radiopharmaceuticals) and immunology/inflammation were drawing much attention in 2023 and are expected to continue to be of interest for M&A and licensing in 2024. Differentiation in the targeted oncology space will be of importance: for ADCs that include novel targets and differentiated platforms, for radiopharmaceutical companies it is becoming increasingly clear that having a manufacturing solution is of importance. In immunology, first-in-class targets are likely to be areas of interest for dealmaking. Moreover, continued interest in the growing fields of cardiometabolic diseases (including obesity, heart failure, liver failure and insulin resistance) and neurology (including genetic, psychiatry, and neurologic disorders) is expected.

Venture financings

Life science is an investment arena where both healthy financial returns and high impact can be achieved. Despite the market sentiment in 2023, venture capital firms continued to raise and close new funds, with 2023 being the fourth largest year in fundraising in this industry according to a Stifel report from November 2023.



As for venture financing rounds, both the number of financings and total amounts raised were significantly lower than the three preceding years and more in line with pre-pandemic levels. Like in 2022, oncology attracted most venture financings, followed by neurology and autoimmune diseases. For seed and series A financings, these three therapeutic areas remained the most attractive for investments. Other areas of interest for early-stage financings were cardiovascular diseases, ophthalmology, and inflammation.

Figure 6: Total amount and number of financings of venture capital deals the last ten years (source: BCIQ).

FDA approvals

The FDA's Center for Drugs Evaluation and Research (CDER) approved 55 new drugs in 2023, almost 50 % more than in 2022 and the second highest in history. This number is more in line with historical levels, and does not include vaccines, blood and blood products, and cell and gene therapies.

Additionally, FDA's center for Biologic Evaluation and Research (CBER) responsible for cell and gene therapies, vaccines, and blood products, approved 14 new products in 2023 (up from 8 last year). Maybe the most noteworthy approval of 2023 was the approval of Vertex Pharmaceuticals and CRIPSR Therapeutics' Casgevy (exa-cel) for sickle cell disease. Exa-cel is the first ever medicine to be licensed that uses the gene editing tool CRISPR (Nobel Prize 2020) and made so only about a decade after the scientific discovery that laid its foundation, which is impressively fast. BlueBird also received approval for Lyfgenia (lovo-cel), another gene therapy for sickle cell disease. As with other approved gene therapies, there is still some disconnect between clinical benefits and commercial value which has been a topic of debate and discussion.

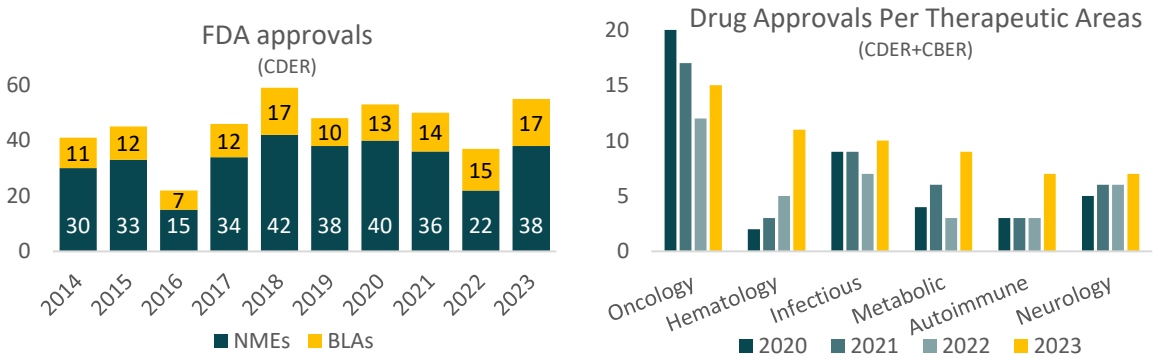


Figure 7: (Left) FDA approvals of new molecular entities (NMEs) and biologics (BLAs) the last 10 years. (Right) Therapeutic areas with highest number of approved drugs (NMEs, BLAs, gene and cell products, vaccines) the last four years (source: FDA)

Accounting for both CDER and CBER approvals, oncology still makes it to the top of the list of most approved drugs in 2023. There seems to be a trend shift from first-in-class to best-in-class approvals, as the percentage of new targets and first indications dropped from last year.

Outlook

The last months of 2023 showed indications of a positive shift in the biotechnology sector and the industry sentiment appears to be more optimistic than last year. XBI is starting to show signs of recovery and there is an emerging anticipation for innovation across therapeutic areas. At HealthCap, we are optimistic about the coming years and have strong confidence in our long-standing precision medicine investment. Our portfolio is well-diversified and represents top-tier companies in their respective therapeutic areas.