Bellevue

Excellence in Healthcare Investments

Healthcare Observer

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Dear investors,
With the gradual return to normality, we have been able once again – for the first time since the outbreak of the coronavirus crisis – to attend specialists' and investors' conferences in person. At the ASCO's annual meeting (the world's most important cancer medicine conference) we witnessed a standing ovation given to the presentation of clinical data on a soon-to-be-authorized medication – the first such accolade for almost 20 years. In the focus article, we discuss the extent to which the latest build-up of positions – i.e. purchases made while share valuations remain low – could herald a new wave of takeovers. Meanwhile, in the medical technology sector diabetes monitoring is one of the areas where the use of digital technologies has made the greatest progress. Moreover, new legislation in the USA reaffirms the principle of free drug-pricing as the basis for innovation.

We wish you an interesting read.
Yours sincerely, Dr. Cyrill Zimmermann, Head Healthcare Funds & Mandates

More M&A on the horizon

The clinical success of new therapies and low valuations are making more and more biotech companies attractive takeover targets.

Pfizer is on a shopping spree. In August, the pharmaceutical giant shelled out USD 5.4 bn to buy Global Blood Therapeutics, a US biotech company that is developing medicines for rare hematological diseases and is a leader in the treatment of sickle cell anemia. This inherited disease changes the shape of red blood cells, so they look like a crescent moon, or sickle. Three months earlier, Pfizer put the finishing touches on the largest transaction so far in the biotech industry this year. It bid USD 11.6 bn for the US biotech company Biohaven, giving it ownership of Nurtec, a migraine pill with a novel mechanism of action. Nurtec was approved in the US in 2021 and in Europe in 2022. Pfizer has already entered into a collaboration with Biohaven in November 2021, through which it acquired rights to commercialize the drug in markets outside of the US, and it also purchased an equity interest of just under 3% in Biohaven as part of their agreement. The full takeover bid was priced at a premium of 80% to the pre-announcement closing price of the Biohaven shares. In December 2021, Pfizer announced the USD 6.7 bn acquisition of Arena Pharma to strengthen its R&D pipeline.

Top 5 acquisition transactions 2022

Buyer	Acquired company	Vol. in bn USD
Pfizer	Biohaven Pharma	11.6
Pfizer	Global Blood Therapeutics	5.4
Bristol-Myers Squibb	Turning Point Therapeutics	4.1
Amgen	ChemoCentryx	4.0
GlaxoSmithKline	Sierra Oncology	1.9

September 7, 2022

In addition to the pharmaceutical companies, the large biotech companies have also been on the acquisition trail. At the beginning of August, Amgen paid USD 4.0 bn for US company ChemoCentryx, valuing the target with a premium of more than 100% to its last closing price. Tavneos is a ChemoCentryx product on the market for the treatment of vasculitis, a rare disorder characterized by inflammation of the blood vessels. Tavneos is projected to generate annual peak sales of more than USD 1 bn. Gilead Sciences paid USD 450 mn in cash for MiroBio, a privately held biotech company focused on inflammatory diseases that is a good fit for Gilead's strategy of establishing a foothold in a third indication area, in addition to oncology and virology.

A large number of biotech companies have presented promising clinical data so far this year.

We see four factors that will keep the M&A carousel spinning. A large number of biotech companies have presented promising clinical data so far this year. Biotech companies have also been prominent

on the new approvals front. One example is Biomarin, which received European market approval of Roctavian, the first gene therapy for patients with severe hemophilia A. After publishing excellent clinical data for patisiran in a rare disease, Alnylam is poised to launch a product in a market niche that could generate billions of dollars in revenues.

The political environment is also a positive factor. The recently passed Inflation Reduction Act in Washington will not impose any price caps on innovative drugs in the US, the world's largest drug market. Under the terms of the new law, the prices of ten high-cost drugs covered by Medicare that have been approved for marketing for at least nine years are expected to be cut by 25%. Sixteen years after receiving FDA approval, the price cut could climb as high as 60%. These provisions are intended to increase competition, especially in the case of high-cost medicines. Companies that take new therapeutic approaches to address markets with high unmet medical needs will retain most of their pricing power.

