4Q18 Portfolio Commentary

Janus Henderson INVESTORS

Global Life Sciences Fund

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Investment Environment

Globally, health care stocks declined as part of a broad equity market sell-off during the period. A federal judge's decision to invalidate the Affordable Care Act (ACA) was another headwind. On a sub-sector basis, health care technology, supplies and services firms underperformed as valuations for some of these companies had become inflated earlier in the year. Although no sub-sectors delivered positive returns, pharmaceuticals and managed care companies suffered smaller losses.

Performance Discussion

The Fund underperformed its primary benchmark, the MSCI World Health Care Index℠, but outperformed its secondary benchmark, the S&P 500® Index, for the quarter. We seek to invest in companies worldwide that are addressing high, unmet medical needs and providing efficient and cost-effective health care solutions. We believe the health care sector, with its rapid growth and high complexity, offers abundant opportunities for differentiated research. We believe understanding both the science and the business behind new therapies and having a disciplined investment process are key to driving long-term results.

During the quarter, the Fund's biotechnology and pharmaceutical holdings weighed on relative performance. Stock selection in health care equipment and life sciences tools and services contributed positively to returns.

On an absolute basis, Neurocrine Biosciences was the largest detractor during the quarter. The stock declined when lead drug Ingrezza failed to meet the primary endpoint in a phase 3 trial for Tourette syndrome. While Ingrezza's development for Tourette syndrome has likely come to an end, we remain excited about the drug's opportunity in its lead indication of tardive dyskinesia (TD), a movement disorder that affects up to 500,000 people in the U.S. So far, Ingrezza's clinical benefit has been supported by higher-than-expected compliance and follow-up data indicating an increased benefit for patients who continue to take the medicine long term. Given the more than $400 million in sales achieved since the drug launched in 2017 and relatively low penetration, we believe Ingrezza has blockbuster potential (a blockbuster drug generates annual sales of at least $1 billion). In addition, Orilissa, a therapy for pain associated with endometriosis, was recently launched by partner AbbVie. As Orilissa represents the first new medicine to come to market for endometrial pain in more than a decade, we also see blockbuster potential.

AnaptysBio also weighed on performance. We believe the biotech was largely caught up in the sell-off of small-cap biotech during the period. However, we continue to like the stock. In

Highlights

- Health care stocks declined during the period as a result of market volatility and uncertainty about the future of the Affordable Care Act (ACA).
- Although the Fund underperformed its primary benchmark, it outperformed its secondary benchmark.
- We believe legal challenges to the ACA will likely come up short while continued innovation should drive long-term growth for the sector.

September, AnaptysBio delivered positive data for its ongoing phase 2 trial for etokimab (previously known as ANB020), a wholly owned antibody for the treatment of atopic (allergic) diseases. The drug showed both efficacy and tolerability in patients with a severe form of asthma. Previous trials also demonstrated the drug's efficacy for atopic dermatitis, a severe form of eczema, and the company will continue to explore potential uses for other indications. In addition, AnaptysBio has a second drug candidate, ANB019, a treatment for rare and severe forms of psoriasis. We believe both ANB019 and etokimab, if successful in late-stage trials, could have significant sales potential.

Teladoc Health was another detractor. After rising through much of 2018, the stock declined during the period as many high-growth, tech-related stocks came under pressure. In addition, the stock suffered from allegations that Teladoc's CFO and another employee had an improper relationship and traded company stock together. Subsequently, the CFO resigned. While disappointed by these events, we still are optimistic about Teladoc's long-term outlook. The company is the largest telehealth platform in the U.S. and continues to benefit from the health care system's focus on improving costs and efficiencies. During the most recent quarter, for example, revenue climbed 62% year over year and paid membership jumped 18%. In addition, the company reported that clients are increasingly making virtual care the first point of access to health care. Given Teladoc's product breadth in telehealth and high market share, we believe such trends could help accelerate the firm's growth.

While disappointed by these results, we were pleased by the performance of other holdings, including Merck & Co., the top contributor. The pharmaceutical giant has reported positive earnings and revenue growth driven, in part, by sales of Keytruda, a cancer-fighting immunotherapy. We believe Keytruda still has significant growth potential. In late summer, both the Food and Drug Administration (FDA) and European Medicines Agency approved a combination treatment of Keytruda and chemotherapy to address non-small cell lung cancer, the largest cancer indication. Late-stage clinical trials showed that this combination significantly improved overall survival for patients, reducing the risk of death by more than 50% compared to chemotherapy alone. In addition, Merck continues to research other potential indications for the drug. The company recently reported positive trial data for Keytruda to treat kidney and esophageal cancers. And in November, the FDA approved Keytruda for recurring cases of liver cancer.

