INNOVATION

INNOVATION DRIVEN INVESTMENT OPPORTUNITIES IN LIFE SCIENCES

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WHITEPAPER | OCTOBER 2024

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Life Sciences encompass a wide field and involves the study of living organisms and how scientists and companies can harness this knowledge to improve life. The rapidly growing knowledge base that allows scientists to understand the root cause of diseases and the aging population will make this a growth industry for decades to come. Life Sciences is both one of the most innovative industries and one of the most important industries for improving human health.

U.S. health care spending grew 4.1% to reach $4.5 trillion in 2022, which represented 17.3% of the gross domestic product (GDP). The CMS Office of the Actuary projects that from 2023 to 2032, the average annual growth in national health expenditures will be 5.6%, outpacing average annual growth in GDP, which will result in an increase in the health spending share of GDP from 17.3% in 2022 to 19.7% in 2032.

Investing in the Life Science industry encompasses opportunities in many areas, including, but not limited to:

- New treatment modalities in the Biotechnology Industry
- More traditional treatments in the Pharmaceutical Industry
- Medical Diagnostics
- Medical Devices
- Novel modes of healthcare delivery
- Health-Tech companies including those that provide AI and analytics
- Synthetic Biology

This white paper provides an overview of some of the unique investment opportunities in the life sciences industry driven by innovative breakthrough science worldwide. In addition, we make the argument that active portfolio management along with fundamental, bottom-up research utilizing both scientific and technical skillsets are the key to consistent, long-term success for investing in the field of Life Sciences.

The Biotechnology Industry

The sequencing of the human genome in 2003 resulted in the identification of over 8,000 genetic diseases and sparked a wave of innovation that continues unabated today. Leading biotechnology companies have become adept at tying genetic data to the cause of diseases, enabling them to develop drugs that target the disease at the source. This process results in higher odds of technical success and a smoother regulatory path. Artificial intelligence and the use of in silico modeling is

in the early days, but the pieces are in place for this to further improve efficiency within the next decade.

Biotechnology companies translate innovative science into drugs. We define an emerging biopharma company as one with <$500M revenue and that spends <$200M per year on Research and Development (R&D). We define mid-sized biotech companies as companies between $500M-$10B in annual sales. There are approximately 800 publicly-traded biotechnology companies, the majority of which have no revenue. As these companies are consuming cash, they issue new equity to fund their next set of experiments. It costs $800M to $2.3B to develop a drug to FDA approval according to recent estimates. The lower end of that range does not account for the investment on other drugs that never reach the finish line. Due to the high levels of innovation and the risk associated with drug development, the reward for a successfully developed drug is lucrative—most biotech drugs have gross margins in excess of 80%.

Biotechnology stocks trade primarily on clinical data events for the company's drug or on data presented by other companies working in the same space that alter the probability of technical success or alter the potential market size if the drug is successfully developed. There is no way to effectively screen for these volatile stocks as most have no earnings, EBITDA, or revenue. Failure rate is high. A recent report by Goldman Sachs estimated that only 10%-12% of drugs that enter the clinic make it to patients. Success as a biotechnology investor requires a deep understanding of the science underlying each drug in a company's development pipeline and the intricacies of the disease being targeted.

The biopharma industry raised roughly $70 billion in 2023, which closely approximates the industry's cash burn. The aggregate enterprise value of the 800 non-revenue generating biopharmaceutical companies listed on any global exchange was $235 billion as of September 6, 2024, according to a September 2024 report from Stifel.

Biotech companies are the innovation engine of medicine.

According to a February 2024 report by IQVIA Institute, emerging biopharma companies were responsible for two-thirds of the clinical trials initiated in 2023. Mid-sized companies were responsible for 11% of the starts, and large pharmaceutical companies were responsible for only 27% of the clinical trial starts. The agility, focus, and lack of bureaucracy of small companies allow them to outperform deep-pocketed pharmaceutical companies in the drug development process. This is more evidence that innovation really does start small!

Of the sixty-nine new active substances approved in 2023, 56% of the drugs originated at emerging biotech companies and 53% of the drugs were launched by emerging biotech companies according to IQVIA Institute. This again shows that small biotech companies are the innovation engine of medicine.

Novel treatment modalities.

