Use of Gene Therapy in the Treatment of Rare Diseases

By

Shreya Garg

Dissertation submitted in partial fulfillment of the requirements of the degree

MBA Hospital and Health Management

Academic year, 2018-2020

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June 15, 2020

EXPERIENCE CERTIFICATE

This is to certify that Shreya Garg (Employee ID – 23484) was interning in our organization from February 3, 2020 to May 29, 2020. At the time of leaving she was working in the capacity of Knowledge Management Associate – Intern based at the New Delhi office.

We wish you all the success in future endeavors.

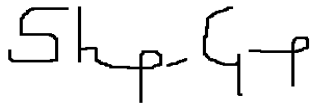
For ZS Associates India Pvt Ltd

Mohit Sood
Office Managing Principal

THE IIHMR UNIVERSITY, JAIPUR

CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled **'Use of gene therapy in the treatment of rare diseases'** and submitted by **Shreya Garg** Enrollment No. **0829** under the supervision of **Dr. Piyusha Majumdar** for award of MBA in Hospital and Health/ Pharmaceutical / Rural Management in Health and Hospitals of the University carried out during the period from **February 3 to June 1, 2020** embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other institute or other similar institution of higher learning.



Shreya Garg

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ORGANIZATIONAL PROFILE

ZS is a professional services firm that works side by side with companies to help develop and deliver products that drive customer value and company results. They leverage deep industry expertise, leading-edge analytics, technology and strategy to create solutions that work in the real world. ZS has more than 35 years of experience and more than 7,000 ZSers in 25+ offices worldwide.

Founders: Prabhakant Sinha and Andris Zoltners

Industry: Consulting, AI, Analytics

Headquarters location: Evanston, Illinois

Chief Executive Officer: Chris Wright

Founded: 1983

ZS' consulting services have helped hundreds of companies worldwide solve their most critical challenges by bringing science to bear on clients' most difficult business problems, helping them make data-driven decisions and achieve insights-fueled success.

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CONTENTS

PROJECT REPORT

INTRODUCTION :

Rare Disease

In USA, a rare disorder is defined as a disorder that affects **less than 200,000 people in the US**. This description of rare disease was given in the Orphan Drug Act (1983). **Rare diseases came to be recognized as orphan disorders as pharmaceutical companies did not adopt them to develop treatments due to low burden of disease of these diseases and their unknown cause**.

The characterization or description of a rare disorder differs in every country. In the **Europe (EU)** a disorder is deemed rare when it affects **less than 1 in 2,000 people**.

There are approximately **7,000 rare diseases in the world**. **While the number of individuals affected by a particular rare disorder are less, the total number of individuals affected by a rare disease is large**.

Most rare diseases are difficult to trace, which makes it hard to determine the exact number of rare disorders or the number of people who are affected by them.

Causes of Rare Disease

Rare diseases have varied and multiple causes. **Maximum number of rare diseases are known to be genetic which means they are usually caused by alterations in genes or chromosomes**. Genetic diseases are caused by two ways. In the first type, genetic changes, which lead to the development of a disease, are inherited. This means that these genetic changes are passed down subsequent generations. In the second type, genetic diseases occur randomly in a person who is the first patient in a family to be diagnosed with a genetic disorder.

Many rare diseases are not inherited. These include infections, some rare cancers, and some autoimmune diseases. This means they are not passed down from one generation to the next. **The exact cause or the etiology of many rare diseases is still unknown**. Examples of rare diseases include : **Acute Hepatic Porphyria, Idiopathic Pulmonary Fibrosis, Scleroderma** etc.

Orphan Drug Act

Orphan Drug Act (also known as ODA) was passed on January 4, 1983. Since the enactment of ODA, there has been a significant shift in orphan drug development.

