Innovation in the Health Care Sector: Investing in the Future of Medicine

February 2011

Marshall Gordon
Nicholas Wu, Ph.D.
Research Analysts for Health Care

www.ClearBridgeAdvisors.com

All data as of December 31, 2010, unless otherwise specified.

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We anticipate several new therapies will come to the market in the next three to five years. If all of these technologies are successful, we forecast that world-wide peak aggregate revenue potential could be $60 billion.

Executive Summary

In the health care industry, innovation is what ultimately drives growth and earnings for companies and returns for their investors. Breakthrough products and improved technologies confer a genuine competitive advantage. This dynamic should hold true even as federal health care legislation is enacted. Demand for game-changing products and processes that enable better and more efficient care will ultimately transcend any changes in distribution and payment systems.

ClearBridge Advisors has a long history of investing in companies whose competitive advantage stems from innovation. In this paper, we examine:

- The particular types of innovation most likely to translate into financial advantage;
- The most attractive pipeline opportunities and their market potential;
- How health care legislation may impact innovative firms;
- Investment implications within the health care industry.

What Makes An Innovation Truly Valuable?

Innovation has long been the driving force in the health care industry. When a company brings a new treatment to market that addresses a crucial unmet medical need, it often generates a significant stream of revenue and earnings for the innovator. Truly innovative treatments may receive expedited review by the U.S. Food and Drug Administration (FDA) and European Medicines Agency, which tend to look favorably on real advancements in patient care. The priority review process at the FDA was created primarily in response to the spread of AIDS and the lack of effective treatments. Currently, therapies designed to treat AIDS and various cancers remain the most prominent beneficiaries of this expedited review process.

- Rituximab was approved by the FDA through its priority review process for the treatment of certain non-Hodgkins lymphomas in 1997. The drug is now a standard treatment for various lymphomas, leukemias, as well as a treatment for some autoimmune diseases.

- Imatinib was the first of a new class of agents that act by specifically inhibiting a protein characteristic of a particular cancer, rather than by non-specifically killing all rapidly dividing cells. The drug received FDA expedited approval in 2001 for the treatment of chronic myelogenous leukemia and is now also used against certain gastrointestinal tumors and other cancers.

- Etravirine was approved through the FDA priority review process for the treatment of HIV/AIDS. The compound is active against HIV in patients with mutations of the virus that are resistant to certain other therapies.

Innovative products and therapies can also encourage government agencies and third party payors to reimburse hospitals and doctors for the use of improvements in medical treatment when those treatments reduce costs to the overall health care system.

Most importantly, financial markets clearly reward medical innovation. Therapeutic companies, including pharmaceutical, biotechnology and medical device companies, represent an aggregate market capitalization approaching $2 trillion. This value is built on the foundation of bringing products to market that advance the practice of medicine.

Paths to Innovation

Certainly, the most newsworthy developments in medicine involve novel treatments that meaningfully alter the course of diseases for which there are no effective therapies.

These "green field" discoveries represent clear breakthroughs in medical science. Examples of successful "green field" therapies include trastuzumab, a monoclonal antibody that has had a major impact in the treatment of breast cancers, and imatinib, a protein inhibitor effective in the treatment of chronic myelogenous leukemia.

However, green field innovations are by no means the only meaningful developments or the only means of obtaining investment returns. New therapies that change how medicine is practiced by replacing older, less safe or less effective drugs and devices also represent important medical and investment opportunities.

Finally, incremental advances in patient care, especially those in large existing markets, can present considerable economic potential. Significant treatments in this respect include angiotensin converting enzyme (ACE) inhibitors, which have, to a significant degree, supplanted angiotensin receptor blockers (ARBs) in the treatment of hypertension. Together these two treatments represent tens of billions of dollars in annual sales.

From an investment standpoint, no one type of innovation is clearly more or less likely to produce superior returns. While "green field" innovations are often the most exciting, investment in unproven drugs and technologies is risky and uncertain. It is also important to assess the commercial size of each opportunity, as well as to what extent the underlying stock price of a company already reflects the potential for value creation.