Another pharmaceutical company, Eli Lilly & Co. was also a top contributor. The stock climbed after the firm reported positive results from a mid-stage clinical trial for a drug that targets two hormones in diabetes patients. In the study, Eli Lilly's drug demonstrated best-in-class blood sugar reduction and body weight loss in patients with type 2 diabetes, the most common type of diabetes globally. Eli Lilly has initiated phase 3 trials for the treatment, with data expected in late 2021. Given the promising results thus far, we believe the therapy could have multibillion-dollar sales potential. This would add to Eli Lilly's expanding roster of recently approved products, including Emgality, a migraine prevention treatment that won FDA approval in 2018. We believe Emgality also has blockbuster potential.

Endocyte also aided performance. The biopharmaceutical company is developing a type of radiotherapy for advanced prostate cancer. Based on preliminary positive data, the FDA offered the company an expedited path to market, with pivotal phase 3 data expected by the second half of 2019. Based on our proprietary statistical models, we believed Endocyte's drug had good odds of success and could have blockbuster potential. Novartis seemingly agreed with our view, announcing in October that it would acquire Endocyte for roughly a 50% premium. As a result, we exited the position.

For detailed performance information, please visit janushenderson.com/performance.

Outlook

Market volatility and regulatory uncertainty weighed on health care stocks at the end of the year. In mid-December, for example, a U.S. federal judge ruled the ACA unconstitutional, which could jeopardize health care coverage for millions of Americans. However, the headline may seem more dire than reality. For one, the decision faces an appeals process that could go to the Supreme Court, which has already upheld the ACA twice. Second, Democrats, who take control of the House of Representatives in January, have announced their commitment to defend the law. Finally, Republicans may be reluctant to see millions of constituents potentially lose their health care coverage in the lead-up to the 2020 presidential election.

We will be monitoring these developments closely, but believe the sector continues to have significant long-term growth drivers. In 2018, the FDA approved 59 new therapies, setting an all-time record for approvals in a year. Over the past two years, more than 100 new medicines have been approved. With branded drugs typically having a life cycle of a decade or longer, we believe these early launches could deliver years of growth for the sector.

Looking ahead, we believe innovation remains robust. The first gene therapy for spinal muscular atrophy – the leading genetic cause of infant death – could launch in the U.S. in the coming year. Progress also continues with immunotherapies, leading to significant survival benefits for patients with devastating forms of cancer. Finally, recent data indicate the potential for dramatic health improvements for patients using mitral valve heart repair devices and drug-eluting stents.

While we know the market volatility that we saw at the end of 2018 could persist into 2019, we believe aging populations and innovative products should drive continued demand for medical products and services, making the health care sector attractive to investors. We also believe the recent market pullback offers opportunities to invest in high-quality companies that are developing therapies for unmet medical needs or improving efficiencies within the health care system. Many biotechnology stocks, for example, have been particularly hard-hit during the market rout; we believe some of these companies are now attractively valued, potentially leading to another pickup in merger and acquisition activity within the group.

Top Contributors and Detractors for the Quarter Ended 12/31/18

Top Contributors	Ending Weight (%)	Contribution (%)	Top Detractors	Ending Weight (%)	Contribution (%)
Merck & Co., Inc.	4.57	0.31	Neurocrine Biosciences Inc	2.18	-1.00
Eli Lilly & Co	3.11	0.23	Celgene Corp	2.14	-0.61
BridgeBio Pharma	0.45	0.20	AnaptysBio Inc	1.14	-0.55
Endocyte Inc	0.00	0.11	Teladoc Health Inc	0.78	-0.50
Argenx SE (ADR)	0.53	0.10	Nektar Therapeutics	0.55	-0.44

The holdings identified in this table, in compliance with Janus Henderson policy, do not represent all of the securities purchased, held or sold during the period. To obtain a list showing every holding as a percentage of the portfolio at the end of the most recent publicly available disclosure period, contact 800.668.0434 or visit janushenderson.com/info.

Top Contributors

Merck & Co.: The pharmaceutical company is benefiting from the rapid sales growth of Keytruda, a leading checkpoint inhibitor for the treatment of certain cancers, including melanoma and non-small cell lung cancer. We believe Merck is well positioned to expand Keytruda for other indications in the near future. We also like the management team, which has executed well on a large clinical development program.

Eli Lilly & Co.: The pharmaceutical company is benefiting from a number of recent drug launches, including Trulicity, which helps lower blood sugar for diabetes patients; Jardiance, a treatment that lowers the risk of cardiovascular death in diabetics; Taltz, used by adults with moderate to severe psoriasis, a chronic skin condition; Olumiant, an oral drug for rheumatoid arthritis; and Emgality, a CGRP inhibitor to prevent migraines. We believe these products will help drive sales growth and lead to significant margin expansion for the company.

BridgeBio Pharma: This private company licenses, develops and markets therapies targeting genetic diseases. So far, BridgeBio has 19 drugs under development, including one in late-stage clinical trials for patients prone to a common form of skin cancer and another for a disease called TTR amyloidosis, a leading cause of heart failure. BridgeBio continues to attract capital from private investors and we believe the company has strong growth prospects ahead.

