V2M® Capital LLC

Medical Breakthrough Products: The Case for Long Term Growth

In 2012, healthcare expenditures were $2.8 trillion in the US and estimated to be nearly $7 trillion worldwide. V2M® Capital believes that, over the next several decades, the fastest growing sector of healthcare will be prescription drugs and medical devices and specifically medical breakthrough products, which address numerous unmet medical needs. There are many macro and industry specific drivers that will contribute to this growth, not the least of which is the number of companies that have been formed to pursue the development of medical breakthrough products. V2M® estimates that there are over 100 public companies that fit this description and many more private companies. The explosion of such products over the next several decades will fuel the growth of many successful companies. As a consequence, V2M® believes that this will be the Century of biology and medicine.

Expanding Middle Class

At a macro level, healthcare expenditures in emerging markets are growing mostly as a consequence of a growing, educated middle class which has the flexibility to move health to a higher priority than uneducated, lower income groups. In China, the middle class has grown from 23 million in 2000 to 150 million in 2010, and is projected to grow 450% to 670 million by 2021. A growing middle class translates into growing expenditures on healthcare overall. China's total healthcare expenditure grew 10.9% in 2009, and consumer spending on healthcare is expected to grow at a CAGR of 11.6% between 2005 and 2025. The prescription drug market in China is expected to grow 650% from $48 billion in 2012 to $315 billion in 2020 according to GlobeData. That compares to their projection for U.S. prescription sales in 2020 of $475 billion. This dynamic is expected to surface in other developing countries over time as well.

Demographics

Demographics is another major macro driver of growth. According to a study conducted by the Deloitte Center for Health Solutions, people 65 years of age and older (Seniors) were 13% of the U.S. population in 2010 but accounted for 37% of total healthcare expenditures and 51% of the $259 billion of prescription drug expenditures. The percentage of the population made up of Seniors is projected to reach 19% by 2030 which means that they will continue trending toward consuming half of all healthcare costs. Of course, this issue affects other countries as well such as Japan and China. In 2011, people 65 years of age and older in Japan constituted over 23% of the population and are projected to be a staggering 40% of the population by 2050. In 2008, about 20% of the population (Seniors) accounted for 55% of the total healthcare expenditures. In China, projections are for 150

million people to be 65 years and older in 2015 and 300 million by 2033 according to the China Daily. The United Nations estimates that the 600 million Seniors today will grow to over 1.1 billion by 2035. Since Seniors as a category consume far more healthcare resources than any other group and tend to have more than a single ailment as they age, growth in healthcare expenditures in general and for medical breakthrough products in particular will be sustained and robust.

Medical Breakthrough Products

A third driver is the growing percentage of revenues generated by medical breakthrough products as a percentage of total prescription revenues. In 2000, the top 50 drugs accounted for 30% of total prescription drug revenues while in 2013, the top 10 prescription drugs accounted for 29% of total prescription drug revenues. Dramatic advances in human biology and the intersection of information technology and biology will accelerate and expand the number of medical breakthrough products. This trend will have enormous implications on the safety and efficacy of therapies, the price of which will be benchmarked against the total savings that such products convey to the healthcare system.

Some may contend that pricing pressure will mitigate the velocity of increasing expenditures on medical breakthrough products. We recognize that pricing will certainly not be as elastic in developing countries as it is in developed nations and that there is bound to be some price pressure even in developed countries. Since there tends to be greater controversy about drug prices than about medical devices, these arguments pertain primarily to drugs. Medical breakthrough products tend to have very high gross margins (often greater than 80%) providing ample cushion for downward pressure on prices and by definition they are better products than the standard of care producing better outcomes and causing fewer complications - often accounting for much of the cost of a disease. Two of the important determinants of price are a) calculating the total cost of care under the existing standard of care and pegging a price that provides the system with some level of a discount on the total cost of care and b) assessing the value of a new drug over existing drugs (improved safety and efficacy) and setting a price that is not more than the result of “a” but potentially much more than the existing drugs. When this formula is followed assiduously, the public outcry tends to be based on false or misleading information propagated by groups with opposite or ancillary self-interests such as prescription benefit managers and politicians. With respect to global pricing and the importance of making therapeutic options available to countries with substantially lower incomes per capita, V2M believes that a sliding pricing mechanism based on the national average per capita income could conceivably provide a solution to the pricing dilemma. Ultimately, embedded bar codes in the drugs will help police black markets which some would attempt to form.

