**Clinical Trials, the Necessary Pain**

In 2019, the FDA approved the second gene therapy ever for treating a rare genetic disease called spinal muscular atrophy (SMA)1. SMA is a serious genetic disorder that causes major weakness in skeletal muscles in babies, which could impact them in different severity levels. Because SMA weakens the respiratory and other muscles close to body’s center, many children with SMA end up having respiratory, lung and heart problems. With the most severe form of the disease, children do not survive past their early childhood2.

As SMA is caused by genetic disorder, it needs gene therapy to treat the condition. The experimental drug treatment from Novartis, marketed as Zolgensma, injects genetically modified viruses into children’s body and these viruses contain healthy copies of the mutated genes. This one-time treatment was known to improve the condition of the patients and it was priced at $2.1 million, which insurers could pay over a period of five years, making it the most expensive drug ever.

The fact that we have a drug that is priced at $2.1 million makes anyone wonder why pharma companies keep the prices so high. The most common response from the drug companies is that they incur enormous research and development costs. According to research published in the journal of health economics that looked at research and development (R&D) costs of 106 new drugs from ten biopharmaceutical companies, as of 2013, new drugs cost the pharma companies on average $2.5 billion before they are approved. This cost includes opportunity cost of losing return on money invested over a long timeline of the R&D process. This cost goes up to $2.8 billion when the post-approval R&D costs are also included.

However, pharma companies are not always the leading spenders of R&D costs across different industries. The semiconductor industry often trumps pharma companies in R&D spending, as a percentage of companies’ revenues. According to an Investopedia article, AstraZeneca spends 25.6 percent, Eli Lilly spends 22.4 percent, Roche spends 21 percent, Biogen spends 19.7 percent and Pfizer and GSK spend around 15 percent of their revenues, all below Broadcom’s spend of around 25 to 28% on R&D3. So, there must be other reasons for pharma companies setting the drug prices so highly.

In this chapter, we will look at drug R&D and clinical trial processes and why the long clinical trial process timeline contributes to higher prices.

***Long timeline of drug discovery, development and approval process***

The process of developing a new drug is a marathon race, not a sprint. New drug research and development processes takes several years, often up to 10 to 15 years to get to the market. Exhibit 8.1 shows the timeline of a typical new drug discovery, research, development, approval and post-approval process.

After a candidate molecule is identified through basic research, the discovery process of a drug begins. According to a brochure from the Pharmaceutical Research and Manufacturers of America (PhRMA)4, after a handful of years in the discovery period, the candidate drug enters pre-clinical stage where the pharma companies test the drug for its efficacy and safety. During pre-clinical stage, the testing is performed inside labs and on animals. Once safety and efficacy targets are met, the drug enters clinical trials. These trials happen in three phases with each first phase involving tens of volunteers, second stage involving hundreds of volunteers, and third stage involving thousands of volunteers.

Each of the pre-clinical and phase 1, 2 and 3 phases take an average of 2 years, and the time period depends on how fast patients are signed up for the clinical trial process. If the clinical trials produce expected results, the pharma companies apply for a new drug approval with the U.S. Food and Drug Administration (FDA). Finally, after a review period that usually lasts for a year or two, if the FDA is satisfied with the clinical trial process and results, the drug would be approved. Biopharma companies then launch the drug into the market and continue to monitor the efficacy and safety of the drug post approval in the final phase called phase IV.

One of the most staggering statistics that is used by the drug industry and research scholars is that out of every 10,000 molecules that enter the discovery phase of the drug R&D, only one or two candidate molecules make it all the way as new drugs to the market.

***Types of drug companies and how R&D timeline differs for those companies***

Let’s quickly talk about two different types of pharma companies: the pharmaceutical companies and biotechnology companies. I briefly introduced these in the previous chapter.

The pharmaceutical companies research and develop drugs that are made of synthetic chemical compounds and molecules, also referred to as small molecules in the industry. Several big pharma companies like Pfizer, Johnson & Johnson, Merck, Novartis and Bayer have been manufacturing these small molecule drugs for years and years, if not decades.

The biotechnology companies, on the other hand, manufacture drugs that are derived from living organisms, also called big molecules or biologics. Biologics contain proteins, DNA vaccinations and monoclonal antibodies that help treat, diagnose and prevent diseases4. Although we have been using vaccines to inoculate children for more than 200 years, biotechnology companies have been making modern-day biologic medicines for only about four decades or so. In late 1970s, Genentech revolutionized the human drug development industry through the discovery of genetically engineered insulin. By late 1980s, only five biologic proteins were approved by the FDA: insulin, human growth hormone, hepatitis B vaccine, alpha-interferon and TPa. Soon after, the industry took off and now there are more than 350 biologics in the market5.

The biggest difference in terms of development and approval process between small and big molecules is that the FDA introduced a new and separate drug approval process for biologics. As biologics are much more targeted than small molecules, they tend to have higher rates of success from discovery to becoming a new drug, take quicker time and lower amount of side effects on patients than small molecules. According to an article, biologics have twice the amount of success rate compared to small molecules6. Once the patent life is over, small molecules can be applied for an additional five years of market exclusivity while biologics can be applied for an additional twelve years of market exclusivity.

After the patent cycle is completed, the small molecules are manufactured and sold as generics while biologics are manufactured and sold as biosimilars7. However, biosimilars are not as easy as generics to be manufactured because they need to be extracted from living organisms. As biosimilars could differ from the original biologics in their cellular structure, biosimilars aren’t used by physicians as true replacement options of the original biologics. In other words, biosimilar manufacturers don’t succeed as much as traditional generic companies do and so, the original biologic making biotechnology companies are less prone to losing their market share after patents are over.

In a nutshell, pharmaceutical and biotechnology companies deal with a decade plus timeline to bring new drugs and biologics to the market and in that process, they have a very low probability to be successful at a molecule level, thus leading to setting up super high prices for successful drugs. Also, biologics are harder to manufacture, but have high target specificity, less side effects for patients, take less time to develop, are protected from longer patent lifecycle and have a high success rate compared to small molecules. Because of that very reason, and after seeing how Genentech revolutionized diabetes treatment, big pharmaceutical companies started acquiring biotechnology companies. We will talk about how these mergers and acquisitions impacted drug pricing in a subsequent chapter.