Is Gene Therapy a Sustainable Business Model?

In 2012, the first gene therapy, Glybera, was approved in Europe, with per treatment cost of around US$ 1 million. It has been used only once in clinical settings, and the manufacturer, Uniqure N.V., decided to withdraw it from market in April 2017. Strimvelis—manufactured by GlaxoSmithKline Plc. (GSK) for the treatment of adenosine deaminase severe combined immunodeficiency (ADA-SCID)—has been used only twice till now post its approval in May 2016; and GSK signed a strategic agreement to transfer its rare disease gene therapies' portfolio to Orchard Therapeutics in April 2018. Therefore, such incidences quite accurately summed up the journey of gene therapy so far, and may have been in mind of the analyst at Goldman Sachs's when he asked the question **"Is curing patients a sustainable business model?"**, in a recent report, which was accessed by CNBC.

In a business, sustainability is usually measured in terms of cash flow. However, it can also be viewed from the product/service perspective i.e. how well the offering can sustain competition, the availability of substitutes, and new technologies that are being developed frequently. In this article, we would try to look at the overall sustainability of gene therapy business.

Flow of Thoughts:

- Gene therapy for rare disease
- Gene therapy for cancer
- Pipeline products
- Challenges
- Reimbursement
- Competition
- Conclusion

Gene Therapy for Rare Diseases

Gene therapies approved for rare diseases did not generate significant profits for its developers

In 1980, the first attempt to modify human DNA was performed, however, first successful gene transfer in human was performed in 1989. The technology, gene therapy, has evolved over the years, like any other technology.

Initially, Gendicine was the first gene therapy product approved in China in 2003, which were never marketed or launched in the U.S. and Europe pharmaceutical markets. Thereafter, companies working on gene therapy were more focused on rare conditions, which had no approved therapies. One among such condition was lipoprotein lipase deficiency (LPLD). In 2012, first gene therapy was approved in Europe, Glybera, for the treatment of lipoprotein lipase deficiency (LPLD), an ultra-rare genetic disorder, which affects not more than one - two humans in every million. According to an interview of Jörn Aldag, CEO of UniQure N.V. then, there were only around 500 LPLD patients in Europe. If the company wants to reach the break-even, it has to price the therapy/ drug at a higher value, since the prevalence of the diseases is relatively low. This is expected to further reduce the actual customer base.

GlaxoSmithKline's Strimvelis, which received approval in Europe in 2016, also falls under this category. Strimvelis is approved for the treatment of a very rare disease, adenosine deaminase severe combined immunodeficiency (ADA-SCID). According to GSK's own estimates, only 15 children are born in Europe with this disease per year. The developer is unable to garner the invested capital in R&D unless the price of this therapy is very high and this is due to very low incidence of the disease. The product is priced close to US$ 700,000 and it has been administered only twice until now.

Business Attractiveness: Low patient pool, high product price, low competition

Gene Therapy for Cancer

Focus of manufacturers shifted to cancer, wherein they can explore the possibilities to target various cancer types

U.S., supposedly the most advanced healthcare market, entered the gene therapy segment quite later than China and Europe. In August 2017, the U.S. FDA approved first gene therapy, Kymriah (tisagenlecleucel) for the treatment of patients aged 25 years or below with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. According to the National Cancer Institute, about 3,100 people aged 20 years or below are diagnosed with ALL each year. Considering this therapeutic indication, only 20% of the U.S. patients are eligible for this treatment, which makes actual population base around 600.

Novartis received the approval for second indication, which is for adult patients with relapsed or refractory (r/r) large B-cell lymphoma in May 2018. Large B-cell lymphoma has higher prevalence compared to earlier indication. Diffuse large B-cell lymphoma (DLBCL) affects about one-fourth to one-third of Non-Hodgkin Lymphoma (NHL) patients in the U.S., and in Europe it affects as high as 50% of NHL patients. According to National Cancer Institute, it is estimated that there would be 74,680 new cases of NHL in 2018. Moreover, Kymriah is in clinical trials for chronic lymphocytic leukemia and relapsed/refractory follicular lymphoma.

Axicabtagene ciloleucel (YESCARTA) was the second gene therapy product to be approved in the U.S. in October 2017. Yescerta was approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL). Furthermore, the drug/therapy is in clinical trial for multiple indications including indolent NHL.