ODA was passed to give an impetus to the pharmaceutical companies and lead to an increase in the manufacturing of drugs for treatment of orphan diseases. In 1984, the Orphan Drug Act was modified. The new amendment defined rare diseases as the diseases which affect less than 200,000 people in the United States. This classification of orphan disease also included the drugs for diseases affecting more than 200,000 people only on the adherence of one condition that there should be no profitable motive. This implies that cost of manufacturing and marketing the drug in the United States should be more than the revenue from the sales in US.

Incentives provided by ODA

A major incentive provided by ODA is that the pharmaceutical companies receive marketing exclusivity of 7 years. ODA also made available various grants which will be granted to academic based researchers or pharmaceutical companies annually and a tax credit of 50% will be incurred for expenditures when orphan drugs are assessed for their curative potential or their ability to cure a disease.

Since the passing of ODA, there has been a tremendous increase in marketing approvals of orphan drugs.

Gene Therapy

Gene therapy is a technique which **uses genes either to prevent a disease or to treat it**. Several approaches to the use of gene therapy are being established by scientists, including:

- **Replacing an altered or mutated gene** that leads to the development of a disease
- **Inactivating an altered gene,** which is a defective gene
- **Introducing a corrected or functional gene** into the human body to cure the disease

Gene therapy is used to introduce a corrected gene into the cells to either produce a beneficial protein or to replace defective genes.

Mechanism of gene therapy

A vector is a **carrier whose gene is modified or altered to transport the corrected gene to the target cells**. Some viruses are often used as vectors. These vectors lead to transference of the non-defective gene, as they inject their genetic material into the cell. The viruses are disarmed to not infect human beings. Some viruses, for instance retroviruses, incorporate their genes (including the corrected or non-defective gene) into the DNA of the human cell. Some other types of viruses, for instance adenoviruses, introduce their genes into the nucleus of the cell without integrating their genes into the cell's chromosome.

The viral vector is either provided intravenously or it is injected into a particular tissue (target tissue) in the affected individual's body. This viral vector is then used by the cells of the patient. Another method of gene therapy involves, removal of a portion of the patient's target cells and infecting those target cells with the viral vector in the research laboratory. The transduced (containing the vector) cells are then transferred back into the body of the patient. Hence, the corrected gene which is transported by the viral vector will produce a functional protein in the affected individual's body when the treatment proves to be effective.

Categories of gene therapy

All the cells of the human body possess genes, which means all the cells are capable of being subjected to gene modification. However, human beings' cells are split into two main types : **somatic cells (includes all the cells of the human body excluding gametes) or germline cells (includes gametes such as eggs or sperm)**. As a hypothesis or an assumption, it is possible to introduce a new gene in either germ cells or somatic cells. But it is quite difficult to do so in reality.

Gene therapy involving **germ line cells** leads to **permanent changes in the human body which are passed down to subsequent generations**. **Germ line gene therapy has the potential to offer an everlasting curative effect for all the patients who inherit the defective DNA**. The success of germ line therapies can lead to the possibility of eradicating some rare disorders from specific families (families in which genetic disorders run in the family), and ultimately removing them from the population.

Somatic cell gene therapy is perceived as a more traditional, safer and appropriate method since it affects only the defective cells in the patient and the new genes are not passed on to subsequent generations. This means that the curative effect of the gene therapy will end with the patient who receives the corrected gene. However, the somatic cell gene therapy presents disadvantages of its own. Generally, the curative effects of somatic cell therapy do not remain for long. It is a well known fact that cells die and that they are substituted by new cells. Hence, repeated or multiple treatments with gene therapy throughout an individual's lifetime are required to sustain the curative effect of the gene therapy. Transporting the gene to the target cells or tissue also poses its own issues. However, despite these challenges of this gene therapy, **somatic cell gene therapy is suitable, apt and recommended for many disorders, such as muscular dystrophy, cystic fibrosis, cancer and certain infectious diseases**.

Till date, **all the gene therapy developments in human beings have been focused at somatic cells, while germline modification in human beings is prohibited and remains controversial** (such as in the European Union).