Alongside the sequencing of the genome, great strides have been made with new treatment modalities. Small molecules (pills) gained prominence in the 20th century and are still being developed. In the 21st century, the precision of monoclonal antibodies has caused them to dominate despite their complex manufacturing. We believe there are cutting edge tools that offer precise means to treat genetic diseases. Below we provide a brief overview of some of the latest innovations in methods of treating diseases:

- Gene Therapy/DNA Editing—Gene therapy and DNA editing are two techniques that insert, delete, or silence genes in a patient. Both gene therapy and gene editing were enabled by the sequencing of the human genome. Both require an understanding of the cause of the disease and both work best for diseases caused by a single genetic mutation. It's been recently estimated that there are >6,500 diseases with known molecular causes. Gene therapy and DNA editing possess the precision to fix monogenic diseases and they have a high probability of success. The key drawback of gene therapy is that it typically requires the administration of a virus to deliver the gene correction and it is expensive to manufacture. The weakness of DNA editing is the same as its biggest strength—it is permanent. Both also have challenges in getting to the anatomical location of the target gene. As of July 2024, there were 20 FDA approved gene therapies.

- Oligonucleotide therapeutics—Oligonucleotide therapeutics encompasses a wide variety of synthetically modified RNA or RNA/DNA hybrids that bind a specific sequence of RNA. The goal is to reduce downstream expression of the protein that is made by the RNA sequence of interest. This is especially useful for proteins that are hard to target by more traditional means and is being explored in some diseases where the long pharmacodynamic effect of the drug can be leveraged. As of July 2024, there have been 17 oligonucleotide therapeutics approved by FDA. The key limitation of oligonucleotide therapeutics is getting the drug into the area of the body where it needs to act. Most oligonucleotide therapeutics work in the liver or the eye as delivery to these two areas is the easiest.

- RNA editing—DNA is transcribed to RNA which is translated to protein. RNA editing provides added precision and safety relative to DNA editing and is useful when the protein made by

the RNA is considered 'undruggable' due to its structure or other characteristics. The other major advantage RNA editing has over DNA editing is that RNA editing is not permanent. From a financial perspective, the RNA editing model is also more attractive as it requires chronic dosing. The finality and potential ramifications of DNA editing coupled with the more attractive revenue model may usher in an acceleration in RNA editors. The first RNA editors are just entering human clinical trials in 2024.

Biotech stocks are ideal for active management.

We believe that biotechnology stocks are best suited for active management strategies. Biotech companies usually don't have revenue, so one cannot screen for attractive investments based on the company's financial profile. Biotech stocks trade on presentation of scientific data which requires an understanding of subtle nuances as investors need to gauge how the data presented alter probability of approval for a drug or potential market penetration. Investing in biotechnology stocks requires an understanding of the science and the ability to determine the probability that a drug is successfully developed and the value of the drug once it is approved.

Biotechnology stocks exhibit significant dispersion.

Absent news flow and data events, biotechnology stocks tend to trade like other high-risk sectors. Even in a biotech bear market that started in 2021 and continues in 2024, there have still been strong performers as clinical data for individual companies leads to idiosyncratic stock movements. The chart below from Goldman Sachs illustrates this point and further demonstrates why biotechnology is an ideal sector for active management.

Performance of Best 5 and Worst 5 Biotech companies (2019-2023)

	2019	Perf	2020	Perf	2021	Perf	2022	Perf	2023	Perf
Best performing	AXSM	3565%	NVAX	2702%	PRTA	311%	VRNA	289%	SLNO	1933%
	RCEL	698%	CLDX	686%	BCYC	239%	MDGL	243%	EYPT	560%
	ARWR	411%	TWST	573%	AVXL	221%	RYTM	192%	OLMA	473%
	MDXG	323%	ALT	497%	BNTX	216%	ATXS	176%	BBIO	430%
	ARDX	319%	MRNA	434%	DVAX	216%	ADMA	175%	AUTL	239%
Most underperforming	ANAB	(75%)	EYPT	(58%)	OLMA	(81%)	CCCC	(82%)	ARQT	(78%)
	WVE	(81%)	RCEL	(59%)	IMVT	(82%)	CVAC	(82%)	NVCR	(80%)
	COGT	(84%)	ATXS	(64%)	DCPH	(83%)	FATE	(83%)	BLUE	(80%)
	VRDN	(84%)	EOLS	(72%)	ARDX	(83%)	NVAX	(93%)	VTYX	(92%)
	NVAX	(89%)	SVRA	(74%)	SPRY	(86%)	TRML	(93%)	ACRS	(93%)
XBI		**33%**		**48%**		**(20%)**		**(26%)**		**8%**