YESCARTA™
(axicabtagene ciloleucel) Suspension for IV infusion

Currently, Kymriah is priced at US$ 475,000 and Yescerta is priced at US$ 373,000, which is much lower than the first generation products that were priced at nearly US$ 1,000,000 for Glybera and US$ 700,000 for Strimvelis. It is quite possible that prices for both, Kymriah and Yescerta might further reduce with increasing approvals of novel products.

Business Attractiveness: Moderate to high patient pool, moderate product price, and fierce competition

Pipeline Products

Gene therapy product pipeline is still dominated by products indicated for rare diseases

Currently, **over two-third of the products in pipeline are for rare diseases** and around one-third of the products for non-rare indication. Among products for rare disease category, there is a significant percentage of products which has considerable patient population. For instance, Spark Therapeutics has SPK-8011 in its pipeline indicated for Hemophilia A. According to Centers for Disease Control and Prevention (CDC), Hemophilia A affects 1 in 5,000 male births and around 400 babies are born with hemophilia A every year in the U.S. Moreover, about 20,000 people are estimated to be suffering from this disease in the U.S. currently, according to Center for Disease Control and Prevention (CDC). Globally, an estimated 400,000 people are suffering from the disease, according to National Hemophilia Foundation.

In 2016, while speaking at J.P. Morgan 34th Annual Healthcare Conference, Spark Therapeutics Co-founder and CEO, Jeffrey D. Marrazzo, outlined its plan to have 10 clinical-stage gene therapy products by 2018. At present, Spark Therapeutics has eight products in pipeline while one (Voretigene neparvovec) was already approved by the U.S. FDA in 2017

Players in the market could focus on pipeline expansion by inorganic growth model (i.e. mergers and acquisition) and it may also prove to be an effective business strategy. In April 2018, GSK transferred its rare disease gene therapy portfolio to Orchard Therapeutics, a clinical stage rare disease-focused gene therapy company. This agreement includes approved product (i.e. Strimvelis), late-stage clinical programmes for rare diseases such as metachromatic leukodystrophy (MLD) and Wiskott Aldrich syndrome (WAS) and also, early stage clinical and preclinical programmes.

For GSK, this was a step ahead in its plan of prioritizing and strengthening core business area which includes respiratory, HIV, oncology, and immuno-inflammation, as highlighted by the newly appointed CEO in July 2017. On the other hand, this acquisition would help Orchard in strengthening and expanding its current gene therapy portfolio.

As per the current situation, rare disease portfolio is concentrated with companies specializing in rare diseases. On the other hand, multinational pharmaceutical companies (like GSK), venturing new in rare disease segment, may partner with companies specializing in rare disease therapeutics to get a flavor of the market before investing huge sum of money.

Challenges

- **Manufacturing/Developmental Challenges**

  There is no established protocol for manufacturing of gene therapies for medicinal use as it is still in its early phase. A number of manufacturing sites have been established in past two years by companies such as Lonza, Novartis, and Cell and Gene Therapy Catapult. Manufacturers have lined up more such sites to be established in the next five years. The unanticipated increase in interest for cell and gene therapy in the medical community has led to drastic rise in number of cell and gene therapy manufacturing units, globally.

  However, developing a gene therapy for those diseases which has multiple mutation in a single gene, or a disease which is caused due to mutation in multiple genes will be a daunting task. Moreover, mutated gene may cause symptoms in more than one cell type. For instance, Cystic fibrosis affects lung cells and the digestive tract, so the gene therapy agent may need to replace the defective gene or compensate for its consequences in more than one tissue for maximum benefit. Thus, designing a multimodality treatment unique to each individual's physiology is a challenge to the researchers.

- **Regulatory Challenges**

  Apart from the scientific challenges, gene therapy also has to comply to various regulations such as proving efficacy and safety in considerable patient population. For instance, if a disease is only affecting about 500 patients in entire Europe then getting considerable patient population in clinical trials is a cumbersome process

- **Challenges in Treatment Delivery**

  Gene therapy products must integrate into the native DNA without affecting activity of any other essential gene in order to establish itself as an effective treatment option. Therefore, precise targeting is very critical. In case it integrates at wrong location, outcome can be life threatening. For instance, in two gene therapy trials, conducted between 1996 and 2006, for the treatment of children with X-linked Severe Combined Immune Deficiency (SCID), the newly integrated gene had affected the functioning of a gene which regulates the cell division process/rate. This resulted in leukemia in five subjects who participated in the trial. Fortunately, four of them were treated successfully, however, one subject died.

