BENTLEY REID
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Theme: Healthcare & Biotech

NOVEMBER 2023

Overview

"In the world of healthcare, the discovery of new therapies is akin to composing the music of progress - a symphony that transforms and heals lives", Dr Sydney Taurel, Former Chairman & CEO, Eli Lilly

The Healthcare sector has long enjoyed the benefits of powerful structural tailwinds, which are set to intensify in the years ahead. The prevalence of disease is rising relentlessly as the global population ages and rates of obesity increase. But, we are also in an era of major technological change that has sparked an acceleration in drug discovery which, in turn, has boosted the sector's profitability. Notably, many Healthcare companies are now integrating artificial intelligence (AI) in their research & development (R&D) programs, which promises to further amplify this trend.

A robust global regulatory framework serves as a bulwark, safeguarding intellectual property and corporate earnings. It creates high barriers to entry that help to maintain profit margins; a distinct advantage over other industries where competition can be fierce.

Furthermore, healthcare spending is a dominant feature of fiscal support across all major economies, highlighting the existence of regular and, oftentimes, outsized capital flows that flow into the sector, regardless of wider economic trends. This makes healthcare companies similar to firms linked to the green energy transition in the sense that they tend to be positively impacted by government policies.

In this report, we delve into the unique attributes of the Healthcare & Biotechnology sectors and the investment opportunities they present.

The theme can be summarised as follows:

- **What?**
  Cutting-edge Healthcare and Biotechnology equity-based investments.
- **Why?**
  As the global healthcare landscape undergoes transformative changes (driven by an aging population, the rise of new diseases and an increasing healthcare spending burden) there is a pressing need for innovative solutions. Breakthroughs in drug discovery and technology have significantly enhanced the sector's profits potential.
- **How?**
  Depending of the stage of the market cycle, a selection of passive and specialist active Biotech and Healthcare managers.
- **Holding Period?**
  5yrs+A more detailed explanation of why gold bullion and the mining stocks are compelling long-term investments is as follows:

A more detailed explanation of why Healthcare and Biotech stocks are compelling long-term investments follows:

Healthcare - A Structural Growth Story

Three key structural trends underpin Healthcare's long-term outperformance (between 31st Dec 1994 and 30th Sep 2023, the MSCI Healthcare index's 1,739% USD return compares with 791% for the MSCI World index):

- **Technological innovation:** is driving down the risks associated with new drug discovery, whilst improving productivity and efficacy. An associated increase in revenue growth in the sector, especially so amongst Biotech firms, helps to underpin share price performance.
- **The 'illderly':** An aging global population is directly linked to a mounting incidence of disease and declining health. This surge is fuelling a rise in total healthcare expenditure, especially in emerging economies, where an expanding middle class is gaining substantial access to modern healthcare on a significant scale for the first time.
- **A regulatory moat:** Barriers to entry stemming from drug approval regulations, sales exclusivity and patent protections not only safeguard profit margins, but also incentivise investments in R&D.

Technological Innovation

"Innovation is our lifeblood. Our success depends on our ability to bring innovative drugs to market that make a real difference in the lives of patients", Leonard Schleifer, CEO, Regeneron Pharmaceuticals

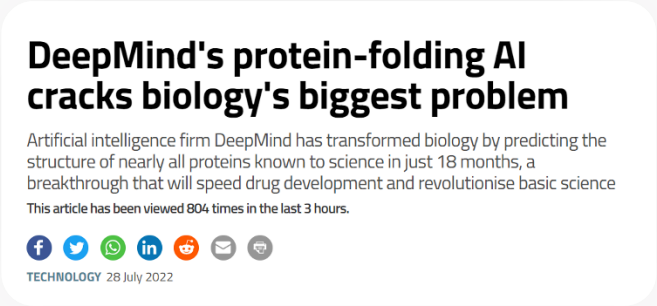
"AI is already having major implications for drug development and I can't think of any that aren't positive. AI is having a direct and material impact on productivity in Healthcare, particularly Biotech", Linden Thomson, Fund Manager, AXA Biotechnology

The fundamental backdrop for Healthcare & Biotech is strong, with evidence of accelerating innovation, not least through the sector's embrace of AI, whereby machine-learning programs are being effectively used to improve patient care, enhance operational efficiencies amongst service providers and advance medical research.

According to Deep Pharma Intelligence, bringing a new drug to market typically costs approximately U$2-3bn with a failure rate of around 90%. Innovation is serving to reduce this cost and improving the success rate of new drug discoveries.

In 2022, DeepMind leveraged AI to map and subsequently open-source (i.e. make available to anyone) the complete catalogue of protein structures. Protein structures refer to the 3D arrangements of atoms within a protein molecule. These structures are fundamental to new drug design since a protein's biological activity and its interactions with other molecules are strongly influenced by its unique structure.

Put simply: diseased protein structure = lock biotech drug = key



DeepMind's protein-folding AI cracks biology's biggest problem

Artificial intelligence firm DeepMind has transformed biology by predicting the structure of nearly all proteins known to science in just 18 months, a breakthrough that will speed drug development and revolutionise basic science

This article has been viewed 804 times in the last 3 hours.

TECHNOLOGY 28 July 2022

Mapping single protein structures used to be a process that took years, but thanks to advancements in technology, it can now be accomplished within seconds. Indeed, the mapping and open-sourcing of these protein structures by DeepMind offer invaluable support for drug discovery for several compelling reasons:

- **Understanding disease mechanisms:** Numerous diseases, including cancer, Alzheimer's and infectious diseases, are intricately linked to specific proteins or protein misfolding. A precise understanding of these proteins' 3D structures empowers scientists to unravel the molecular underpinnings of diseases, thereby facilitating the development of targeted therapies.
- **Target identification & drug design:** Drug discovery involves crafting molecules capable of binding to specific disease-related proteins, known as 'targets' and modulating their activity. Knowledge of a protein's structure provides a foundation for more logical and efficient drug design, enabling researchers to pinpoint binding sites and design molecules with optimal efficacy.
- **Reducing trial and error & improving drug safety:** In the absence of known protein structures, drug discovery historically relied on extensive trial and error. In the pre-computing era, it involved countless chemists studying the interactions of soil samples collected from distant places like Easter Island on disease targets in petri dishes using microscopes. Accurate protein structures can substantially curtail the time and resources required for the selection of candidate molecules.
- **Accelerating Research:** The open sourcing of protein structures grants researchers worldwide access to this critical data, fostering scientific advancement and accelerating research progress.