Source: FactSet, Goldman Sachs Global Investment Research

The Pharmaceutical Industry

The pharmaceutical industry is a $1.04T industry and is expected to deliver 6% growth through 2028, according to a recent TD Cowen report. Pharmaceutical companies discover, develop, produce, and distribute medications. Pharmaceutical companies operate globally, though the United States market is approximately half of the group's sales. We define pharmaceutical companies as companies that sell drugs and have annual revenue >$10B. Growth for pharmaceutical companies is driven by the entry of new pharmaceutical products to the market and from acquisition of smaller pharmaceutical or biotech companies.

The drug approval process is gated by the Food and Drug Administration (FDA). From 2014-2023, the FDA has approved an average of 46 new drugs per year. Approximately half of the approvals are drugs that pharmaceutical companies own. The pharmaceutical industry also has strong innovation. Recent new product cycles that have been unlocked by pharmaceutical companies include obesity, Alzheimer's Disease, and non-opioid pain. These markets seem poised to drive pharmaceutical growth for the next decade.

In addition to unlocking new therapeutic categories, pharmaceutical companies will also grow by acquiring external innovation. Goldman Sachs estimates that pharmaceutical companies will have products that generate $280B in annual sales go generic by 2030. However, they are well-capitalized and Goldman estimates that if each company was willing to lever up to 2.5x EBITDA, the industry would have $490B in balance sheet capacity. As of September 6, 2024, Stifel estimates the total enterprise value of all of the global biotech companies to be $235B. Pharmaceutical companies and biotech companies have an important dynamic: biotech companies develop drugs in early-stage clinical trials, while pharmaceutical companies acquire the most lucrative drugs as they progress through clinical trials. The acquisition allows the investors in biotech to recycle the capital to form new companies. The job of pharmaceutical companies is rather similar to ours—selection is key.

The Medical Device Industry

We estimate that the medical device industry in the United States is a little over $200 billion in size and is expected to grow 5-6% over the next five years. According to Fortune Business insights the global medical device industry was valued at $518 billion in 2023 and is expected to grow around 6% annually over the next decade. Over the past three decades, the United States has been at the forefront of medical innovation and the U.S. exports more in this sector than it imports. The medical device industry employs more than 550,000 people in the U.S. and it is a significant positive contributor to the U.S. economy. Our focus remains on identifying new innovations in the medical device industry that can bring disruptive change and result in better healthcare outcomes.

An example of an area with disruptive growth is the innovation occurring in the organ transplant end market. The demand for organ transplants remains strong with 104,506 patients on the waiting list in the United States as of October 11th 2024 according to the not for profit organization – "*United Network of Organ Sharing*". The key challenge facing this industry has been the need to procure more organs. A key challenge that existed in this industry had been the limitations associated with cold storage of an organ. Cold storage is a rudimentary approach to organ preservation in which a donor organ is flushed with cold pharmaceutical solutions, placed in a plastic bag on top of ice, and transported in a cooler. Cold storage is useful to transport organs over short distances but has limitations when transporting organs over longer distances. Over the past decade, several companies have worked towards modernizing the process and have used ex-vivo perfusion of the donor organ with oxygenated blood. This allows organ transplant teams to store an organ more efficiently and to monitor its vitality during transport. In addition, it allows transplant centers to plan procedures more effectively and, in some cases, utilize more organs from the same patient when multi-organ transplants are required. This would have been difficult without these modern transportation and storage technologies because of the limitations of prolonged cold static cardioplegic preservation. Organ Transplant centers are now also able to source organs for their patients from much farther distances allowing for more access, which is helpful for supporting more patients. The FDA announced approval of Organ Care System (*Liver*), Organ Care System (*Lung*) and Organ Care System (*Heart*) in 2021 and 2022, which has allowed transplant centers to procure organs from almost 2,000 miles away, distances which would have been almost impossible without these newer innovations. The impact of organ transplant innovation can be immediately seen in the acceleration in the number of Heart, Lung and Liver transplants done in the United States in 2023.

