1Q21 Global & International Equity

FUND COMMENTARY

Global Life Sciences Fund

Market Environment

- Health care stocks underperformed the broader equity market as investors favored sectors levered to a post-pandemic recovery.
- Political worries returned as Democrats revisited drug-pricing reform. The U.S. Food and Drug Administration (FDA) also delayed several drug approvals and the U.S. Federal Trade Commission challenged a proposed multibillion-dollar merger, raising concerns about a stricter regulatory backdrop.
- However, these headwinds were offset by a number of successful initial public offerings (IPOs) in biotech, continued capital raises and the accelerating rollout of COVID-19 vaccines in the U.S.

Performance Summary

The Fund underperformed its primary benchmark, the MSCI World Health Care Index℠, and secondary benchmark, the S&P 500® Index, for the quarter ended March 31, 2021. Positioning in biotechnology weighed the most on relative performance. Stock selection in pharmaceuticals aided returns.

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

Portfolio Discussion

The enthusiasm that we saw for small- and mid-size biotech firms at the end of 2020 reversed during the quarter, as rising Treasury yields made stocks requiring long investment time horizons less attractive and investors favored areas expected to benefit from an economic recovery. These factors, along with political headwinds and a handful of clinical trial setbacks, worked against our Fund's overweight to small- and mid-cap biotechs.

The Fund's top individual detractor was Sarepta Therapeutics. This biotech is developing SRP-9001, a gene therapy for Duchenne muscular dystrophy, a fatal, hereditary muscle-wasting disease that affects tens of thousands of children. During the quarter, Sarepta reported that SRP-9001 failed to hit the primary endpoint in a phase 2 trial. Although the result was disappointing, the study did show activity in younger age groups. Furthermore, we believe the trial may have missed due to many of the patients receiving a lower dosage than in previous trials. Consequently, while regulatory approval certainly will be delayed, we believe this gene therapy still has a good chance of ultimate success.

Acadia Pharmaceuticals also weighed on performance. The company's lead drug Nuplazid is being developed as a treatment for hallucinations and delusions associated with dementia-related psychosis. However, during the quarter, the FDA denied approval due to a lack of statistical significance for some patient subgroups. The decision came as a surprise since the issues flagged were not part of agreed-upon criteria for approval. Unfortunately, Acadia will likely have to begin a new clinical trial, pushing out a potential launch by several years.

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Other holdings contributed positively to performance, including GW Pharmaceuticals. The stock rose after Jazz Pharmaceuticals announced it would acquire GW for $7.2 billion, a roughly 50% premium. The offer reflects GW's strong growth potential, as lead drug Epidiolex, a cannabinoid for patients with severe childhood-onset epilepsy, saw sales increase more than 70% in 2020. GW also recently launched Epidiolex for a new indication called tuberous sclerosis complex, a genetic condition that affects 30,000 patients, representing a relatively untapped market opportunity.

Horizon Therapeutics was another significant contributor. During the period, the company reported better-than-expected results for 2020, with sales of lead drug Tepezza hitting $820 million, far exceeding Street expectations and representing one of the best rare disease medicine launches in history. Horizon's other franchises also showed promise, including Krystexxa, a therapy for severe gout, which overcame COVID-19 headwinds to surpass Street expectations. Finally, Horizon announced the well-received acquisition of Viela Bio, adding several potential blockbuster products to the pipeline. (A blockbuster drug has annual sales of $1 billion or more.)

Top Contributors	Average Weight (%)	Relative Contribution (%)
GW Pharmaceuticals Plc (ADR)	0.43	0.65
Horizon Therapeutics Plc	1.31	0.25
Edgewise Therapeutics	0.10	0.24
Design Therapeutics Inc	0.08	0.17
BioAtla Llc	0.39	0.15

Top Detractors	Average Weight (%)	Relative Contribution (%)
Sarepta Therapeutics Inc	1.23	-0.81
Acadia Pharmaceuticals Inc	1.05	-0.69
Amicus Therapeutics Inc	0.55	-0.47
Olema Pharmaceuticals Inc	1.18	-0.36
Ascendis Pharma A/S (ADR)	1.27	-0.34

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

Once again, political concerns are weighing on health care, particularly as it relates to drug pricing. However, while some proposals may be worrisome, we take comfort in President Biden's record of championing medical research and believe it would be politically unpalatable to punish biopharma after the industry's heroic response to COVID-19. In our view, a more likely outcome is legislation that focuses on improving drug affordability for consumers, which we believe would help safeguard innovation while benefiting patients.

In the meantime, the average health care stock now trades at a substantial discount to the broad market. Progress continues to be made in therapeutic areas that could be life-changing for patients, such as precision oncology, cell and gene therapies, and early cancer screening. Some FDA approvals have been delayed, but we think this has more to do with the lack of leadership at the top, as a new FDA commissioner has yet to be named by the Biden administration.

We have seen a few disappointing clinical trial setbacks, several of which have impeded our portfolio. However, this is a part of investing in novel products for unmet medical needs. We know drug development is inherently volatile, which is why we apply our "value at risk" framework in an attempt to mitigate losses. Long term, we remain as excited as ever about health care's growth potential and expect the opportunity set to continue to expand. This is evidenced by the success of recent IPOs and the biopharma industry's growth globally, including in China, where we are increasingly finding attractive investment opportunities. In the near term, we expect COVID-19 vaccinations will help drive a recovery in demand for routine medical care, bolstering areas of the sector that lagged during the pandemic.

Portfolio Management

Andy Acker, CFA

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

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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 3/31/21 the top ten portfolio holdings of Janus Henderson Global Life Sciences Fund are: UnitedHealth Group Inc (4.01%), AstraZeneca PLC (3.87%), AbbVie Inc (3.22%), Merck & Co Inc (2.98%), Roche Holding AG (2.78%), Novartis AG (ADR) (2.77%), Humana Inc (2.56%), Abbott Laboratories (2.47%), Boston Scientific Corp (2.46%) and Vertex Pharmaceuticals Inc (2.30%). There are no assurances that any portfolio currently holds these securities or other securities mentioned.

The opinions are as of 3/31/21, are subject to change and may not reflect the views of others in the organization. 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.

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 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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