In addition, the legislation was signed into law at a time when patent expiries are on the rise again. The decline in prices resulting from the ensuing generic competition are generally significantly higher. This means most pharmaceutical companies will be under increasing pressure to harness new growth drivers. According to FDA estimates, blockbuster drugs with an aggregate annual sales volume of more than USD 250 bn will come off patent during the current decade. At the same time, some small and mid-sized biotech companies that are not yet turning a profit due to a lack of revenues continue to trade on very low valuations after seeing their stocks slump. This wave of selling over the past twelve months was fueled by the rising discount rates investors applied in their valuation models as interest rates moved higher in the face of higher inflation. Pfizer, for example, issued its bid for Biohaven in May after Biohaven shares had shed almost 30% of their market value within the space of six months.

That said, the stalled takeover negotiations between US pharma major Merck & Co and Seagen are an indication that the negotiating position of biotech companies has steadily improved during recent years as they build up their own cash piles and grow the value of their R&D pipeline. Most of the big pharmaceutical and biotech companies need to make acquisitions to bolster their organic growth. Approved drugs with sales potential in the billions remain an important factor here. In order to keep a leadership position, biotech companies that have proprietary technology platforms for developing novel drugs are also attracting attention.

Biotech companies with groundbreaking technology that have launched their maiden products, or are about to do so, will attract

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increasing attention. Looking at the transactions announced so far this year, oncology remains the most important therapeutic area for prospective buyers. Several smaller biotech companies active in neurology have made good clinical progress with new therapies for schizophrenia and depression in recent years. In view of the high costs associated with pivotal trials, it is very likely that these companies will welcome a pharma company as a partner or be open to an outright takeover.

In the current market environment, we assume that acquisition activity will focus on biotech companies with technology platforms and, to a lesser extent, on biotech companies with approved products. Larger transactions of USD 15 bn or more will likely remain the exception. In our investment strategy, the prospect of a company becoming a takeover candidate is not one of our key investment criteria, but the substantial takeover premiums offered for our portfolio companies Alexion Pharma and Biohaven did lift the portfolio's returns.

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Interview

Dr. Lukas Leu
Biotech Analyst

«Combination therapies are gaining momentum»

A variety of approaches are making great strides toward market readiness in cancer care. Lukas Leu tells us which treatments and companies stood out at the ASCO 2022 cancer conference.

Cancer care has the most clinical trials and continues to attract major investment. What new treatment breakthroughs can we expect?

Lukas Leu: We don‘t anticipate one big breakthrough by one specific approach; instead, we‘re seeing a process of differentiation across a broad front. As a result, it’s likely that a number of companies will make the leap to commercialization with their products during the next few years. Combination therapies using medicines from different drug classes and targeted therapies are gaining momentum.

The ASCO Annual Meeting every June is the best barometer of sentiment in cancer research. What are the main takeaways from this year‘s meeting?

Attendees were meeting in person for the first time since 2019, and that physical presence created a completely different atmosphere compared to the online setting of the last two years. People meet up for coffee away from the presentation space buzz and can share observations, ideas and background information. Ultimately, personal interaction of this kind is also the starting point for a collaboration arrangement or an M&A arrangement.

Social factors aside, what are your ASCO takeaways?

Big pharmaceutical and biotech companies generated the most buzz with their presentations. AstraZeneca and Daiichi Sankyo drew a standing ovation for their presentation of pivotal clinical results for Enhertu, their jointly developed antibody drug conjugate (ADC) for breast cancer. Enhertu is likely to generate billions of dollars in revenues for both pharma companies. It will be exciting to see what the industry learns from the Enhertu story and what other ADC developments that leads to.

Amgen and Mirati’s KRAS inhibitors were another big talking point at ASCO 2022.

After the conference, it is still unclear how the biotech company Mirati Therapeutics can differentiate its KRAS inhibitor candidate from Amgen‘s Lumakras, which has already been approved to treat lung cancer. An interesting question is how effectively KRAS inhibitors will be able to pass through the blood-brain barrier and target malignant brain tumors (glioblastoma). Mirati reported initial findings indicating clinical activity for adagrasib, but their significance is not clear yet due to the lack of data.