Investments in AI-driven drug discovery companies have tripled since 2019, reaching U$24.6 billion in 2022. Notably, both US and Chinese Healthcare companies have taken the lead in AI R&D, although they are not the sole players in this field. An example from the UK includes GlaxoSmithKline, a company not often considered an innovation leader, which has already assembled a team of 100 dedicated AI researchers. Similarly, its UK-based peer, AstraZeneca, says AI "is the future of drug development".

AI Drug Discovery Is a $50 Billion Opportunity for Big Pharma

Artificial intelligence can shave years off the development process, and companies like Japan's Takeda are making large investments.

Evidence of how AI is benefiting the sector continues to grow. In February 2023, Japan's Takeda Pharma bought an experimental psoriasis drug from Nimbus Therapeutics for U$4 billion. Using AI, the compound was selected in just six months; a stark contrast to the typically prolonged multi-year selection process.

Remarkably, just a month after Takeda's acquisition, the drug successfully advanced through its mid-stage study with its final trial scheduled for late 2023. Investment bank Jefferies estimates that this drug has the potential to generate as much as U$3.7 billion in annual sales, underscoring the substantial impact of AI on expediting drug discovery and development in the pharmaceutical industry.

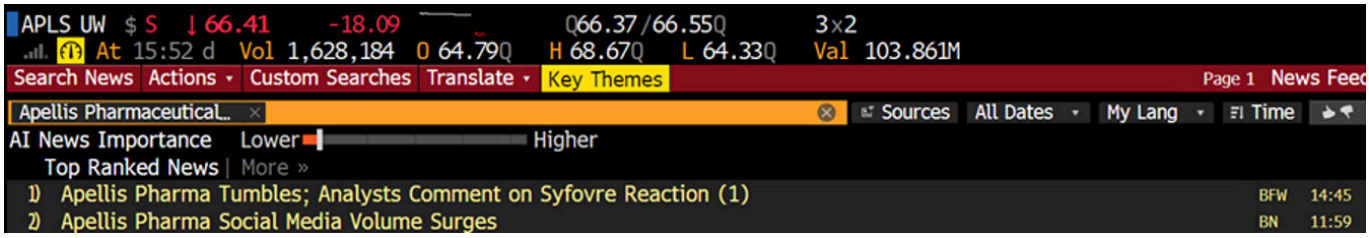
Takeda's $4 Billion Psoriasis Pill Helped Clear Skin in Mid-Stage Study

- Two final-stage studies expected to be enrolled this year
- Company plans head-to-head study versus Bristol-Myers' Sotyktu

One of our favoured active funds in this space (the Polar Biotechnology fund) has also witnessed the benefits of rising drug discovery.

In a single day in July 2023, three of the fund's stock rallied by more than 10% following positive drug announcements. Particularly striking was Argenx, which saw a 35% gain after its Vyvgart medicine demonstrated successful efficacy in treating a muscular autoimmune disease.

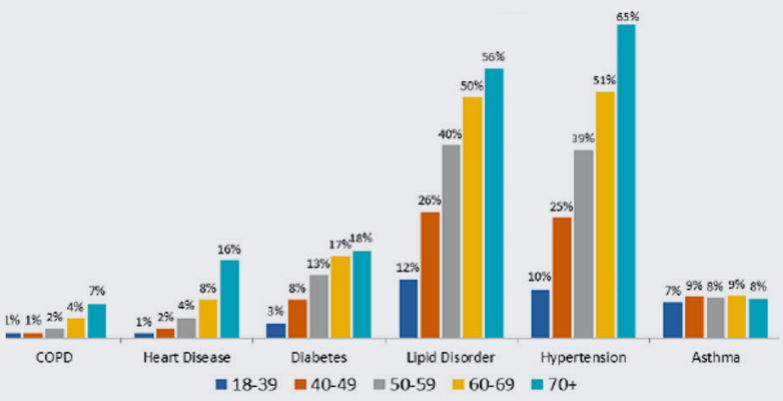
However, Biotech investing remains intensely speculative and stock-specific risk is exceptionally high. On that same July day, Apellis Pharma fell by 21% after announcing a severe reaction in one of its clinical trials. This serves as a reminder that the Biotech sector is subject to significant volatility and uncertainties, emphasising the need for careful assessment and a diversified approach.



Rising Demand from the 'illderly'

As a larger share of the world's population enters their later years, there is a direct and notable increase in the prevalence of chronic illnesses and age-related conditions, such as heart disease and cancer. Concurrently, a global obesity crisis is compounding the burden of lifestyle-related illnesses, including diabetes and cardiovascular disease. This demographic and health trend underscores the growing demand for healthcare services and innovations, making the healthcare and biotech sectors pivotal for addressing these challenges.

Fundamentals supported by structural shifts in demographics and lifestyle



Source: FiercePharma

Indeed, as we age, the incidence of cancer rises significantly. In the UK, the number of people diagnosed with cancer is projected to surge by a third by 2040, pushing the annual count of new cases to over half a million for the first time. According to Cancer Research UK, this increase is expected to result in 208,000 cancer-related deaths in the UK each year by 2040, with a substantial 60% of these cases occurring in individuals aged over 70.

HEALTH

Scientists race to hold back the tide as cancer 'tsunami' looms

'Groundbreaking' treatments could help doctors fight a growing number of cases in ageing populations

These conditions frequently require continuous medical intervention, further complicating existing health challenges. This, in turn, fuels the growing demand for healthcare products and services.

For instance, consider the escalating demand for obesity drugs, a category that was relatively non-existent just a few years ago. Recent times have seen a remarkable surge in demand for obesity drugs and, according to Barclays, they are projected to reach U$100 billion in annual sales by 2023.