The somatic gene therapy is categorized into two main types:

Ex vivo implies exterior i.e. in this category of gene therapy, the cells are altered outside the patient's body and are transferred back to the patient's body again.

In vivo implies interior i.e., in this category of gene therapy, the genes are changed in cells when the cells are still inside the patient's body. Since the new gene is transported to cells within the affected individual's body, this type of gene therapy is known as in vivo.

AIM : To study the use of gene therapy in treatment of rare diseases

OBJECTIVES :

1.To review the strengths and weaknesses of gene therapy in treatment of rare diseases

2.To determine present approved gene therapy treatments for treatment of rare diseases

3.To determine the scope of gene therapy in the treatment of rare diseases

LITERATURE REVIEW : An article by M Ian Phillips and Andrew B Burns (Taylor & Francis Online; 2014) stated, "Gene therapy has shown significant potential in the treatment of rare diseases. Most gene therapy trials today are focused on gene replacement, gene correction or knockdown of gene products for monogenetic or single gene diseases via viral vectors that cure or slow down progression of disease. The definition of gene therapy can be broadened to include non-viral vectors, such as antisense oligonucleotides and small interfering RNA. Gene modification of stem cells is a type of gene therapy which works by providing cells with corrected genes."

An article by Marina O'Reilly et al. (National Center for Biotechnology Information; 2013) stated, "Gene therapy for rare diseases demonstrates tremendous potential as is evident from the success of clinical trials in several diseases till date. To use gene therapy for other disorders will depend on various factors. Diseases such as hemophilia in which the severe clinical manifestations can be improved by administering low levels of protein, are feasible options for gene therapy. Some diseases which require long-term gene correction such as diseases with hematologic stem cells as target cells can be manipulated outside the body and can lead to the development of gene therapy for such diseases."

An article by Petra Kaufmann et al. (Orphanet Journal of Rare Diseases; 2018) states "There is a need for efficient and effective models for development of gene therapy which should be scalable and sustainable so that all the patients affected by rare diseases can be treated. Such models must quicken and augment timelines and processes, promote new and robust platform approaches, stimulate extraordinary innovation in the development of treatment, ensure timely regulatory approvals and must possess a feasible trial design. All these factors must be taken into consideration along with fostering greater collaboration among the different stakeholders who are required to successfully manufacture and develop new treatments for rare diseases."

METHODOLOGY :

Material and methods : Articles and journals on the internet (13 articles and journals)

Study design : Descriptive cross-sectional study

Duration of study : April to May 2020

Data collection procedure : Secondary research based on available literature on the internet

RESULTS:

Gene therapy for rare diseases

- Patients affected by rare disorders have limited number of treatment options. In total there are about 7,000 known rare disorders. Out of which, less than 5% have an approved therapy by FDA
- Approximately 85% of the known rare diseases are caused due to an alteration or mutation in the gene. This makes them ideal disorders for treatment using gene therapy
- In order to approve gene therapies, an all-inclusive and robust understanding of designs of clinical trials and their execution, along with awareness of the regulatory scenario with regard to rare disorders is necessary
- Adeno-associated virus (AAV) is the most often used viral vector for administering gene therapies
- Most advancements in research of gene therapy are taking place with regard to hemophilia and ocular diseases
- Within a span of 3 years (2016-2019), the number of clinical trials concerned with gene therapy for ocular diseases rose more than 200 percent
- The advancement of gene therapy as a cure for biallelic RPE65 mutation which is associated with retinal dystrophy is deemed as the most successful stories in rare ocular diseases

Years of research, designing clinical trials and their execution, conducting extensive follow up appointments and simultaneously collaborating with the concerned governing and monitoring authorities in order to deliver these new gene therapy drugs to the market, are all the factors which are essential in making a particular gene therapy a successful treatment option. Clinical trials play a vital role in the drug development process. They require plenty of time and funds to complete, but they are a crucial part of the manufacturing and approval process of a drug.

