3Q20 Global & International Equity

FUND COMMENTARY

Global Life Sciences Fund

Market Environment

- The health care sector saw gains as medical procedures rebounded following COVID-19 lockdowns. Testing for COVID-19 also drove demand for diagnostic tools and services.
- Having adapted operations for a slower-growth environment, many firms delivered consensus-beating results.
- Consequently, on average, health care technology and health care facilities firms delivered the biggest returns during the period.
- In contrast, biotechnology was among the sub-sectors that lagged, as worries about drug pricing reform picked up in the face of the U.S. election. In addition, the Food and Drug Administration (FDA) delayed approvals for several high-profile drug candidates.

Performance Summary

The Fund outperformed its primary benchmark, the MSCI World Health Care Index℠, but underperformed its secondary benchmark, the S&P 500® Index, for the quarter ended September 30, 2020. Positioning in health care services aided relative performance, while an overweight to biotechnology detracted from returns.

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

Portfolio Discussion

Looking at individual holdings, Horizon Therapeutics was the top contributor. The stock climbed after the company reported strong second quarter results. Specifically, sales of the firm's lead drug, Tepezza, came in at over $165 million for the period, well above Street expectations. Horizon also raised sales guidance for 2020 for the second time to over $650 million. Tepezza was approved by the FDA in January and is the only available treatment for thyroid eye disease. Our experience has found that consensus estimates either over- or underestimate the revenue potential of a new product about 90% of the time, with Horizon being a case in point, in our opinion.

Although biotechnology as a sub-sector experienced losses during the quarter, many of the Fund's biotech stocks contributed positively to performance, including Mirati Therapeutics. Mirati is focused on producing small molecule kinase inhibitors for cancer, including an exciting program targeting a protein called KRAS. KRAS has long been considered the holy grail of cancer targets, not only for its role in promoting tumor growth but also because it has been difficult for drug developers to effectively target. Mirati's drug, MRTX849, addresses a mutant form of KRAS that is present in roughly 12% of non-small cell lung cancers. During the quarter, a competitor reported promising data for a similar drug, which could be a positive indication for MRTX849. Mirati is expected to deliver updated results by the end of the year. In addition, the company has had preclinical success with a separate drug addressing another mutation, which we think could have an even larger market opportunity.

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At the same time, other holdings weighed on performance, including BioMarin Pharmaceutical. The stock declined after the company received a complete response letter from the FDA requiring two-year follow-up data for BioMarin's highly anticipated gene therapy for hemophilia. The market had expected approval in 2020. We think investors are too focused on the near term. European regulators, for one, have reiterated that only one-year data are required for filing. A successful launch in Europe could help ease the pathway to approval in the U.S. Meanwhile, BioMarin has a growing, $2 billion revenue business in rare diseases and a pipeline including additional gene therapies and a novel treatment for achondroplasia (dwarfism) in late-stage development.

Odonate Therapeutics was another detractor. This small pharmaceutical company is developing tesetaxel, an oral taxane (orally administered chemotherapy agent) for breast cancer. During the month, tesetaxel met its primary endpoint in a phase 3 study, though at the lower end of an expected range. The company also said its FDA filing would be slightly later than expected. The market interpreted these results negatively, causing a sell-off in the stock. However, we believe tesetaxel remains a promising breast cancer therapy, with oral administration every three weeks (instead of a weekly IV) and improved tolerability. We believe the lower stock valuation makes the risk/reward in Odonate more attractive, and we added to our position on weakness.

Top Contributors	Average Weight (%)	Relative Contribution (%)
Horizon Therapeutics Plc	1.65	0.50
Immunomedics Inc	0.32	0.45
Mirati Therapeutics Inc	1.21	0.42
Elanco Animal Health Inc	1.51	0.30
Silk Road Medical Inc	0.56	0.25

Top Detractors	Average Weight (%)	Relative Contribution (%)
BioMarin Pharmaceutical Inc	1.33	-0.52
Neurocrine Biosciences Inc	1.91	-0.50
Odonate Therapeutics Inc	0.44	-0.48
GW Pharmaceuticals PLC (ADR)	1.04	-0.29
Bristol-Myers Squibb Co	0.44	-0.26

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.
Relative contribution reflects how the portfolio's holdings impacted return relative to the benchmark. Cash and securities not held in the portfolio are not shown.

Manager Outlook

As we saw late in the third quarter, the U.S. election is likely to put pressure on health care stocks as investors worry about potential reform. Although we recognize the risk, in our experience policy often differs greatly from campaign proposals. Thus, while drug pricing reform has weighed on the sector, we think the next administration will be reluctant to curb innovation given biopharma's key role in addressing the pandemic. Similarly, while a Supreme Court case set to begin in November challenges the validity of the Affordable Care Act, we see a number of pathways for the legislation to remain largely in place, minimizing disruption to the U.S. health care system.

We think these risks are priced into stocks, as the sector now trades at a substantial discount to the market. Meanwhile, health care has several near-term growth drivers. Demand for elective procedures, for one, is rebounding, with new technologies improving patient outcomes and expanding end markets for medical device companies. Lower costs have led to strong earnings growth for health insurers, while innovation in biotech remains robust. Indeed, in the coming months, we expect to see late-stage clinical data for gene therapies, precision oncology treatments, and COVID-19 vaccines and treatments. These types of advances have been driving mergers and acquisitions, which we think could accelerate given attractive valuations and rock-bottom interest rates. Near term, investors may have to endure heightened volatility as we get through the U.S. election, but longer term we think health care's high growth potential could come back into focus.

Portfolio Management

Andy Acker, CFA

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

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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 9/30/20 the top ten portfolio holdings of Janus Henderson Global Life Sciences Fund are: Merck & Co Inc (3.70%), UnitedHealth Group Inc (3.51%), Novartis AG (ADR) (3.35%), Thermo Fisher Scientific Inc (3.11%), Roche Holding AG (3.05%), AbbVie Inc (3.01%), AstraZeneca PLC (2.99%), Abbott Laboratories (2.60%), Humana Inc (2.57%) and Boston Scientific Corp (2.42%). There are no assurances that any portfolio currently holds these securities or other securities mentioned.

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For equity portfolios, relative contribution compares the performance of a security in the portfolio to the benchmark's total return, factoring in the difference in weight of that security in the benchmark. Returns are calculated using daily returns and previous day ending weights rolled up by ticker, gross of advisory fees, may exclude certain derivatives and will differ from actual performance.

High absolute short-term performance is not typical and may not be achieved in the future. Such results should not be the sole basis for evaluating material facts in making an investment decision.

Investing involves risk, including the possible loss of principal and fluctuation of value.

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.

Concentrated investments in a single sector, industry or region will be more susceptible to factors affecting that group and may be more volatile than less concentrated investments or the market as a whole.

Initial Public Offerings (IPOs) are highly speculative investments and may be subject to lower liquidity and greater volatility. Special risks associated with IPOs include limited operating history, unseasoned trading, high turnover and non-repeatable performance.

MSCI World Health Care IndexSM 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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