Big pharma's blockbuster obesity drug battle is just getting started, and it's headed for $100 billion

PUBLISHED SAT, SEP 9 2023-9:19 AM EDT

The success of Novo Nordisk's obesity drug, Ozempic, is a case in point. It has proven to be highly effective, evidencing a 20% reduction in the incidence of serious cardiovascular events, such as strokes and heart attacks, especially in overweight patients.


PHARMA

High-flying Novo Nordisk again dials up its 2023 sales and profit expectations

By **Angus Liu** · Oct 13, 2023 11:44am

Ozempic serves as a prime example of the success of "complex biologic drugs," commonly referred to as "biologics." These biologics are advanced, custom-made biotech-derived medications that have gained prominence over the past two decades.

One notable characteristic of biologics is their potential to address more than a single therapeutic issue. Often, via only a minor adjustment in their design.

In October 2023, Novo Nordisk announced it would prematurely conclude its trial of Ozempic for the treatment of kidney failure due to clear and promising indications of success.

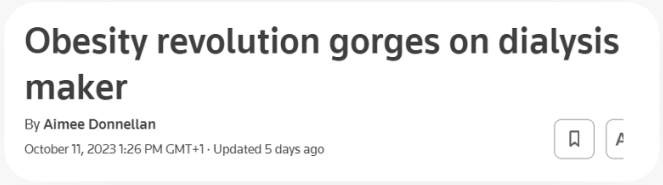

Healthcare & Pharmaceuticals

Novo Nordisk stops Ozempic kidney trial after early signs of success

By **Patrick Wingrove**

October 10, 2023 5:42 PM CDT · Updated 3 days ago

The success of Ozempic has had a disruptive effect on the dialysis manufacturer and German medical technology company, Fresenius. In response to the news of the trial being successful, Fresenius experienced a 20% drop in its share price, further highlighting why we favour an actively-managed strategy.


Obesity revolution gorges on dialysis maker

By **Aimee Donnellan**

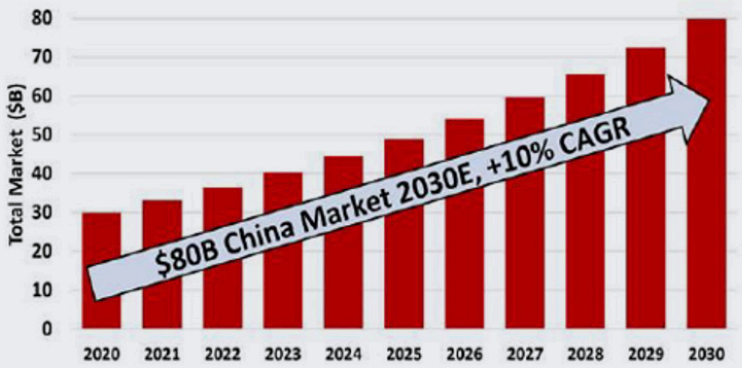
October 11, 2023 1:26 PM GMT+1 · Updated 5 days ago

The rise of emerging market healthcare spending

The healthcare sector is a direct beneficiary of the growth in healthcare spending stemming from the expanding middle classes in developing nations.

Notably, the rate of growth in healthcare spending in countries like China significantly surpasses that of developed economies, as demonstrated in this chart provided by Cowen.

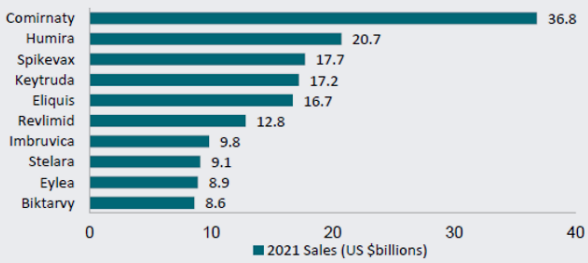
Meaningful geographic expansion opportunities



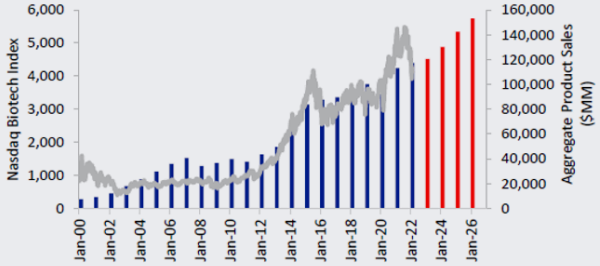
The intellectual property 'moat'

In 2021, all of the top 10 bestselling drugs by revenues were biologics, developed by Biotech companies. The production and replication of biologics are known to be intricate and costly processes. However, if we were to encapsulate the Biotech theme into a single chart, this one (below right) effectively illustrates the positive correlation between the increasing revenues from biotech drugs and the corresponding rise in share prices.

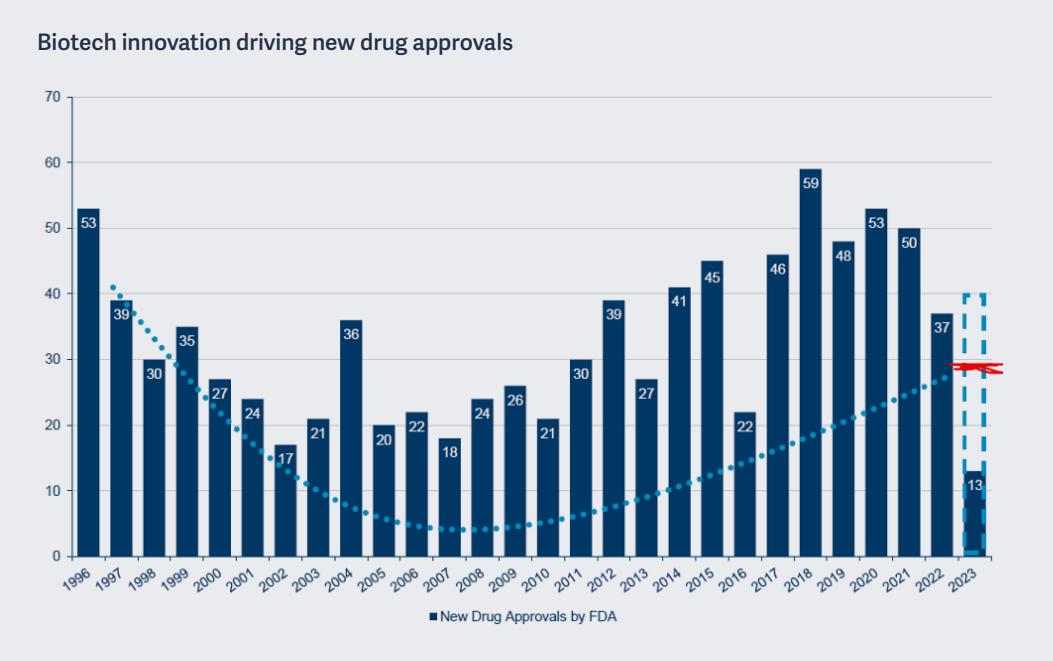
Top 10 selling drugs globally are all biotech derived