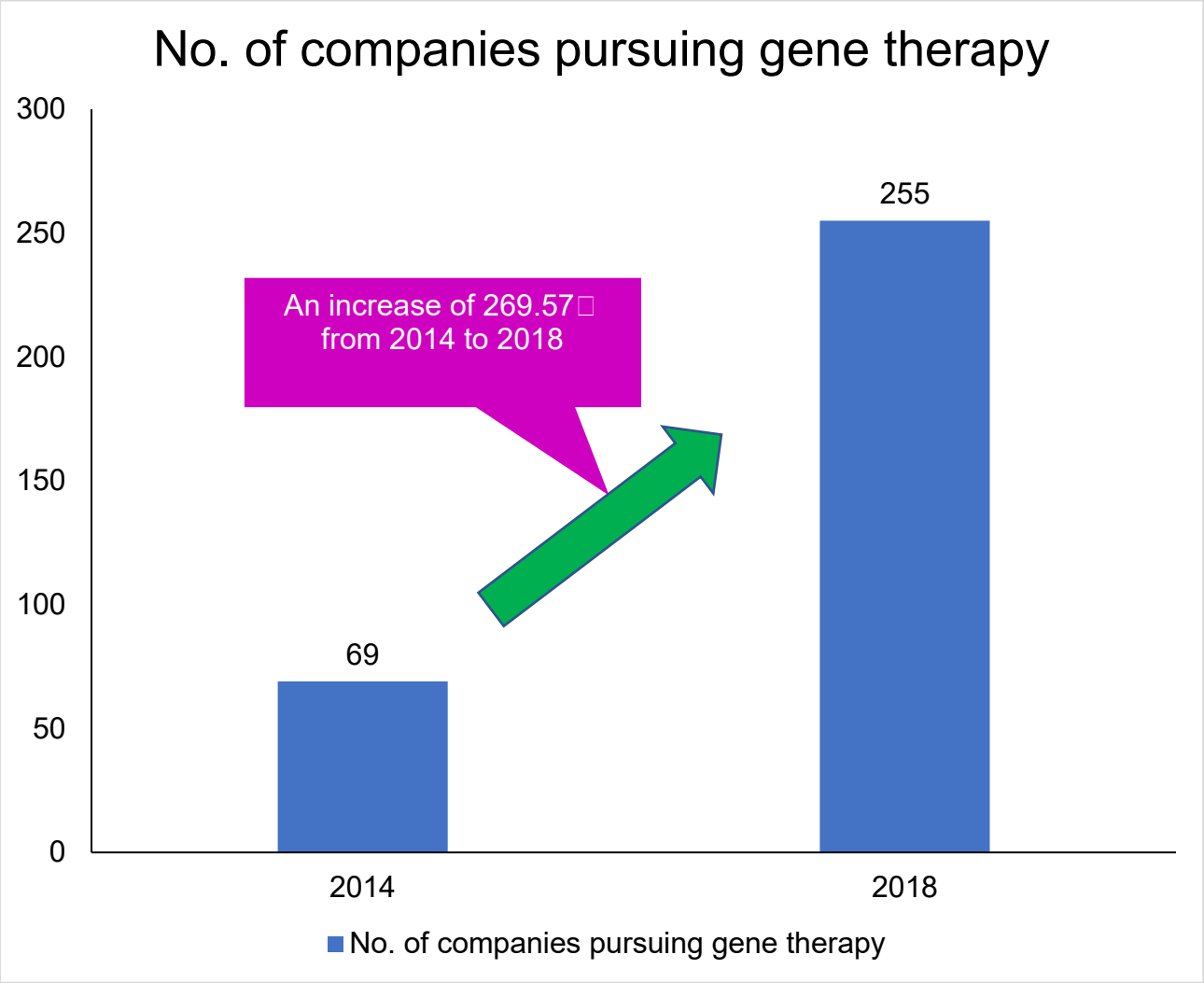
Rare disease trials present a unique set of the following challenges:

1. **There is limited knowledge of disease etiology of rare diseases**
2. **There are few or non-validated biomarkers or clinical endpoints**
3. **There are significantly fewer patients with a high degree of geographical dispersion**
4. **There are a less number of experienced or well-versed clinical investigators**

Evaluation of a gene therapy is a difficult and often time consuming task, as trial sponsors have to make do with a lengthy feasibility process of the clinical trial and must ensure that potential clinical trial locations have the necessary resources, human capacity and the required expertise to run a trial for gene therapy.