Amgen or Mirati – which is the better investment?

Amgen is an established biotech company with a wide range of products, so you have a diversified investment risk. Mirati, on the other hand, needs to deliver convincing results from the combination study with PD-1 checkpoint inhibitors to differentiate meaningfully from Lumakras, or show strong data in combination with an EGFR inhibitor in the treatment of patients with advanced colorectal cancer. If successful, the prospects of commercial success will increase and so will the likelihood of Mirati becoming a takeover target.

BIOTECHNOLOGY

The biotech sector has clearly outperformed the total market since the early days of summer.

Positive sector news flow and other factors, such as certain provisions of the "Inflation Reduction Act", contributed to the improvement in sentiment. Under the act, Medicare, the US government health insurer, will negotiate price discounts for top-selling drugs that have been in the market for 9 to 13 years, but it will not have a say in the pricing of new drugs. At ASCO, the world's largest oncology conference, AstraZeneca and its partner Daiichi Sankyo presented data from their groundbreaking trial of Enhertu in breast cancer. The antibody-drug conjugate showed excellent results in previously hard-to-treat patients. In cardiology, Alnylam's siRNA-based therapeutic patisiran showed impressive results in patients with transthyretin cardiac amyloidosis. The trial data revealed that reducing pathogenic protein is an effective approach for treating patients with this type of amyloidosis, which has attracted increasing attention as an important cause of heart failure.

Dr. Christian Lach, Portfolio Manager

MEDTECH & SERVICES

Between May and August 2022, the medtech & services sector (-4.4%) slightly outperformed the broader healthcare market (-5.6%) – all figures in US dollars.

A development of note is the significant appreciation (+5.6%) in the US dollar over the period under review. Medtech corrected by -9.6%, whereas the services subsector gained 1.8%, due in part to health insurers and hospitals. These sizeable differences in performance are attributable primarily to macro factors such as rising interest rates and inflation expectations, combined with shortages of qualified healthcare staff.

US health insurers such as United Health, Cigna and Elevance are benefiting from the increase in short- and medium-term interest rates, as premium revenues are generating higher interest income. On top of this, their business – like the medtech sector – has merely marginal exposure to business cycles. In the current market environment shaped by recession fears, the medtech & services sector is well positioned. Earnings reports for the second quarter were also largely positive. Investors' great uncertainty with regard to the recovery in the number of people undergoing medical treatment after the last wave of coronavirus has given way to muted optimism.

Stefan Blum, Portfolio Manager

PHARMA & GENERICS

Large-cap pharmaceutical stocks came under selling pressure between May and August after having benefited from their safe haven status during the preceding months.

The NYSE Arca Pharmaceutical Index showed a negative return of 7.9% (in USD) and underperformed the MSCI World Index (-5.5%) and the MSCI World Health Care Index (-5.6%) over the period. Sector rotation was to be expected after Big Pharma's big gains in the preceding period. However, the weak performance was also magnified by news about the one-time blockbuster Zantac. This heartburn drug is suspected of exposing consumers to the risk of cancer, and scores of lawsuits have since been filed in the US. Zantac has been marketed by various pharmaceutical companies since the 1980s and all of their stocks sold off sharply in the wake of these developments. The "Inflation Reduction Act" that was recently signed into law in Washington, D.C. includes measures to lower US drug prices, so it created additional headwinds for biopharmaceutical stocks that have substantial exposure to the US market.

Samuel Stursberg, CFA, Head Research Healthcare Fonds

ASIA & EMERGING MARKETS

Geopolitical developments, international monetary policy developments and macroeconomics all had a growing impact on Asian stock markets during the past few months.

Jerome Powell's speech at the meeting of central bankers in Jackson Hole and his statement that the Federal Reserve would maintain a more restrictive stance for longer than anticipated poured some very cold water on stock market sentiment. The diverging monetary policies of the Japanese and US central banks led to a sharp depreciation in the value of the yen versus the dollar.