- **Shelf-life**

  Gene therapy products have much shorter shelf lives, therefore, requiring development of novel ways for transportation of frozen and thawed products. They can last for as little as three hours compared to a tablet that will not go out of date for years. This increases the challenge in terms of logistics and requires novel methods for cryopreservation and this could lead to high cost.

With increasing knowledge, time, and effective planning, the aforementioned challenges related to gene therapy can be addressed successfully. For instance, a gene therapy for more prevalent disease such as cancer, may not face challenges in getting considerable patient population in clinical trials; and increasing research on the therapy would help in finding ways for precise targeting.

Reimbursement

With the announcement of FDA approval for Kymriah (tisagenlecleucel) in August 2017, Joseph Jimenez, then CEO of Novartis AG, also announced that the company is collaborating with Centers for Medicare & Medicaid Services (CMS), a U.S. federal agency that manages Medicare and Medicaid, to make an outcome-based payment. As per the agreement, payment will be provided for only those patients who respond to the treatment by the end of first month. On April 1, 2018, CMS announced that it would pay US$ 395,380 for Yescarta and US$ 500,389 for Kymriah to health providers using these therapies on an outpatient basis.

Furthermore, Strimvelis manufactured by GSK was recommended by National Institute for Health and Care Excellence (NICE) in October 2017. The agency, NICE, said that the National Health Services (NHS) should fund this therapy.

Recognition of gene therapies by reimbursement agencies would support expansion and sustainability of the business on a long term. Also, it will encourage other market players to invest in development of gene therapies, which are more effective compared to conventional drugs.

Competition

In ultra-rare diseases such as lipoprotein lipase deficiency (LPLD) or adenosine deaminase severe combined immunodeficiency (ADA-SCID), there is no existing direct competition. However, gene therapies for cancer face intense competition from existing therapies available at a lower cost. For instance, Kymriah (Tisagenlecleucel) has to compete with blinatumomab (Blincyto, Amgen), inotuzumab ozogamicin (Besponsa, Pfizer), and several others.

Alternative products such as Blincyto (manufactured by Amgen Inc.) and Besponsa (manufactured by Pfizer Inc.) are available at significantly lower price. In the U.S., Amgen launched Blincyto at US$ 178,000 in 2014 and Pfizer's Besponsa annual therapy was valued at US$ 168,300 in 2017. On the other hand, Kymriah was launched with yearly price of US$ 475,000 in the U.S. in 2017. This means that both the competitive drugs are available at almost 40% of the cost of Kymriah.

Moreover, entering a market such as the U.K. wherein, cost-effectiveness is mandatory to prove before entering in the market, may be tough for these products. However, it is possible that these products may be able to impress regulatory guidelines at current price range or with some discounts. For instance, a study by The University of York calculated the price and gains for Kymriah in both scenario - (1) as a bridge to stem cell transplantation, and (2) with curative intent.

For first case, examined price and gains were close to US$ 450,000 and 7.5 Quality-adjusted life year (QALY) respectively; in second case, price was over US$ 600,000 and gains was 10 QALY. Therefore, in both scenarios, the current price of US$ 475,000 seems good to pass the regulatory scrutiny.

Conclusion

Manufacturers of gene therapy have changed their business focus by learning some early lessons

Glybera could potentially generate a revenue of US$ 500 million (500 patients x US$ 1 Mn cost of therapy) in Europe alone. However, it would require additional investment to reach out to all the patients, consequently adding to the cost of product. Furthermore, accessibility and affordability for such therapies in emerging economies in Asia Pacific, Latin America, Africa, and Middle East is very low. Thus, assessing the business opportunity and market attractiveness before the launch is the key to save millions for the company.

Kymriah and Yescarta were launched in second half of 2017 and are yet to complete one year in the market. In this short period of time, Yescarta, with relatively big customer base has performed well financially, whereas Kymriah, with relatively small customer base has seen slow start. According to a Gilead Sciences Inc.'s quarterly report, Yescarta earned US$ 7 million in fourth quarter of 2017 and US$ 40 million in first quarter of 2018 i.e. 471.4% quarter-on-quarter increase. Kymriah generated US$ 12 million in first quarter of 2018. Considering the early trends, it would not be surprising if both of these products generate close to US$ 100 million or even more in 2018. Moreover, with increasing confidence on gene therapy among prescribers and rising incidence of respective cancer types, the products may generate expected revenues over the patent period.

Therefore, to conclude, gene therapy can be a sustainable business with the compliance to following parameters:

- **Better cost-benefit ratio**
- **Higher patient pool**
- **Affordability to patients**
- **Availability of adequate reimbursement**

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