True to their name, rare diseases are indeed very 'rare'. Researchers must take into consideration the natural history of a disease for an improved understanding of the prognosis of a disease. Researchers can use this strategy and can determine the endpoints expected to be

accomplished by the gene therapy which is being examined. As the burden of disease of rare diseases is low, authentication of these outcome measures is difficult.

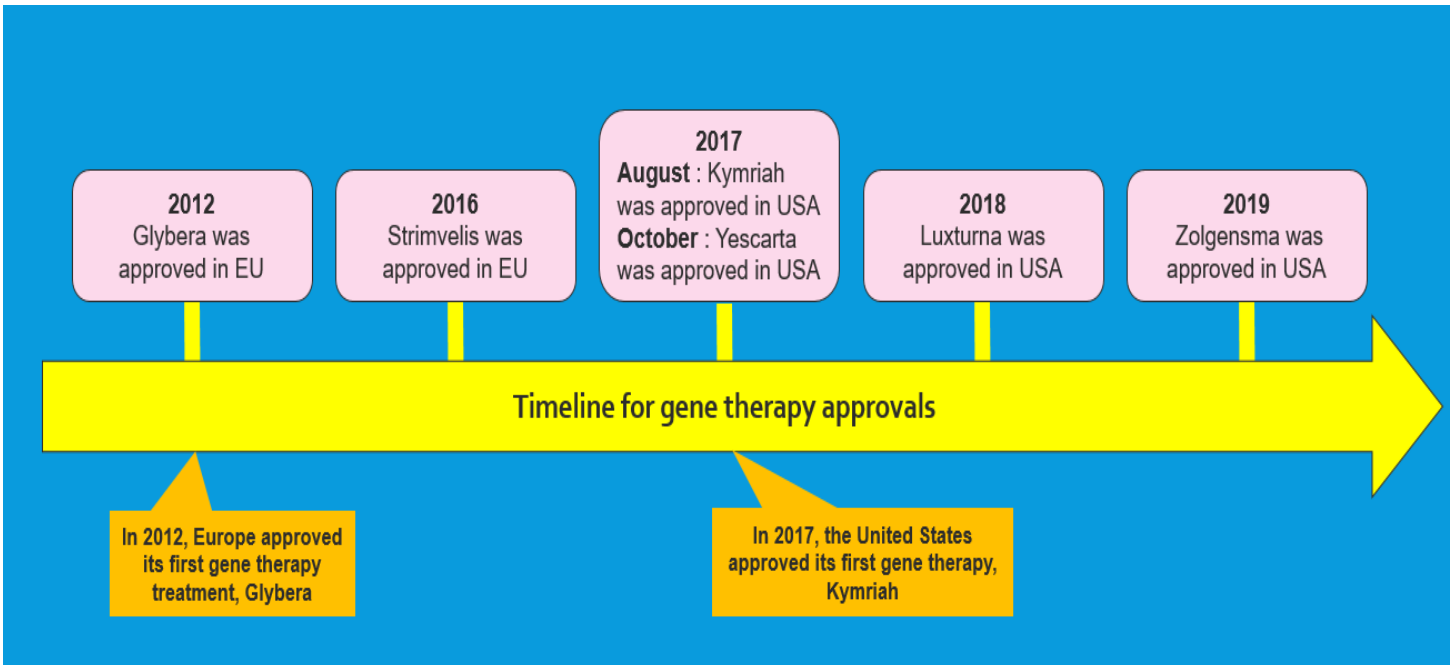


A rapid increase in the number of pharmaceutical companies which are pursuing the development of gene therapies has been witnessed. The Alliance for Regenerative Medicine estimated that 69 companies were pursuing gene therapy in 2014. This number had risen to 255 in 2018. This indicates an increase of 269.57% from 2014 to 2018.