Real world examples like the one above bolster our confidence that this industry will continue to innovate. The medical device industry also benefits from the tailwind of the aging population where there is an increasing need for innovations that keep our seniors healthier and maintain quality of life. Over the past twelve months, hospitals and providers within the U.S. have seen an increase in the utilization of healthcare services and we believe that it is most likely tied to the age of the average baby boomer crossing 70 years. Based on the demographic needs of the society in the U.S., we see a continued higher utilization level of healthcare services.

The Medical Diagnostics Industry

We estimate that the medical diagnostics industry in the U.S. was approximately $85 billion in 2023 and is anticipated to grow 6% over the next decade. According to Nova One Advisors, the global diagnostics industry was $211 billion in 2023 and expected to grow at a faster rate of 8% annually

over the next 10 years. Diagnostic services play a key role within the healthcare industry by providing tests used to detect diseases and to monitor disease progression. There are many areas in healthcare such as diabetes where utilization of newer technologies, including continuous glucose monitors and insulin pumps, has led to better management of the disease and decreased the longer-term burden of living with these chronic conditions.

Looking forward, we see many areas where diagnostic services will play a key role. We highlight the following two areas:

- Cancer Detection and Management – Traditionally, the diagnosis and treatment of cancer required a pathologist to evaluate a biopsy obtained from a surgical procedure. With advancements in science over the past decade, there has been a major transformation in our ability to detect cancer earlier because of the advancements in a technique called liquid biopsy. A liquid biopsy is a non-invasive test that analyzes any liquid sample (typically blood, urine, or saliva) to detect cancer or other conditions. As a tumor grows, it sheds DNA fragments and cancer cells that travel in the blood stream. It is this circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs), that are interrogated using modern technology to detect cancer and learn more about the nature of the tumor. Today this technology is experiencing rapid adoption because it is easy to use and it plays a role in both identifying a tumor and in monitoring a response to therapy. Liquid biopsy tests are now approved by FDA for some cancers and several companies are conducting further clinical studies to expand their utilization into other cancer types. The liquid biopsy market size was a little over $3 billion in 2021. According to a report by Nova One Advisors, the global liquid biopsy market was approximately $11 Billion in 2023 and they anticipate it to grow to $33 Billion by 2033. TD Cowen in their recent report have estimated that the TAM for liquid biopsy in the Oncology Diagnostic end markets exceeds $100 Billion. We would agree with the significant market potential for innovators focused on this segment and believe this will be one of the faster growing segments within the field of diagnostics.

- New tests for neurological diseases – Discovery of new biomarkers in neurological diseases will result in significant expansion of testing opportunities. As life expectancy increases globally, there are several neurological conditions that will be major challenges faced by our society. Alzheimer's disease is one of the major challenges of the 21st century with an estimated 6.7 million Americans living with the disease in 2023. According to the Alzheimer's Association, one in nine Americans over the age of 65 will be impacted by this disease. Leqembi was the first amyloid beta-directed antibody to be granted FDA approval for the treatment of Alzheimer's disease. The drug works by reducing amyloid plaques that form in the brain, a defining pathophysiological feature of the disease. We believe there will be

renewed interest among patients suffering from dementia and memory loss to evaluate their symptoms to determine if they have Alzheimer's dementia and would be candidates for these newer therapies. We also believe more patients would benefit from these treatments if their disease was identified earlier. The gold-standard for diagnosing Alzheimer's disease is PET scans. While very accurate, the expense of a PET scan limits access. We believe novel Blood-Based BioMarkers (BBBM) such as pTau-181, pTau-227, NfL protein and others will provide significant value and become a non-invasive way to diagnose Alzheimer's Disease and potentially monitor the efficacy of the therapy. The overall opportunity for Alzheimer's disease is between $10B and $50B according to various industry reports. In a recent report from Goldman Sachs they estimated a total addressable market of $29.7 Billion by 2030 for the overall screening opportunity for the 65+ US population and $26.9 Billion market opportunity by 2030 for therapy monitoring market for those prescribed AD-related therapies. We believe we are at an inflection point in our ability to diagnose many neurological conditions such as Alzheimer's Disease earlier in the disease progression when drugs can prevent further loss of function.