Share prices correlate to sales growth long-term



The approval of biologics in the United States is overseen by the Food and Drug Administration (FDA) and it typically comes with a period of sales exclusivity and protection from cheaper generic competition. Critically, the trend in drug approvals remains favourable.



The exclusivity period for biologics in the United States is regulated by the Biologics Price Competition and Innovation Act (BPCIA). It shares similarities with the exclusivity granted to traditional, less complex small-molecule drugs, like Aspirin, which became available in generic form after Bayer (the original patent owner) lost exclusivity during World War 1.

Here are the key elements of biologic exclusivity:

- **Data Exclusivity:** Under the BPCIA, new biological drugs can enjoy a data exclusivity period. This period prevents other manufacturers from using the innovator's clinical trial data to support the approval of a biosimilar (generic) version. Typically, the data exclusivity period spans 12 years, during which no biosimilar application can be submitted using the innovator's data.
- **Market Exclusivity:** In addition to data exclusivity, a biological product may receive market exclusivity; a separate form of protection. This means that for a specified period (often 12 years) no biosimilar version of the drug can be approved even if the biosimilar manufacturer has its own independent data.
- **Patent Protection:** In addition to data and market exclusivity, the originator of a biological drug can employ patents for further protection. Patents can provide additional safeguards and their duration varies based on the specific patents involved. Patent protection can extend beyond the exclusivity period
- **Generic approval:** The approval process for generic versions of biologics, known as 'biosimilars,' is rigorous. It requires demonstrating the similarity and safety of the biosimilar even after the exclusivity period has ended.

The United States serves as a primary hub for drug innovation, and it often leads the way in granting approvals through the FDA. The standards and regulations established in the U.S. are frequently considered a model for other governments when they formulate their own approval and licensing standards for pharmaceuticals and biologics.

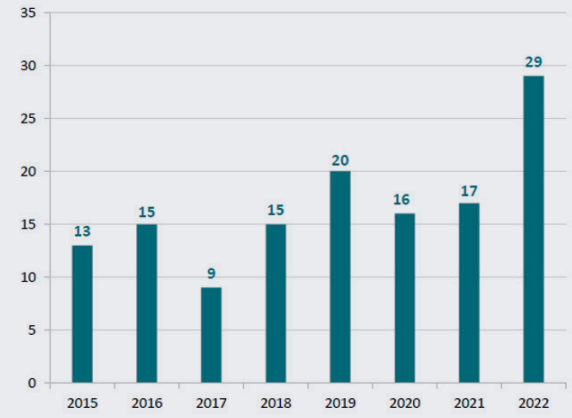
As biotech companies have proven successful incubators of innovation and new drug discovery, traditional large pharma companies have adopted a role of funding innovation, often via joint ventures and equity ownership of smaller biotech peers.

Large pharmaceutical companies have been active acquirers of Biotech companies over the past decade. They leverage their resources, distribution networks, and regulatory expertise to scale up and commercialize promising therapies developed by these smaller Biotech peers. Developing biologics involves a unique set of challenges and expertise and this is an area where large pharmaceutical companies often find it more advantageous to collaborate or acquire Biotech firms.

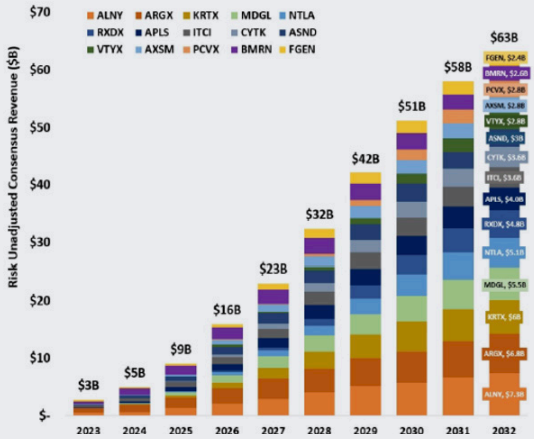
The innovation and acquisition model in healthcare has indeed proven to be a 'win-win' for investors. Biotech investors embrace the inherent risks but also stand to reap the most substantial rewards when their early-stage ventures lead to successful products. On the other hand, pharmaceutical company investors often avoid the majority of the R&D risks and instead enjoy the cash flow generated from acquisitions, making it a profitable approach.

Per this Jefferies' research, and given the outlook for continue growth in Biotech revenues over the coming decade, this momentum in M&A activity is unlikely to wane.

Number of M&A Deals



Top 15 Biotech launches can Fill £60BN+ Revenue



Regulatory support

The FDA continues to support innovative medicine, but it's worth noting that opinions vary regarding the pace of its approval timelines. Some argue that the FDA could be more aggressive in expediting approvals, as evidenced by the swift approval of novel mRNA COVID vaccines, which represent a pace the industry would prefer for other innovative therapies.

In 2023, there have been signs of approval delays and an increased regulatory burden, particularly in the field of oncology. Notably, the rejection of a high-profile therapy from Biotech company, Regeneron, by the FDA in 2023 highlights the challenges and uncertainties that the pharmaceutical and Biotech industries face when navigating the regulatory landscape. Striking a balance between safety, efficacy, and timely access to ground-breaking treatments remains an ongoing discussion within the Healthcare sector.