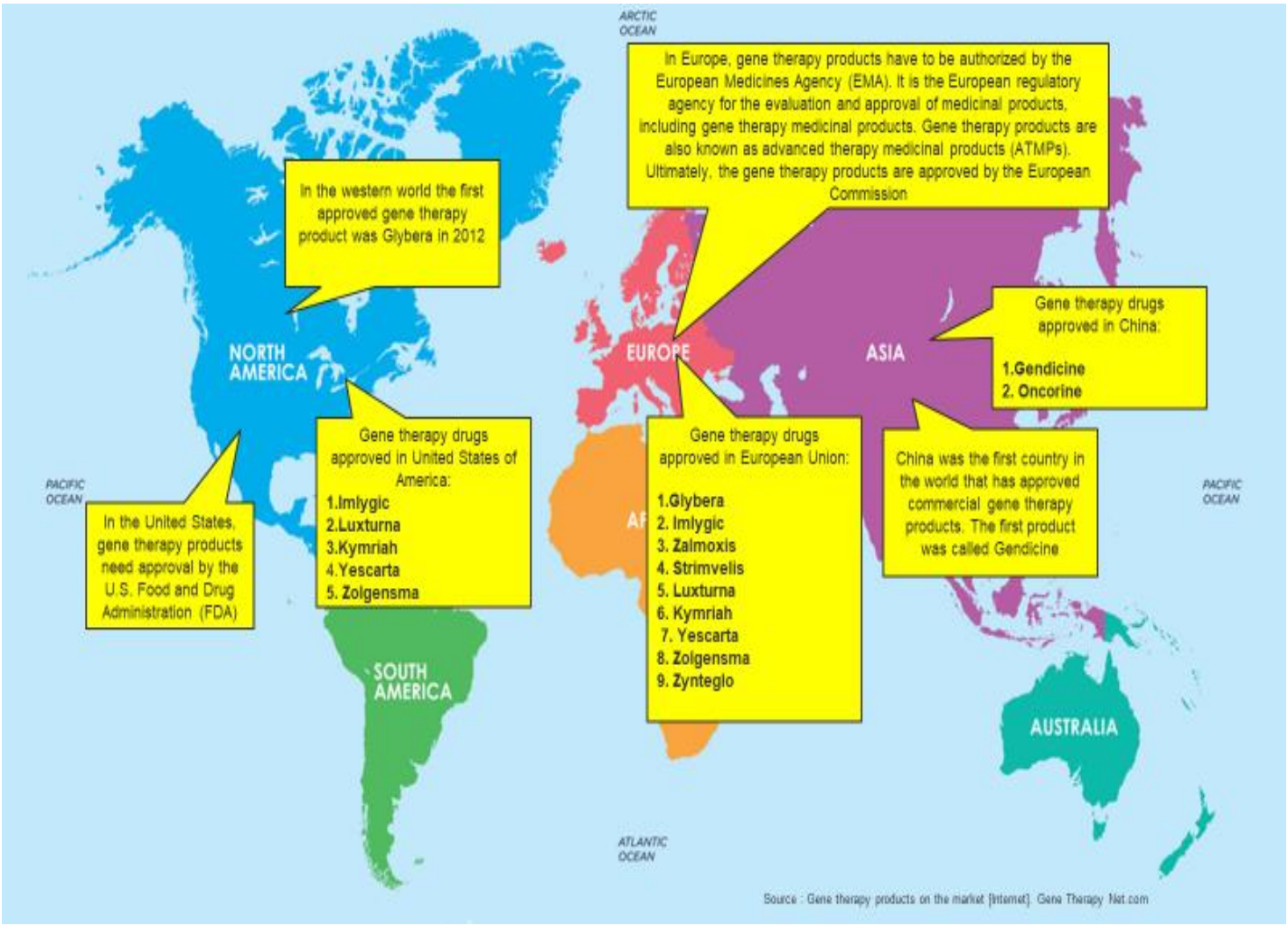
SWOT Analysis of gene therapy in rare diseases:

