PORTFOLIO COMMENTARY

Global Life Sciences Diversified ADR Managed Account

Market Environment

- Health care stocks delivered gains, outperforming the broader market.
- On a sub-sector basis, health care suppliers and facilities saw the largest returns as rising COVID-19 cases led to increased demand. In contrast, health care technology firms lagged on worries about disruptions to routine medical care.
- However, the pandemic did not stop clinical trials from continuing, helping life sciences tools and services firms to also outperform in the sector.

Performance Summary

The Portfolio underperformed its benchmark, the MSCI World Health Care Index[SM], for the quarter ended September 30, 2021. Detracting from returns was positioning in pharmaceuticals and biotechnology. In contrast, the Portfolio's stock selection in health care equipment and underweight to health care technology contributed positively to performance.

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Portfolio Discussion

Looking at individual holdings, biotechnology stocks made up many of the top contributors and detractors, reflecting the binary nature of this area of health care. It also shows how some market participants can focus too much on near-term events, in our view. For example, Seres Therapeutics, the top detractor, reported that its drug candidate for ulcerative colitis failed to meet a primary endpoint, leading Seres to end the drug's development. However, we think Seres still has a promising pipeline, including SER-109, a treatment for C. difficile infection (CDI). A leading cause of hospital-acquired infections, CDI is responsible for 20,000 deaths per year in the U.S. Last year, Seres delivered positive phase 3 data for SER-109, and in July, announced a licensing agreement with Nestlé Health Science to commercialize the drug.

ESSA Pharma also weighed on performance. The company is developing novel treatments for prostate cancer and has created a new class of drugs that target the N-terminal domain of the androgen receptor. ESSA hopes the approach can manage resistance seen with similar therapies, a multibillion-market. Although early clinical data have been promising, in August, management declined to provide updated data for their lead drug, citing they wanted to better understand dosing requirements and expand the targeted patient population, who tend to be unresponsive to medication. We believe the decision was a prudent one and still like the prospects for clinical development.

The top contributor was Sarepta Therapeutics. The biopharma is developing SRP-9001, a gene therapy for Duchenne muscular dystrophy (DMD), a muscle-wasting hereditary disease that affects tens of thousands of children. The stock climbed after Sarepta reported it would begin a phase 3 trial for the therapy this fall, a positive step after SRP-9001 delivered mixed results during a phase 2 trial earlier in the year. In addition, Sarepta announced it would soon begin phase 3 trials for an

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improved version of its alternative DMD program, known as exon skipping. This new platform could provide dramatically better clinical benefits than the existing franchise, which is on track to deliver $570 million in sales in 2021.

Acceleron Pharma was also a significant contributor. The stock benefited after Merck announced at the end of the quarter that it would acquire Acceleron for $11.5 billion. Acceleron is developing sotatercept for pulmonary arterial hypertension, a progressive and life-threatening blood vessel disorder. We had initially invested in Acceleron in 2018, when the company had a much smaller market capitalization, as we thought the platform behind sotatercept had significant market potential. Sotatercept has delivered strong data from late-stage studies, and we believe Merck's acquisition now validates our view.

Top Contributors	Representative Account Average Weight (%)	Representative Account Relative Contribution (%)
Sarepta Therapeutics Inc	1.47	0.30
Acceleron Pharma Inc	0.76	0.27
Ascendis Pharma A/S	1.32	0.26
Biohaven Pharmaceuticals	0.80	0.26
Travere Therapeutics Inc	0.37	0.19

Top Detractors	Representative Account Average Weight (%)	Representative Account Relative Contribution (%)
Seres Therapeutics Inc	0.37	-0.35
Moderna Inc	0.68	-0.29
ESSA Pharma Inc	0.28	-0.28
Jazz Pharmaceuticals Plc	0.90	-0.25
Humana Inc	2.47	-0.22

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

This year's sell-off in small- and mid-cap biotech may be coming to an end, with the S&P Biotechnology Select Industry Index (a benchmark of small- and mid-cap biotech stocks) consistently trading above a low hit in August. The drawdown was one for the record books. From February 8 through August 19, small- and mid-cap biotech underperformed the health care sector by almost 50% (the widest margin ever), weighed down by concerns about drug-pricing reform in the U.S., an unpredictable Food and Drug Administration (FDA), a broad-based market rotation, and worries that mergers and acquisitions (M&A) could face stricter regulatory oversight.

Throughout, we believed these headwinds were largely transitory, and we are beginning to see signs of recovery. Low valuations have attracted the interest of large-cap biopharma, with several multibillion-dollar deals announced in the last two months. The FDA – despite lacking a permanent commissioner and being inundated with applications for COVID-19 treatments – is on track to approve a near record number of novel drugs in 2021. And drug-pricing reform has met with stiff resistance in Washington, D.C., making drastic proposals such as direct drug price negotiation by the government less likely to pass.

Meanwhile, health care's innovation engine is running at full throttle, with advances continuing to be made in biologics, medical devices, research and development, and health care delivery. Although demand for routine medical care could face near-term challenges from the Delta variant and supply-chain and staffing shortages, the momentum created by long-term trends such as advanced biological understanding, new technology and aging populations remains firmly in place. What's more, the pressure to compete while keeping costs in check has focused companies on prioritizing medical breakthroughs and finding efficiencies, which in turn are leading to new end markets. In short, we believe the health care sector remains well positioned for growth and that small- and mid-cap biotech's recent pullback, while extraordinary, is more an opportunity for long-term investors than a broad-based concern.

Portfolio Management

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For more information, please visit janushenderson.com.

Past performance is no guarantee of future results.

Discussion is based on performance gross of fees and expenses.

Information relating to portfolio holdings is based on the representative account in the composite and may vary for other accounts in the strategy due to asset size, client guidelines and other factors. The representative account is believed to most closely reflect the current portfolio management style.

As of 9/30/21 the top ten portfolio holdings of the Representative Account are: AstraZeneca PLC (ADR) (4.74%), UnitedHealth Group Inc (4.27%), Roche Holding AG (ADR) (2.74%), Merck & Co Inc (2.66%), Thermo Fisher Scientific Inc (2.65%), AbbVie Inc (2.61%), Boston Scientific Corp (2.51%), Abbott Laboratories (2.50%), Danaher Corp (2.42%) and Humana Inc (2.32%). There are no assurances that any portfolio currently holds these securities or other securities mentioned.

Portfolio holdings are as of the date indicated, and are subject to change. This material should not be construed as recommendation to buy or sell any security.

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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.

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.

Global Life Sciences Diversified ADR Managed Account Composite, benchmarked to the MSCI World Healthcare Index, includes portfolios that concentrate on finding growth companies located both inside and - through ADR shares - outside of the United States that have a life science orientation. "Life sciences" industries may include the following industry groups: health care; pharmaceuticals; agriculture; cosmetics/personal care; and biotechnology. A typical portfolio invests in 80 to 90 equity securities. Prior to January 1, 2020, returns for the composite are for the Global Life Sciences Composite, which consisted of separately managed institutional accounts, proprietary mutual funds as well as sub-advised pooled funds. The composite was created in January 2020.

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

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