Endocyte: The company is developing Lu-PSMA-617, a type of radiotherapy for advanced prostate cancer. Recently, Novartis announced it would acquire Endocyte for roughly a 50% premium. As a result, we exited the position.

Argenx: Argenx is a Belgian biotech company with expertise in antibody engineering that has led to two proprietary, wholly owned programs in immunology and cancer. We are optimistic about the lead program, efgartigimod (ARGX-113), which has shown positive data in myasthenia gravis and other potential indications caused by the generation of antibodies against a patient's own cells.

Top Detractors

Neurocrine Biosciences: Neurocrine Biosciences' lead drug, Ingrezza, treats tardive dyskinesia, a debilitating condition characterized by involuntary and repetitive movements. Since the drug launched, uptake of Ingrezza has exceeded estimates, and we believe the market for the therapy remains underpenetrated. In addition, Neurocrine's partner recently launched Orilissa, an oral medicine to treat pain caused by endometriosis, which we believe has blockbuster potential.

Celgene: Celgene develops innovative treatments for cancer and inflammatory diseases. Notably, it has a leading position in the treatment of hematological disease, with 2018 sales expected to exceed $10 billion. We are excited about Celgene's late-stage pipeline, which includes five key assets, each with more than $1 billion sales potential. Two of the firm's late-stage medicines are cell-based therapies, with one showing more than a 90% response rate in patients that had failed multiple therapies.

AnaptysBio: AnaptysBio's antibody discovery platform has produced two leading drug candidates. The first, etokimab, is a wholly owned antibody for the treatment of atopic (allergic) diseases. The second, ANB019, is another wholly owned antibody for rare forms of psoriasis. We believe both drugs, if successful in late-stage trials, could have blockbuster potential. Lastly, the firm's antibody discovery platform has resulted in out-licensing deals, which could result in significant royalties for AnaptysBio.

Teladoc Health: Teladoc is the largest telehealth platform in the U.S., delivering on-demand health care via mobile devices, the Internet, video and phone. We believe the company will benefit from an increased focus on improving costs and efficiencies within the health care system. We also think it is differentiated by its scale (Teladoc has 75% market share), brand, relationships (the company has access to millions of patients through major health care providers), technology infrastructure and patient engagement strategies.

Nektar Therapeutics: Nektar Therapeutics is a clinical-stage biopharmaceutical company, which engages in developing therapies to address chronic pain, cancer and autoimmune diseases. The company has two leading drug candidates, NKTR-181, a treatment for moderate-to-severe chronic low back pain, and NKTR-214, a novel immuno-oncology (IO) therapy. We believe both drugs could have significant market potential.

For more information, please visit **janushenderson.com.**

Please consider the charges, risks, expenses and investment objectives carefully before investing. For a prospectus or, if available, a summary prospectus containing this and other information, please call Janus Henderson at 800.668.0434 or download the file from janushenderson.com/info. Read it carefully before you invest or send money.

Past performance is no guarantee of future results. Call 800.668.0434 or visit janushenderson.com/performance for current month-end performance.

Discussion is based on the performance of Class I Shares.

As of 12/31/18 the top ten portfolio holdings of Janus Henderson Global Life Sciences Fund are: Merck & Co Inc (4.57%), Novartis AG (ADR) (3.22%), Eli Lilly & Co (3.11%), AstraZeneca PLC (3.01%), Abbott Laboratories (2.98%), AbbVie Inc (2.78%), Humana Inc (2.71%), Shire PLC (ADR) (2.64%), UnitedHealth Group Inc (2.59%) and Anthem Inc (2.58%). There are no assurances that any portfolio currently holds these securities or other securities mentioned.

The opinions are as of 12/31/18 and are subject to change without notice. Janus Henderson may have a business relationship with certain entities discussed. The comments should not be construed as a recommendation of individual holdings or market sectors, but as an illustration of broader themes.

Security contribution to performance is measured by using an algorithm that multiplies the daily performance of each security with the previous day's ending weight in the portfolio and is gross of advisory fees. Fixed income securities and certain equity securities, such as private placements and some share classes of equity securities, are excluded.

Performance may be affected by risks that include those associated with non-diversification, portfolio turnover, short sales, potential conflicts of interest, foreign and emerging markets, initial public offerings (IPOs), high-yield and high-risk securities, undervalued, overlooked and smaller capitalization companies, real estate related securities including Real Estate Investment Trusts (REITs), derivatives, and commodity-linked investments. Each product has different risks. Please see the prospectus for more information about risks, holdings and other details.

Foreign securities are subject to additional risks including currency fluctuations, political and economic uncertainty, increased volatility, lower liquidity and differing financial and information reporting standards, all of which are magnified in emerging markets.

MSCI World Health Care Index℠ reflects the performance of health care stocks from global developed markets.

S&P 500® Index reflects U.S. large-cap equity performance and represents broad U.S. equity market performance.

Index performance does not reflect the expenses of managing a portfolio as an index is unmanaged and not available for direct investment.

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