STRENGTHS	WEAKNESSES
• Gene therapy offers the possibility of correction of genetic defect • The scope and potential of gene therapy is humungous • Gene therapy is a viable treatment option for rare diseases • The gene therapy can possibly lead to permanent changes • Several products in the pipeline • Gene therapy can work in combination with cell therapy techniques	• Adverse events or immune reactions can be common • Gene therapy methods can sometimes target the non-target cells • The viral vector may become pathogenic and can cause disease • Gene therapies could lead to the development of a tumor • Uncertainty about the outcome of gene therapy • New genes may be incompatible with the patients • Possible development of resistance to gene therapy by patients • Exorbitant cost of development • The existence of ethical concerns about gene modification • Gene therapy is predominantly suited for monogenic mutation • Gene therapy requires huge investment
OPPORTUNITIES	**THREATS**
• Extensive research on what causes rare diseases in humans • Availability of affordable genetic and genomic analyses for research and diagnosis • Evolution of new technologies such as gene disruption and modification, ex vivo and in vivo gene therapy	• Extremely high cost of development and production • Very long development and research timelines • Presence of many diseases which affect few patients

Gene therapy: Marketed products



- **The first country in the world to have approved or authorized a gene therapy product was China, with the first gene therapy product being Gendicine**
- **Glybera was the first marketed gene therapy product in the western world in 2012**
- **In Europe, gene therapy products have to be authorized by the European Medicines Agency (EMA)**. It is the European regulatory agency for the evaluation and approval of medicinal products, including gene therapy medicinal products. **Gene therapy products are also known as advanced therapy medicinal products (ATMPs)**. Ultimately, the gene therapy products are approved by the European Commission
- **In the United States, gene therapy products need marketing approval of the U.S. Food and Drug Administration (FDA)**



Following is a summarization of the various gene therapy products that have been marketed worldwide :

S.No.	Gene Therapy	Indication	Developer	Countries
1.	**Gendicine**	Head and neck squamous cell carcinoma	SiBionoGeneTech Co	China
2.	**Oncorine**	Late stage refractory nasopharyngeal cancer	Shanghai Sunway Biotech Co. Ltd	China
3.	**Glybera**	Lipoprotein lipase deficiency (LPLD)	Amsterdam Molecular Therapeutics (AMT)	EU

			(acquired by UniQure)	
4.	**Imlygic**	Melanoma	BioVex /Amgen	USA and EU
5.	**Zalmoxis**	Additional treatment for adults who have received a Haematopoietic stem cell transplant (HSCT)	MolMed S.p.A	EU
6.	**Strimvelis**	ADA-SCID (Adenosine Deaminase deficiency - Severe Combined Immunodeficiency)	GlaxoSmithKline (GSK)/ Orchard Therapeutics Ltd.	EU
7.	**Luxturna**	Inherited form of retinal dystrophy	Spark Therapeutics/Novartis	USA, EU
8.	**Kymriah**	B-cell acute lymphoblastic leukemia (ALL)	Novartis	USA, EU
9.	**Yescarta**	Large B-cell lymphoma	Kite Pharma (acquired by Gilead Sciences)	USA, EU
10.	**Zolgensma**	Spinal muscular atrophy	AveXis (a subsidiary of Novartis)	USA, EU
11.	**Zynteglo**	Beta thalassaemia	bluebird bio	EU

DISCUSSION:

Approvals of gene therapy in EU and USA (2000-2020)

Research on gene therapy continues in this decade.