New Products: Rarely Cures, Often Iterative

With respect to the ability to treat disease, one little appreciated fact is that modern medicine has come up with some (smallpox, polio when vaccinated) but not a lot of “true” cures for diseases

(though this is now beginning to change). While there are treatments for many diseases, most either halt or slow the progress of disease, not cure it. For example, statins have materially improved the blood lipid chemistry of individuals with high cholesterol, LDL, and triglycerides and postponed or prevented what would have been inevitable cardiovascular diseases among other ailments. The largest selling drug was Pfizer's Lipitor, which reached over $10 billion in annual revenues before going off patent in 2011. As good as the drug is, it was not right for everyone with blood lipid issues and had some deleterious side effects on others. In addition, it did not cure the disease; statins need to be taken for life to experience the benefits. Furthermore, the benefits were not always a complete resolution of one's blood lipid chemistry. Today, there are several companies working on innovations that represent an improvement on the current statins, the end result of which may be another important but incremental improvement or, one can hope, a complete cure. Diabetes is another example of a chronic disease that is only moderately well treated though there has been considerable progress, particularly Type 1 diabetes which typically strikes in one's youth. Yes, insulin injections help diabetics maintain a more normal blood glucose level but it doesn't cure the disease. In recent studies, Type 1 diabetics' life expectancy and fewer co-morbidities have improved to the point that male diabetics' lives are about 10 years shorter and females' are about 14 years shorter than non-diabetics. If the diabetic does not control blood glucose levels within a very narrow range as they age, they will ultimately suffer from numerous co-morbidities (concomitant health issues or diseases) such as diabetic retinopathy (vision problems), cardiovascular disease, and kidney disease. Diabetes is the leading cause of kidney failure, non-traumatic lower-limb removal, and new cases of blindness among adults in the U.S. A National Diabetes Information Clearinghouse reports that there are 18.8 million diagnosed and 7 million undiagnosed Type 1 and Type 2 diabetics. The total cost to the healthcare system is currently $176 billion according to the CDC. According to the World Health Organization, there were 347 million people worldwide with diabetes in 2010. International Diabetes Federation projects that there will be 592 million people with diabetes by 2035, and the CDC estimates that 79 million people in the U.S. are at risk for developing diabetes. Another example is Alzheimer's disease, which afflicts over 5 million individuals in the US and is projected to affect over 7 million by 2025 and nearly double that by 2050. The total costs are estimated to be $214 billion (and there is no effective treatment at all currently, let alone a cure) and are expected to increase to $1.2 trillion by 2050 according to the Alzheimer's Disease Association. These are but a few examples. On top of this, there are many acute diseases that are inadequately addressed. For example, only 5% of pancreatic cancer patients are alive 5 years after diagnosis. In 2012, WHO estimates that there were 207 million cases of malaria resulting in 627,000 deaths. Sepsis affects more than 750,000 U.S. patients causing 215,000 deaths and costing the healthcare system more than $17 billion per year.

Rare Diseases

In addition to the common diseases which are present somewhere in almost everyone's family, there are rare or orphan diseases, those that afflict a few to 200,000 people in the U.S. (50,000 or fewer in Japan and roughly 250,000 or fewer in the EU) and affecting about 25 to 30 million Americans. Children are particularly hard hit by orphan diseases, 30% of whom will die by the time they are 5 years old. There are estimated to be around 7,000 such diseases of which only about 300 currently have some sort of treatment. Examples of rare diseases include Huntington's disease, Lou Gehrig's disease, Duchenne muscular dystrophy, gastric cancer, Hodgkin lymphoma, sickle cell anemia, to name but a few. Since the first orphan drug was approved in 1983 when Congress passed the Orphan Drug Act, the FDA has approved a total of 451 drugs through 2013. A couple of decades ago, Lysosomal Storage Disorders had no therapies. Genzyme developed Cerezyme for the treatment of just one of approximately 50 forms of Lysosomal Storage Disorders, Gaucher's disease (there are about 10,000 patients worldwide). It was commercialized in 1994 and generated about $800 million in revenues per year at its peak. There are numerous other severe, chronic rare diseases that will witness new therapies in the coming years.