China's rigid zero-COVID policy and increasingly bellicose language towards Taiwan pressured sentiment, too, especially in Hong Kong's stock market. Meanwhile most Chinese healthcare companies published good half-year results, so valuation indicators drifted down to record lows. Daiichi Sankyo received US regulatory approval for its groundbreaking breast cancer drug Enhertu, a mere two weeks after submission of a biologics license application for Enhertu with the FDA. Daiichi Sankyo also won its patent dispute with Seagen.

Oliver Kubli, CFA, Portfolio Manager

News

New drug pricing legislation will drive innovation

Just in time before the mid-term elections to the US Congress, the passing of the Inflation Reduction Act points to a solution ahead for the United States in the political discussion around the lowering of prescription drug prices. Under this Act, firms that bring new innovative treatments onto the market will continue to enjoy price-setting powers. At the same time, however, it will clamp down on aggressive annual price increases. The new ruling applies to the ten biggest-selling drugs. For small molecule drugs, prices will become eligible for a discount of 25% after nine years on the market. Biologic drugs will become eligible for discount after 13 years. The discount as a percentage of the total price will be as high as 60% after 15 years on the market.

We view this development as positive for the overall sector, as private insurers are exempt from these price caps and the incentive for developing innovative new treatments remains intact. The discounts are of relevance for state insurance schemes. The Medicare government health insurance programme can begin negotiating prices downward for the first ten drugs in 2026. The timing of the new legislation comes alongside a fresh spate of patent expiries. Price discounts resulting from generic competition tend to be significantly higher.

Digital diabetes management: a market worth billions

In the medical technology sector, diabetes is one of the diseases for which digital technologies in treatment are most advanced. The better the disease progression is controlled, the greater the likelihood that expensive secondary conditions such as blindness, stroke, heart attack or renal failure can be avoided. According to surveys by the International Diabetes Foundation, 530 million people worldwide had diabetes in 2021. The number has trebled since 2000.

The interaction of two products plays a key role. CGM systems measure glucose levels in the subcutaneous fat every few minutes and send the data by Bluetooth to an AID insulin pump. Algorithms evaluate the trend in glucose levels, which should be within a target range of 70–180 mg glucose per decilitre of blood, and decide whether and how much insulin should be administered automatically. A number of new products have broken through onto the market in recent years. Abbott and Dexcom have established themselves as market leaders in CGM devices, while Insulet and Tandem Diabetes are technology leaders in AID insulin pumps. Shares in these companies have been included in the holdings of the Medtech & Services and Digital Health strategies for many years.

Video Update
Medtech & Services

Stefan Blum and Marcel Fritsch, Senior Portfolio Managers

Singapore as door opener

Singapore is becoming a hub for the international activities of Chinese healthcare firms. In 2021, China's fixed investments in the city-state amounted to some USD 16.7 bn, with 15% of this making its way into the healthcare sector.

Wuxi Biologics is a pioneer here. The company invested a total of USD 210 mn in the establishment and expansion of a production facility that commenced operations in 2017. In July of this year, Wuxi Biologics announced an investment of USD 1.4 bn in an R&D service centre, together with a further significant expansion of its production capacities. Yidu Tech, which specializes in AI-based analysis of medical data, opened an operations centre for its international activities in Singapore. Kawin Technology, a group that is already profitable and is active in drug research, diagnostics and contract drug manufacturing, is also looking to establish a branch. These three companies illustrate the endeavours on the part of Chinese firms to use investments in Singapore as a means of harnessing the high-end R&D expertise in the city-state to put their own business on a more international footing.

Outlook

Two key conferences on the horizon

The annual meeting of the European Society for Medical Oncology (ESMO) in Paris is Europe's premier cancer care conference. A week ahead of the ESMO conference, Gilead Sciences released topline news that powered stocks up, announcing that Trodelvy extended by 3.2 months the survival of patients with advanced stages of a common type of breast cancer. It means Trodelvy has good prospects of establishing itself as a cancer drug of first choice in this indication alongside AstraZeneca and Daiichi Sankyo's Enhertu. ESMO 2022 has delivered multiple highlights, including Regeneron Pharma's bispecific antibodies, various combination immunotherapies, clinical results on next-generation CTLA-4 inhibitors that promise fewer systemic side effects, and data on cell therapies to treat solid tumors.