Innovations on the Horizon

We anticipate many therapies will come to the market in the next three to five years. If all of

If new treatments are successful, the potential impact on the management of patients with Alzheimer's Disease could be enormous.

these technologies are successful, we forecast that world-wide peak aggregate revenue potential could be $60 billion, and many individual new-drug markets could reach or exceed $2 billion. The tables on page 6 outline the areas of medical advancement where we see the greatest potential for near-term innovation. While researchers continue to work on advancing treatments for numerous illnesses, we highlight particular promise from new treatments in three specific areas:

Heart Valve Replacement

- Key innovation: Catheter-based systems
- Estimated market potential: $2 billion plus

As people age, the valves in their hearts can deteriorate or harden, which can lead to progressive heart failure. It is estimated that more than 2 million people in the U.S. alone suffer from some level of reduced function of their aortic valve. Today, the only treatment for this condition is surgical replacement of the valve. While effective, this open heart procedure poses great risk to patients and requires weeks, if not months, of recuperation. Still, approximately 70,000 people undergo surgical aortic valve replacement annually in the U.S.

Competing companies have developed catheter-based systems for aortic valve replacement, which we believe may revolutionize therapy for patients with failing heart valves. These devices are minimally invasive, not requiring the risk and trauma of open heart surgery, and the procedure is very similar to the use of stents to hold open the arteries of patients following a heart attack. Stents have overtaken open heart bypass surgery as the preferred means for treating coronary heart disease. We anticipate that new devices for heart valve replacement will first allow physicians to treat the estimated 30,000 to 40,000 heart valve patients who are too old and frail for open heart surgery. Over time, we expect minimally invasive approaches to replace a significant proportion of standard open heart surgery, much as stenting has replaced arterial surgery over the past 20 years. From an economic perspective, we estimate that the market for new heart valve replacement technology could exceed $2 billion.

Blood Thinners

- Key Innovation: Safer and easier-to-administer drugs
- Estimated market potential: $10 billion plus

Physicians use blood thinners, drugs that prevent the formation of clots, to prevent and treat a variety of life threatening disorders. The primary drug used today is warfarin, a generic drug approved in the mid-1950s. More than 36 million prescriptions are written for the drug each year in the U.S. While effective, warfarin is a difficult drug for physicians to use and for patients to tolerate because it interacts with many common drugs and foods and its effect can vary widely from person to person. A patient's clotting ability must be monitored carefully and frequently. Even small changes from desired parameters, which can happen up to one-third of the time in real-world practice, can result in grave complications, including debilitating strokes or fatal blood clots.

Since the 1950s, academic research and the pharmaceutical industry have greatly advanced our understanding of the clotting process. This research has yielded a number of possible new approaches for safer and more efficacious blood thinners. Several global pharmaceutical companies are conducting late-stage clinical trials of new drugs, and the results of these studies are beginning to emerge. One drug, dabigatran etexilate, has already proven to be superior to warfarin in both efficacy and, more importantly, safety.[1] We anticipate that additional drugs could prove similarly effective over the next two years. At branded drug prices, we estimate the market potential for new blood thinners could be in excess of $10 billion per year.

Alzheimer's Disease

- Key Innovation: Therapies to halt or reverse mental decline
- Estimated market potential: $10 billion plus

Alzheimer's Disease is a degenerative neurological disorder that affects an estimated 5 million people in the U.S. and 26 million worldwide. According to the Alzheimer's Association, the U.S. government paid $112 billion in 2005 in direct medical costs for patients with Alzheimer's Disease and other dementias, while indirect costs to the economy for caregivers are estimated at an additional $36 billion.

Although there are available therapies that help slow the progression of Alzheimer's Disease, they generally provide only a modest benefit to patients, do not stop or reverse cognitive decline, and have no effect on the underlying disease. Still, patients worldwide consume more than $5 billion of prescription pharmaceuticals for this disease.

Recent scientific advances have increased our understanding of the causes of Alzheimer's Disease, and several companies now have therapies in late-stage development that attempt to alter the course of the disease. These potential therapies include traditional oral medicines and monoclonal anitibodies that bind to target specific cells and trigger the patient's own immune system to respond. If successful, the potential impact on the management of patients with Alzheimer's Disease could be enormous. We estimate that the worldwide market opportunity for therapies with an impact on disease progression could easily exceed $10 billion.

[1] New England Journal of Medicine, September 17, 2009.