PHARMA

Regeneron's high-dose Eylea hit with surprise FDA rejection over manufacturing hiccups

By **Zoey Becker** • Jun 27, 2023 05:14pm

However, 2023 also witnessed some significant positive developments from the FDA. Notably, the regulatory body approved two crucial drugs in the field of gene therapy. Gene therapy represents a cutting-edge technology with transformative potential for addressing a range of diseases, making these approvals a remarkable step forward in advancing innovative medical treatments.


FDA NEWS RELEASE

FDA Approves First Gene Therapy for Treatment of Certain Patients with Duchenne Muscular Dystrophy

FDA NEWS RELEASE

FDA Approves First Gene Therapy for Adults with Severe Hemophilia A

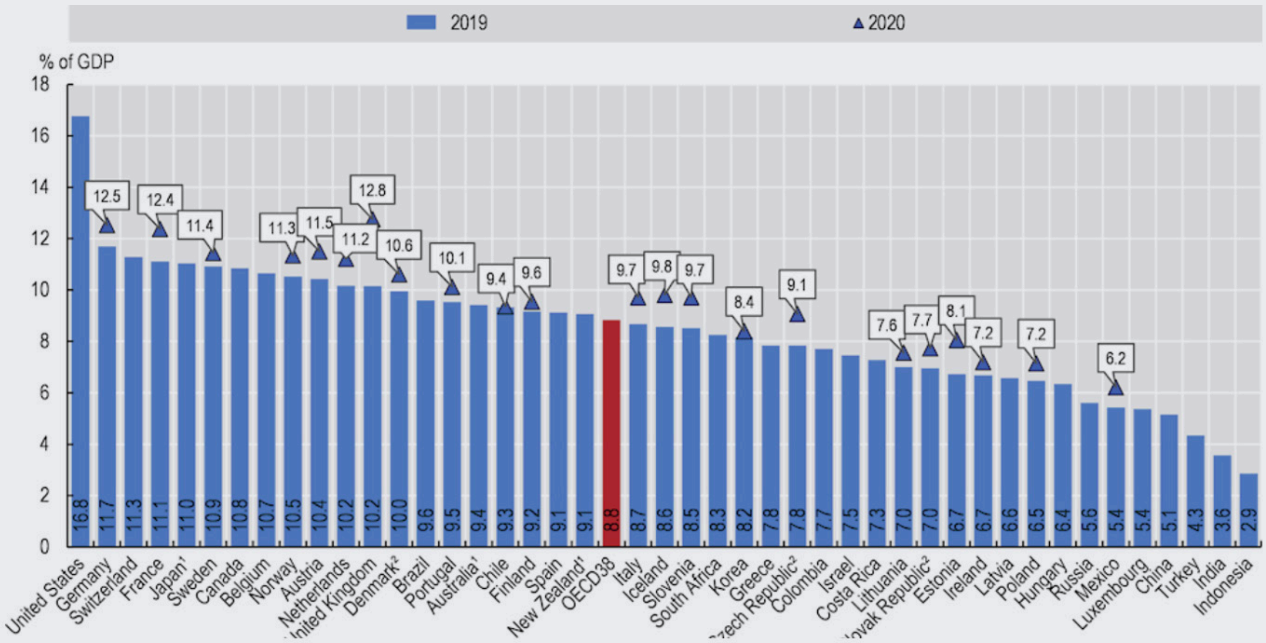
Deflating the cost of Healthcare; cure versus care

"In Biotech, we turn scientific discoveries into life-changing treatments. It's a journey of innovation that never ends", Dr Michel Vounatsos, CEO, Biogen.

The high and rising share of global economic output (GDP) spent on healthcare ensures it is a hot political topic the world over. As the number of individuals in the 'illderly' category continues to rise, societies are faced with challenging decisions regarding how to fund and allocate resources for healthcare.

The United States, with its private healthcare model and its world-leading healthcare expenditure as a share of GDP (approximately 17%), places the U.S. political landscape at the forefront of considerations and risks for investors in the Healthcare and Biotech sectors. This is especially pertinent because both global Healthcare and Biotech equity indices are predominantly comprised around 70% U.S.-listed companies.

Health expenditure as a share of GDP, 2019 (or nearest year) and 2020



Pharmaceuticals often represent a cost-effective solution, particularly when they offer a high or absolute level of efficacy, such as a cure. The development and approval of drugs like Sovaldi in 2013, by Biotech company Gilead, have brought about life-changing and cost-effective treatments for millions of individuals suffering from Hepatitis C.

The introduction of Sovaldi sparked considerable controversy due to its headline cost of $84,000 for a 12-week course. However, when taking a holistic view of the cost-benefit analysis, it becomes a worthy investment.

Hepatitis C patients often require ongoing medical care including hospitalisations, liver transplants and treatments for complications. Over time, the cumulative expenses associated with this ongoing care can far exceed the upfront cost of Sovaldi, often by a significant margin.

The Inflation Reduction Act

Like many of our other high conviction investment ideas, government intervention is a notable feature in this theme and, whilst substantial fiscal spending creates a strong tailwind in the sector, we are alert to outsized political and regulatory risks.

The Biden Administration's 2022 Inflation Reduction Act (IRA) represents a notable development in this context. This Act effectively places the U.S. government in a position to directly influence drug pricing by expediting the transition of patent-protected drugs to generic or biosimilar status.

This move could lead to some lowering of drug prices, which would negatively impact certain healthcare firms, but benefit others. Consider atorvastatin (Lipitor), a leading cholesterol-lowering statin. When Pfizer held the patent for Lipitor, it sold as a brand-name drug at a highly profitable U$5 per tablet. After the patent for Lipitor expired in 2011, generic versions lowered the price by almost 95%, to U$0.31.

The IRA has been approved by Congress, but faces legal challenges, particularly regarding the terms and definitions governing when and how drug patents transition to generic status.

Drugmakers Are 'Throwing the Kitchen Sink' to Halt Medicare Price Negotiations

The government will soon announce the first 10 medications that will be subject to price negotiations with Medicare under a new law. Drugmakers are fighting the measure in court.

Despite this, President Biden remains firmly committed to implementing the policy.