Groundbreaking results in Alzheimer's disease may be presented at the CTAD meeting in San Francisco, which opens its doors in late November. Immediately after the opening ceremony, Eisai Pharma will present additional Phase III clinical data for Lecanemab, its Alzheimer's disease antibody. For many people, the data will be a litmus test of whether antibody therapy targeting the hallmark amyloid-beta plaques is effective in treating Alzheimer's disease. The results will also have a direct impact on the January 6, 2023 meeting of the FDA's advisory panel, which will make its recommendation for the US agency's upcoming approval decision. CTAD conference highlights also include new biomarkers for earlier diagnosis and better monitoring of the disease. Another focus of interest is new research into the psychotic manifestations of Alzheimer's disease, such as hallucinations and emotional agitation.

Before the year is out, Eli Lilly also plans to present results of clinical trials of its Alzheimer's candidate, donanemab, including a direct comparison with Biogen's Alzheimer's antibody aducanumab. The latter was approved as Aduhelm in a controversial decision in 2021 but withdrawn from the market this May when health insurers refused coverage. Also before the end of 2022, Roche plans to present further Phase III data for subcutaneous gantenerumab. If the results are very good, approval might be granted as early as 2023. Following the conflicting aducanumab data, the data for the three above-mentioned antibodies is awaited with great anticipation.

Struggle for cost reductions

Amid mounting economic challenges, the US and China are approaching critical points that will impact the political course their nations chart going forward. China's President and Communist Party leader Xi Jinping is likely to be elected to a third term as party leader in middle October. In China, a deepening crisis in the real estate sector, an important section of the country's economy, and the effects of the government's rigid zero-COVID strategy have led to a prolonged economic slowdown.

In the US, the Fed is trying to rein in inflation before the congressional midterm elections in November by jacking up interest rates. In the healthcare sector, inflationary pressures have clearly pushed prices higher. How to curb rampant government spending on Medicare and Medicaid benefits is becoming an increasingly urgent question that must be addressed. This is especially true for stationary and outpatient clinical care, and lab work. President Obama's main goal of making healthcare affordable for more people without letting government healthcare spending increase more than overall GDP growth was not achieved with the passage of the Affordable Care Act (ACA). For example, without the cap on insurance premiums provided for under the recently passed Inflation Reduction Act (IRA), the 13 million people who buy subsidized coverage through an ACA exchange would have seen a 50% increase in their health insurance premiums in the fourth quarter of 2022. One positive impact of the provisions of the IRA could be a slower rise in the prices of the most commonly prescribed medicines.

Bellevue – Excellence in Healthcare Investments

Bellevue is a specialized asset manager listed on the SIX Swiss Exchange with core competencies covering healthcare strategies, entrepreneur investments and selected niches strategies. Established in 1993, Bellevue, a House of Investment Ideas staffed by 100 professionals, generates attractive investment returns and creates value added for clients and shareholders alike. Bellevue managed assets of CHF 9.6 bn as at June 30, 2022.

One of Bellevue's core areas of expertise dating back almost 30 years is the global healthcare sector. Besides the investment company BB Biotech AG Bellevue offers a diversified range of investment funds covering medical technology, digital health, biotechnology and Emerging markets healthcare themes. Bellevue ranks as one of Europe's largest investors in the healthcare sector.

Independent – entrepreneurial – committed.

Interested in further information?

We are at your disposal at any time

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«HEALTHCARE INVESTMENTS IN EAST & WEST – DEVELOPMENTS & TRENDS»

Cyrill Zimmermann and Samuel Stursberg look forward to giving you an overview of the current situation and key developments in the healthcare sectors. In addition, our long-standing experts from Boston and Singapore, Prof. Michael Mullen and Marvin Ng, will report on current healthcare policy, innovations and market developments in the USA and Asia.

Bellevue Healthcare Events:
10.11.22: Breakfast in Basel – bellevue.ch/healthcare-breakfast
11.11.22: Breakfast in Zurich – bellevue.ch/healthcare-breakfast

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