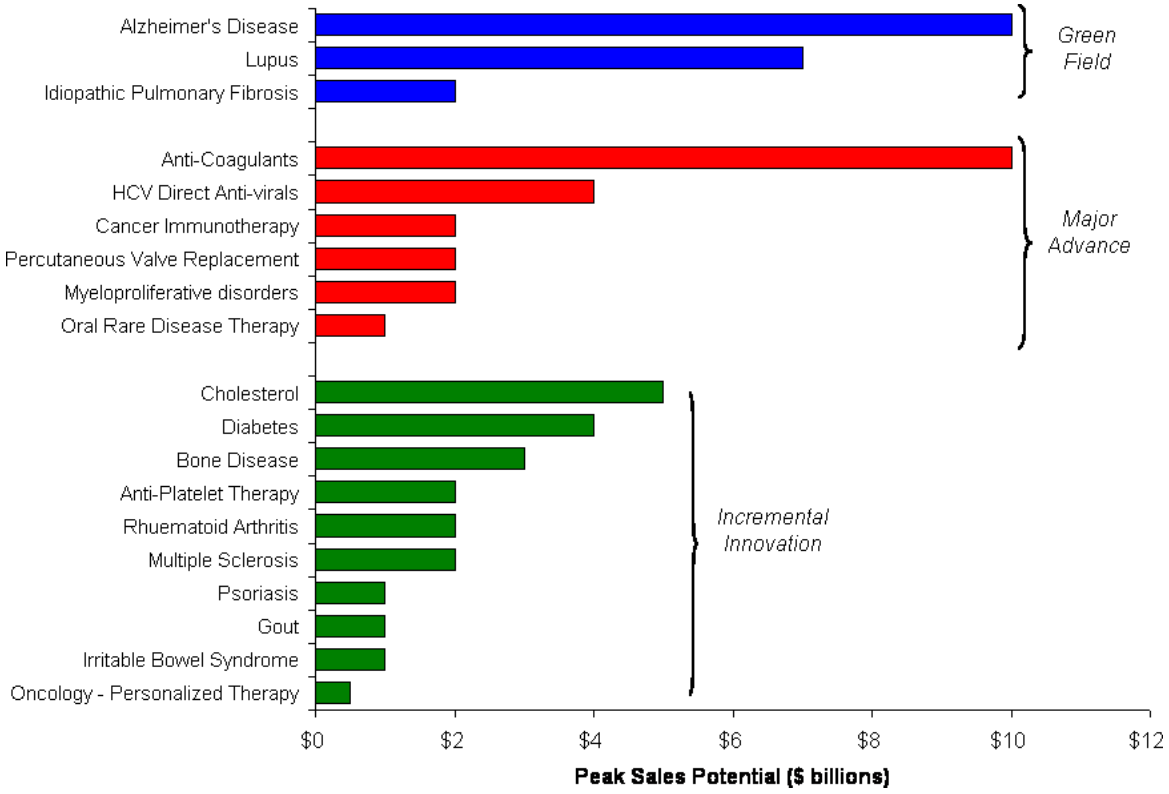
Potential Major Advances in Health Care

	Description
Lupus	No new treatments approved for this potentially fatal condition in 50+ years
Alzheimer's Disease	Potential to stop or reverse cognitive decline while current drugs have only a modest impact on symptoms
Idiopathic Pulmonary Fibrosis	Slow the scarring of tissue in progressive, fatal lung disease
Blood Thinners	Safe, easy to use replacement for widely used drug with a risky profile
Hepatitis C	New drugs designed to eradicate Hepatitis C infections, including patients who have failed current treatments
Cancer Vaccines	Activating patients' immune systems to fight their cancers
Heart Valve/ Replacement	Transition from open heart operations to catheter based approaches, similar to move from bypass surgery to stents
Oral Rare Disease Therapy	Oral drugs to reverse the effects of fatal genetic mutation-based diseases, including Cystic Fibrosis and Muscular Dystrophy
Myeloproliferative Disorders	Targeted therapies to improve the quality of life of patients with rare blood cancers

Key Areas of Incremental Product Innovation

	Description
Clot/Heart Attack Prevention	New drugs will work in patients who do not benefit from current ones and are easier for physicians to use
Inflammation (Arthritis, Psoriasis)	Easier, possibly even oral, dosing regimens and options for those who fail standard therapies
Bone Disease	Twice per year preventative injection to replace poorly tolerated oral therapies for osteoporosis
Gout	New treatments to help patients for whom existing drugs are not effective enough; also targeted drugs to prevent or stop painful flares
Multiple Sclerosis	Several therapies with better efficacy than current standards that are also more convenient for patients
Diabetes	Alternative and complementary medications to lower blood sugar and induce weight loss
Cholesterol	New approaches to raise levels of "good" cholesterol
Personalized Cancer Medicines	Designer drugs targeted to genetic mutations that increase efficacy and reduce toxicity compared to chemotherapy

Market Potential of Health Care Innovations



Source: ClearBridge Advisors, LLC, February 1, 2011.