President Biden @POTUS

The Pharma lobby is upset that I'm forcing them to bring prices down. And to that I say: Bring it on.

Nathaniel Weixel @NateWeixel · Jun 21

BREAKING: @PhRMA announces they are suing over the inflation reduction act's drug price provisions

Under the IRA, there will be a phased approach to Medicare (the federal government's healthcare program) negotiating drug prices. Starting in 2026, Medicare will negotiate the prices of 10 drugs, followed by an additional 15 drugs in 2027 and then an additional 20 drugs in 2029 and beyond. The negotiation process applies to drugs that lack a generic alternative. A list of the first 10 drugs selected for negotiation is expected to be made public in 2023.

It's noteworthy that the Republican Party opposed the Act's drug pricing provisions. However, the issue of high drug prices is a politically sensitive one and there is widespread concern among Americans about the cost of medications. This makes it challenging for the Republicans to strongly advocate for the pharmaceutical industry's interests, as public sentiment often aligns with efforts to address and lower drug prices.

The key point is that the political dynamics surrounding healthcare and pharmaceutical pricing are complex and continue to evolve. Hence, why Healthcare and Biotech investing tends be best managed by sector specialists. The focus of good active managers will be on areas beyond the reaches of the IRA, typically where patent protection is longest and where molecules are the most complex.

How bad could it be for investors? AXA's Linden Thomson opines: "while other topics are, for now, dominating the political agenda, expect a bifurcation between winners and losers, but the sector to adapt and broadly maintain margins".

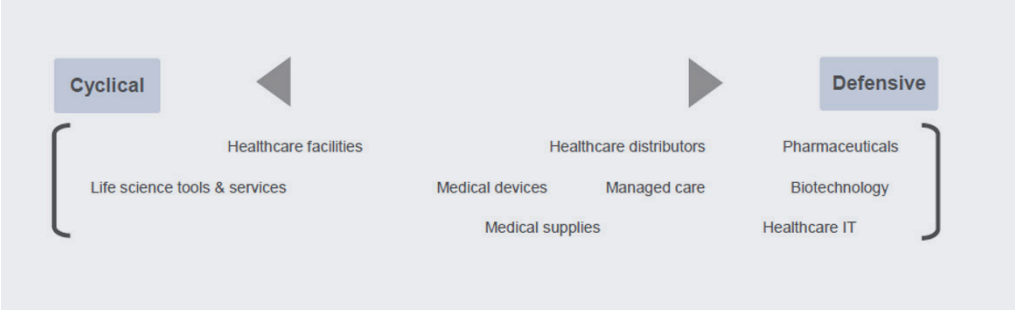
Investing in Healthcare

The healthcare sector is a substantial and highly diverse field, consisting of four major sub-sectors that collectively contribute to its size, liquidity, and diversification:

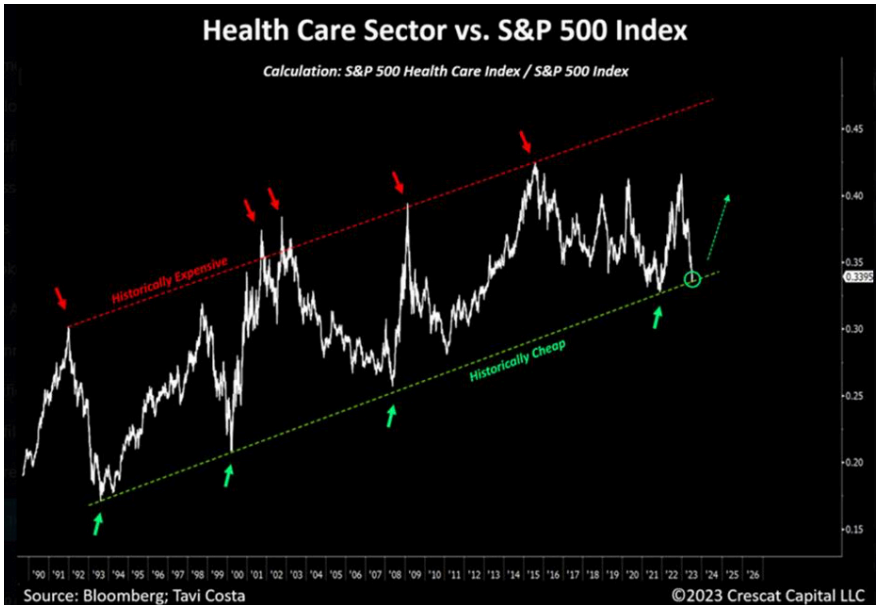
- **Pharmaceuticals:** This sub-sector is primarily concerned with the research, development, production, and distribution of drugs and medications.
- **Biotechnology:** The biotechnology sub-sector encompasses advanced biological research and the development of complex biologic drugs. Biotech companies often focus on innovative medical treatments, including gene therapies and immunotherapies.
- **Healthcare Services & Insurance:** This sub-sector brings together healthcare service providers, such as hospitals, clinics, and healthcare systems, with health insurance companies. Healthcare services involve the provision of medical care to patients, while health insurance companies offer coverage and financial management solutions for medical expenses, making healthcare services accessible to a broader population.
- **Medical Technology and Equipment:** This sub-sector is dedicated to designing, manufacturing, and supplying medical devices and instruments used in healthcare settings. These devices can encompass a wide range of equipment, from diagnostic tools to surgical instruments.

Each sub-sector has a unique sensitivity to the business cycle, which allows active investors to tactically evolve their Healthcare exposure depending on underlying economic trends. The sales and earnings of medical tech and equipment businesses are often highly cyclical, so they tend to produce better returns during economic upswings.

At the other extreme, large pharma and biotech companies are characterised by their defensive qualities, because demand for their products tends to be unaffected by economic conditions. Consequently, these sub-sectors typically outperform during recessions.



Turning to historical performance, as noted above the Healthcare sector has outperformed the broader stock market over the long-term. Between 31st Dec 1994 and 30th Sep 2023, the MSCI Healthcare index's 1,739% USD return compares with 791% for the MSCI World index) and it has achieved this with a slightly lower volatility of returns (15.8% vs 16.6% p.a.).