Artificial Intelligence (AI) in Healthcare

Artificial Intelligence (AI) plays a key role in many areas within the Life Sciences industry and we look forward to understanding the value created by companies that build new AI products and those that most effectively use AI to enhance their productivity. Areas where we believe AI will play an increasing role over the next decade are:

- AI in drug discovery and development – In the U.S. it takes an average of twelve years from candidate nomination to FDA approval. The process also involves significant resources with costs estimated to range from $800M-$2.3B. With advancements in AI over the last decade, it has found utility now in many steps along the way from structure-based drug designing to homology modeling to virtual screening. AI has the potential to accelerate the drug discovery process meaningfully as recent AI-incorporated biotechnology companies have shown the ability to take a drug from initial conceptualization to clinical testing within twelve months which historically used to take five years. Using bio-simulation models and AI algorithms, researchers can now optimize the lead candidates by predicting their efficacy, toxicity, and pharmacokinetic properties along with various organ toxicity prior to the start of clinical testing.

- AI as a diagnostic tool – AI can enhance the productivity of radiologists and improve the accuracy of diagnosis of cancer. FDA has approved AI solutions for reading mammograms which will improve the cancer detection rate and decrease the recall rate. We expect that AI

will be used ubiquitously for screening mammograms as healthcare payors and providers see the cost savings from early detection and the improved overall health outcomes with these technologies.

- AI applications across other medical specialties – In cardiology, physicians are using AI for detecting arrythmias and other abnormalities while analyzing electrocardiograms. Clinicians also can now predict fractional flow reserve or FFR from CT images. In dermatology, there is a need for better diagnostic tools for detecting melanoma and AI can be applied to image analysis of moles to determine which moles could be malignant. We also see the significant role that AI will play in neurology where it can be used to predict, detect, and classify epileptic seizures. Finally, there is potential for AI in remote patient monitoring to identify patients at the greatest risk for brain injuries and the potential complications post injury.

THE EMERALD ADVANTAGE:

Life Sciences is a large and rapidly growing industry with United States healthcare expenditures reaching $4.5 trillion in 2022. The growth of the industry is fueled by innovation driven primarily by small cap biotechnology and medtech companies. Innovation is both creating new markets and expanding existing markets. These innovative smaller companies often represent attractive acquisition candidates for large pharmaceutical companies and medtech companies seeking to leverage their extensive distribution, revenue management, and production capabilities while offsetting sizable impending patent cliffs.

We believe the key to consistent, long-term investment success in the life sciences industry is the application of both scientific and financial analysis skillsets. The combination of these skillsets enables an effective evaluation and analysis of the scientific and technical factors driving innovation, as well as the market opportunities and potential future revenue and earnings streams. As such, the Life Sciences industry is uniquely positioned to benefit from intense, bottom-up fundamental research and active portfolio management strategies. **We call this the Emerald Advantage.**

IMPORTANT DISCLOSURE

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The dispersion of biotech performance is presented for illustrative purposes and is not indicative of possible returns.

EBITDA - Earnings Before Interest, Taxes, Depreciation, and Amortization, is an alternate measure of profitability to net income. It's used to assess a company's profitability and financial performance.

Sources:

- BridgeBio Corporate Presentation – September 2024 - (slide 13)
- Stifel Biopharmaceutical Sector Update – September 9, 2024 - (slide 23)
- FDA – Novel Drug Approvals for 2023 – October 11, 2024
- Fortune Business Insights – Industry Reports/Medical Devices Market-1000850 - October 7, 2024
- Biospace - Diagnostic Testing Market Size to Reach USD 449.78 Billion by 2033 – April 16, 2024
- Biospace - Liquid Biopsy Industry is Rising Rapidly Up to USD 32.54 Bn by 2033 – April 19, 2024
- TD – Cowen report – Liquid Biopsy – 10 Years In & We've Only Just Begun – December 18, 2023
- Alzheimer's Association – 2024 Alzheimer's Disease Facts & Figures – Special Report: Mapping A Better Future for Dementia Care Navigation
- Alzheimer's Association - 2024 Alzheimer's Disease Facts & Figures – Quick Facts
- GS – Scratching the Surface – The Opportunity for Blood Based Biomarker Diagnostics in the Detection of Alzheimer's Disease - Sept 27, 2023
- Global Trends in R&D 2024 Activity, productivity, and enablers. IQVIA institute. February 2024
- Goldman Sachs Research The ABCs of Biotechnology. Published September 12, 2024

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