Infectious Disease

Another development that will require the discovery and development of new medical breakthrough therapies and that has erupted over the last few decades has been the movement of infectious diseases from confined geographies to virgin, urban territories. With the advent of travel and increased global physical connectivity, these diseases can easily spread. As long as such diseases remained confined to remote areas in developing nations, they were not a high priority for pharmaceutical and biopharmaceutical companies in the developed world. When introduced to developed nations' urban areas, priorities change. An example is West Nile Virus which historically was found in Africa, parts of Asia and the Middle East. It is spread via infected mosquitos. It first appeared in the U.S. in 1999. There were 149 cases reported between 1999 and 2001. In 2002, the incidence increased to 4,156 in 39 States and Washington DC. From 2003 and 2013 the number of cases has fluctuated between 700 and nearly 10,000 and have now been reported in 48 States and DC. HIV Aids is another example and was first reported in the U.S. in 1981. Through 2011, approximately 1,155,792 have been diagnosed with AIDS. A disease which did not exist in the U.S. before 1981 now costs about $400,000 per patient to treat the existing pool of patients. Other examples of infectious diseases introduced from other countries are SARS, Dengue fever, Chikungunya, and influenza.

Progress in Biology

The many untreated existing or new ailments are the gloomy backdrop for the medical breakthrough products sector. However, the good news is that we are exponentially growing our understanding of human biology and expanding the number of tools we have at our disposal to dissect the myriad of

pathways that work together to create a healthy, functioning human being. In the last forty years, recombinant DNA (the ability to harness genes in the lab to produce therapeutic proteins), monoclonal antibodies as drugs (over a $40 billion industry since their introduction in the late 1990's), the human genome, the human proteome, the human metabolon, and the Microbiome, the last three being at a very early stage of understanding. How gene therapy can be harnessed to maybe actually cure disease is making great strides after almost 3 decades of clinical failures, and regenerative medicine in some cases using stem cells is attracting many company participants. This explosion in understanding fundamental biological processes ultimately leads to the creation of innovative, disruptive approaches to the treatment and in some cases the cure of disease.

Impact of Information Technology

In addition to knowing more, interdisciplinary tools are now being brought to bear on the puzzle. In part, the technology industry has made a material contribution through computational power, software, nanotechnology, physics and microfluidics. To piece together how the many biochemical pathways in our body function together, computational power is essential if this is to be done in decades rather than centuries. Without computation, the proteome, metabolon and microbiome is virtually impenetrable. It is essential, for example, if we are to piece together a roadmap to a cure for the many forms of cancer. The impact of computational power on the development of therapeutic, diagnostic, imaging and monitoring products is only at an embryonic stage today. Over the course of the next few decades, the progress will become exponential.

Regulatory Improvements

Finally, and not surprisingly, a more nuanced approach by the regulators with respect to the approval of products for use in humans is in process. From tailoring clinical trial design to diseases based on whether the disease is acute or chronic or on the availability of therapeutic options (instead of an historical one size generally fits all approach) to the provision of compassionate use of unapproved products for people who will inevitably die without a shot at some kind of intervention, the regulators are beginning to take a more common sense approach to the regulatory process. The FDA now has the following designations: medical breakthrough, expedited review, special protocol assessment, fast track, compassionate use (and a broader application of this designation) and orphan drug, all of which can expedite the regulatory process. Once again, this evolution is at an early stage but at least is promising.

Conclusion

All of these developments convince us that innovation in the development of medical breakthrough products representing material improvements on previous products, filling stark voids in therapeutic options, and providing actual cures for more diseases than ever before in history of medicine, will result in dramatic disruptions to the practice of medicine and to the medical products industry. The

breadth of the opportunity is staggering and will likely fuel the growth of the medical products industry for decades to come, creating new powerful commercial entities and marginalizing some legacy entities. No doubt, the challenge from an investment perspective is identifying the disruptors who will succeed.

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