We estimated the commercial potential for key areas of medical innovation based on a broad range of research, including internal and external analysis, sell-side research, corporate documents and health care industry publications.

In general, we looked at the size of patient populations, the number and value of individual prescriptions written for existing treatments, market share and market penetration, as well as a variety of other factors.

Why Health Care Reform Won't Stifle Innovation

The potential for federal legislation to significantly restructure the U.S. health care system has created investment uncertainty and weighed on the performance of health care stocks in 2009 and 2010. However, we believe the legislation signed by President Obama should not materially impair the drive for medical innovation.

The changes to the health care system are focused primarily on access, creating affordable coverage options for more U.S. citizens, rather than on costs, which would reduce utilization or prices/reimbursement. Insurance market regulation is the primary legislative means for covering the uninsured, little of which would directly impact innovative companies in the product segments of the health care market.

In fact, health care legislation is likely to increase the market for innovative health care products and provide greater incentives for the companies that develop them. The Congressional Budget Office has estimated the health care reform legislation will extend adequate insurance coverage to 30 million additional citizens, which should increase the demand for all medical products and services. The health care reform act also explicitly enhances the intellectual property protections for biologic drugs, a class of therapies that is already generating many innovative products.

Finally, and perhaps of greatest importance, comparative effectiveness initiatives contained within the legislation are designed to curb system-wide costs and should shift resources from out-dated and "me too" drugs and technologies to newer and more effective therapies. Cost pressures from covering millions more individuals will require better approaches to treatment and many of the best innovations reduce overall costs, rather than add new spending burdens to the system.

Implications for Portfolio Construction

ClearBridge Advisors believes the pharmaceutical industry presents a potentially attractive investment opportunity and one that the broader market may be underestimating. Both U.S. and European major pharmaceutical stocks are trading at, or near, historically low valuations that reflect little value for new drugs that are being developed. Our review of promising new therapeutics reveals many companies have meaningful drugs that could emerge from their pipelines over the next one to three years. While not all promising compounds will be proven through clinical trials, we believe a number of the important products will be brought to the market and a positive re-rating of the pharmaceuticals sector is likely.

In the biotechnology sector, we find many of the promising therapies in the development pipelines of the major pharmaceutical manu-

facturers have been licensed from public or private biotechnology companies. In many cases, these innovative enterprises retained significant economic interests in the eventual products that were conceived in their laboratories. Moreover, a handful of biotechnology companies own total world-wide rights to potential blockbuster drugs.

Among medical device companies, we see few compelling investment opportunities. Through the mid-2000s, manufacturers of medical devices—particularly makers of stents, implantable defibrillators and orthopedic joint replacements—rewarded investors with substantial outperformance. These companies introduced many incremental innovations that catalyzed rapid sales and earnings growth. However, these same technologies have matured and are increasingly commoditized, while the developers of these devices have not adequately reinvested in new technologies to continue their growth.

Conclusion

Innovation remains the ultimate driver of growth and earnings in the health care industry. Companies that develop breakthrough therapies, technologies or products can achieve leading market positions that strengthen the underlying business, while also rewarding investors. The incentives for medical innovation remain in place and appear unlikely to be affected significantly by health care legislation enacted into law this year. Demand for products and processes that enable better and more efficient care will ultimately transcend any regulatory or legislative changes in distribution and payment systems.

About the Authors

Marshall Gordon is a Research Analyst for health care at ClearBridge Advisors. He has 10 years of investment industry experience and earned his MBA at the University of Chicago and his Bachelor of Science degree in finance at the Wharton School at the University of Pennsylvania.

Nicholas Wu, **Ph.D.** is a Research Analyst for health care at ClearBridge Advisors. He has 8 years of investment industry experience and previously served as a research scientist at Kosan Biosciences Inc. He earned his Ph.D. in chemistry at Stanford University and his bachelor's degree in chemistry from Washington University.

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Past performance is no guarantee of future results.