In addition to these compelling long run gains, the Healthcare sector has proven resilient during past bear markets, which raises its appeal for investors, particularly those seeking defensive assets.

For instance, the Biotech sector's 20% decline was only a little more than half of the World index's peak-to-trough decline during the 2008/09 Great Financial Crisis.

Performance - GFC

Time Period: 06/07/2008 to 28/02/2009 Calculation Benchmark: MSCI World GR LCL

	Return	Max Drawdown	Beta (non-excess return)	Correlation (non-excess return)
MSCI World/Health Care GR USD	-26.62	-30.92	0.82	0.88
NASDAQ Biotechnology TR USD	-19.88	-32.60	0.83	0.85
S&P 500 TR GBP	-40.69	-42.47	1.00	0.98
Russell 2000 TR USD	-40.92	-47.95	1.14	0.92
FTSE AllSh TR GBP	-47.90	-48.29	1.36	0.94
TOPIX TR JPY	-35.78	-35.78	0.56	0.76
MSCI Europe Ex UK GR USD	-49.83	-50.67	1.24	0.95
MSCI EM Latin America 10/40 GR USD	-53.39	-59.78	1.76	0.92
MSCI China A GR USD				
MSCI AC Asia Ex Japan GR USD	-44.27	-48.95	0.96	0.83
MSCI World GR LCL	-38.89	-39.93	1.00	1.00

Perhaps it is not surprise that Healthcare and Biotech stocks fell by far less than most headline stock markets during the 2020 "Covid crash".

Performance - Covid crash

Time Period: 02/02/2020 to 21/03/2020 Calculation Benchmark: MSCI World GR LCL

	Return	Max Drawdown	Beta (non-excess return)	Correlation (non-excess return)
MSCI World/Health Care GR USD	-20.37	-23.43	0.96	0.96
NASDAQ Biotechnology TR USD	-13.57	-20.10	0.94	0.94
S&P 500 TR GBP	-28.30	-31.66	1.06	0.96
Russell 2000 TR USD	-37.02	-39.81	1.28	0.98
FTSE AllSh TR GBP	-37.12	-37.63	1.19	0.92
TOPIX TR JPY	-25.80	-26.92	0.62	0.71
MSCI Europe Ex UK GR USD	-29.12	-31.29	1.04	0.83
MSCI EM Latin America 10/40 GR USD	-45.45	-46.12	1.23	0.93
MSCI China A GR USD	-9.02	-13.79	0.65	0.79
MSCI AC Asia Ex Japan GR USD	-19.09	-22.96	0.78	0.96
MSCI World GR LCL	-27.90	-30.93	1.00	1.00

During the inflation-induced equity bear market in 2022, Healthcare and Biotech stocks were relative outperformers as investors sought the safety of their perceived pricing power and robust earnings streams.

Performance - 2022 Crash

Time Period: 02/01/2022 to 08/10/2022 Calculation Benchmark: MSCI World GR LCL

	Return	Max Drawdown	Beta (non-excess return)	Correlation (non-excess return)
MSCI World/Health Care GR USD	-14.90	-16.74	0.81	0.83
NASDAQ Biotechnology TR USD	-18.81	-25.49	1.00	0.70
S&P 500 TR (1989)	-22.68	-23.87	1.15	0.99
FTSE 250 TR GBP	-37.85	-38.42	0.92	0.74
MSCI Europe Ex UK GR USD	-30.59	-31.40	0.91	0.76
Russell 2000 TR USD	-23.40	-25.37	1.22	0.93
TOPIX TR JPY	-22.16	-25.19	0.63	0.71
MSCI AC Asia Pac Ex JPN GR USD	-24.49	-27.19	0.53	0.59
MSCI EM GR USD	-25.05	-28.39	0.50	0.56
FTSE Act UK Cnvt Gilts All Stocks TR GBP	-40.87	-40.87	0.36	0.41
FTSE AllSh TR GBP	-23.22	-25.98	0.81	0.76
MSCI China A GR USD	-28.70	-28.82	0.12	0.13
MSCI World GR LCL	-20.20	-21.56	1.00	1.00

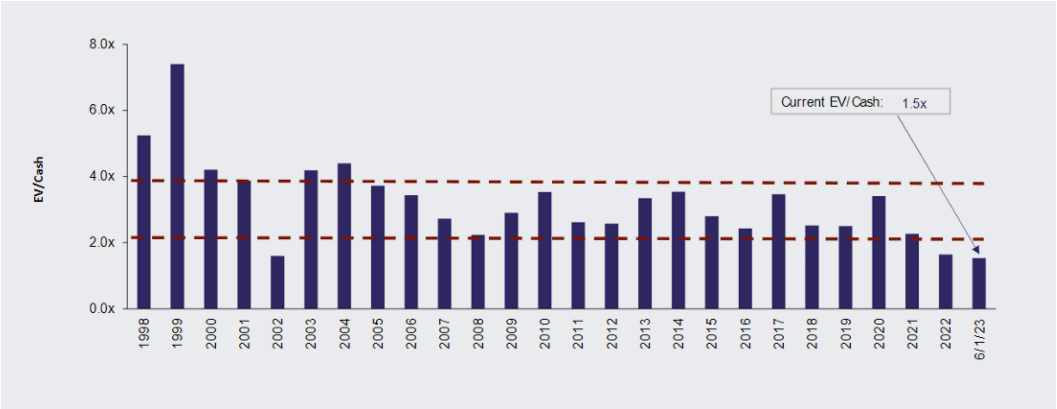
Valuation

Like any equity sector, the valuation of Healthcare and Biotech stocks varies significantly over time, although sentiment is prone to extremes in these sectors. Investors periodically become overly optimistic with respect to the benefits from innovation and overly pessimistic in regards to the threat from political interference, where worst cases rarely materialise.

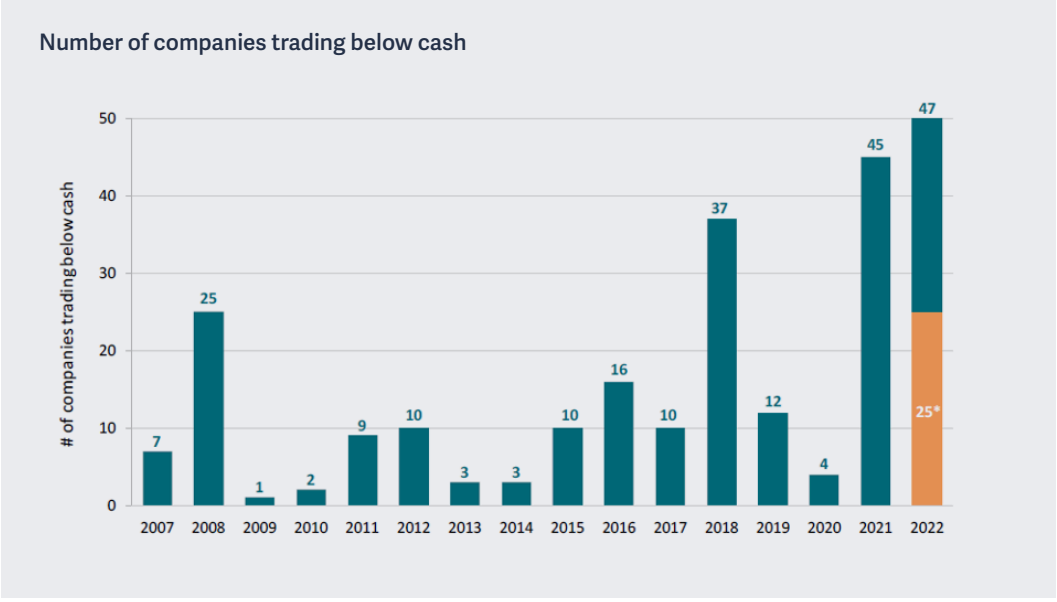
The Enterprise Value (EV) to Cash ratio is a useful metric for measuring Biotech valuations because it factors in a gauge of the company's financial health and liquidity characteristics, which is particularly relevant for firms in more speculative industries, like Biotech.

EV is a comprehensive measure of a company's total value, which combines its market capitalisation and total debts, but excludes the amount of cash it has on hand. A low EV/cash ratio is generally interpreted as an indicator of cheapness and an attractive entry point for investors.

As of mid-2023, based on this metric the biotech sector was about as cheap as it's ever been.



Furthermore, the fact that a record number of biotech companies currently have cash balances greater than their market capitalisations is an interesting development in the sector. It suggests they are well positioned to weather any economic or market challenges and have ample resources to fund R&D initiatives.



Active vs passive investing

Given the numerous risks and volatility associated with investing in this high-return sector, our typical preference is to allocate capital to specialist third-party Healthcare and Biotech fund managers. This typically helps to generate a better return outcome, whilst also reducing many of the key risks.

The Polar Biotechnology fund, managed by David Pinniger from London, is a case in point. Since its launch in 2013 to September 2023, the fund has outperformed its benchmark (the iShares Biotech ETF) by almost 8% p.a. net of all fees (in USD terms).

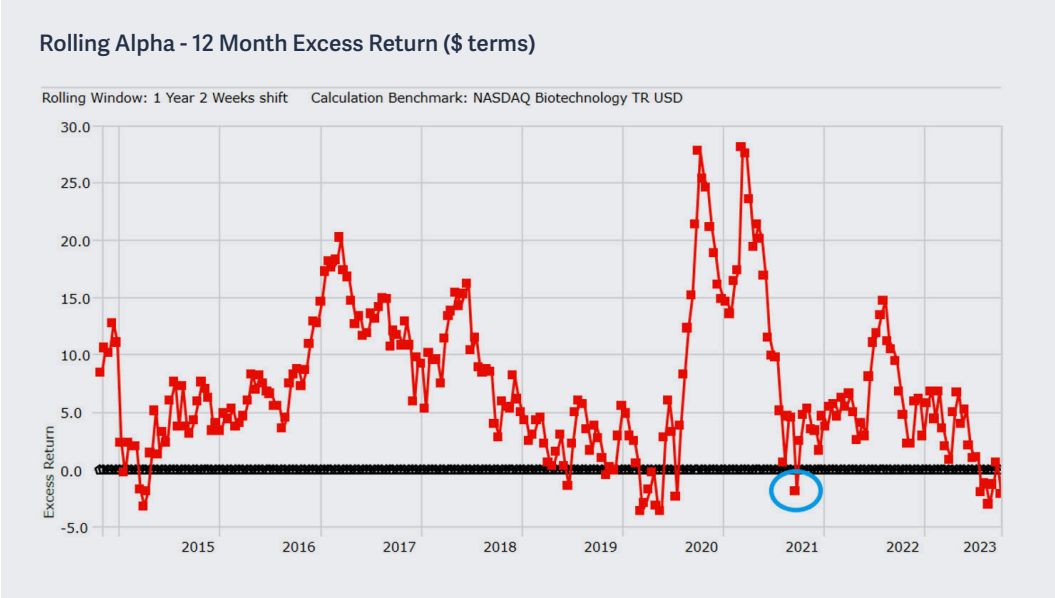
However, the Polar fund is also prone to temporary periods of extreme over- and underperformance which has encouraged us to occasionally alternate back into a passive vehicle (and vice versa).

We track the over- and underperformance of active funds versus their benchmarks over a variety of time periods and use this "rolling alpha" to identify buy signals for the active fund (typically after a period of underperformance) and sell signals (usually after a spell of outperformance).

The chart below shows the rolling 12-month relative performance of Polar Biotech versus its NASDAQ Biotechnology benchmark. Only rarely has the fund underperformed its benchmark since inception, which means it qualifies as an active fund of interest.

We first invested in the Polar Biotech fund at the end of July 2021 (marked by the blue circle on the chart below), after an abrupt period of underperformance left the fund's rolling 12 month return below that of the benchmark. The rarity of this underperformance gave us confidence that the manager would soon return to form and produce a (much) better return than the benchmark.

Indeed, the manager's underperformance did not last for long and the fund produced a materially higher return than the index in the two years that followed. This highlights the appeal of occasionally and temporarily switching from an active to passive exposure within the Biotech space.



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