The European Union's foremost or pioneer gene therapy drug was approved in 2012. Glybera, a viral treatment, was authorized by EMA to cure a type of pancreatitis. This disorder of the pancreas is triggered when a gene known as *lipoprotein lipase* is not present. **In 2015, Glybera's cost was $1 million dollars**. **Hence, with such an exorbitant price, Glybera was touted as the most expensive treatment of 2015.** The potential benefits of gene therapy are well understood and established but the paradox of its high cost definitely presents a major challenge as **patients are unable to pay for it,** thus, making these therapies a complete failure. UniQure was the pharmaceutical company that manufactured Glybera and it has already halted the manufacturing of this drug after treating a very less number of patients. Till 2018, **Glybera was no longer included in the pipeline of UniQure's products**.

In 2016, the EMA approved another gene therapy called Strimvelis. Strimvelis was developed by GalaxoSmithKline (GSK), which is a stem cell gene therapy to treat ADA-SCID patients. ADA-SCID is a rare disorder that affects approximately 14 people every year in Europe. Strimvelis' fate was on similar lines to that of Glybera's. The gene therapy was at first priced at $665,000 (it was believed that a single treatment of Strimvelis could cure ADA-SCID). Till 2017, only 2 patients had been provided with a treatment of Strimvelis and GSK was aiming to put on sale this gene therapy. Finding a healthcare provider to cover the high treatment cost is a huge challenge when treatment is priced unreasonably high. Strimvelis was sold to Orchard Therapeutics from GSK in 2018. At the point of this agreement, approximately 5 patients had been provided treatment with Strimvelis (it was later priced at $730K).

2017

CAR-T was the foremost or pioneer gene therapy drug to be authorized in the United States of America in 2017. CAR-T is similar to gene therapies such as Glybera and Strimvelis and it involves removal of blood from the body of a patient and genetically modifying some particular blood cells (target blood cells) and ultimately transferring the re-engineered cells (with the new gene) into the affected patient's body.

FDA authorized the use of the foremost gene therapy, a CAR-T therapy called Kymriah for the treatment of ALL (acute lymphoblastic leukemia) in August of 2017. Kymriah was developed by Novartis.

FDA authorized the use of Yescarta, which is another CAR-T therapy in October of 2017 for treatment of adults affected with diffuse large B-cell lymphoma. Large B-cell lymphoma is a very frequent occurring type of NHL (non-Hodgkin lymphoma). Yescarta was manufactured by Kite Pharma and it was acquired by Gilead for US $11.9 billion in August 2017.

2018

Luxturna was approved by FDA in 2018. Luxturna is developed by Spark Therapeutics. Luxturna is used as a curative option for RPE65 mutation-associated retinal dystrophy.

Since Luxturna is injected directly into the patient's body (also known as in vivo gene therapy), this gene therapy is touted as the first true (or actual) gene therapy. In, Kymriah and Yescarta , the affected cells are removed from the body before treatment. The new gene is delivered to the removed cells and the treated cells are transferred back to the body (ex vivo gene therapy).

For any patient to be eligible for treatment with Luxturna, the patient must have viable retinal cells. As of 2018, commercialization of Luxturna in United States of America was being done by Spark Therapeutics. Novartis planned to commercialize (marketing rights) Luxturna in Europe.

2019

FDA approved Zolgensma in 2018. Zolgensma is being developed by Avexis. Novartis is the owner of Avexis. Zolgensma acts as an AAV9 viral vector. This vector only target motor neurons. The SMN gene is injected by AAV9 virus into the nucleus of the motor neurons of the Spinal Muscular Atrophy patients. Zolgensma has a unique mechanism of action as it is an IV injected AAV gene therapy and its therapeutic effect reaches neurons effectively.

The future and scope of gene therapy

It is expected that more number of gene therapies will reach the market in the subsequent years. **An approval for a gene therapy for hemophilia is being expected soon. Many pipeline products are in Phase III or have established efficacy in Phase I/II trials.**

However, pharmaceutical companies are focused on addressing two major challenges at the present moment, reducing cost of manufacturing and determining the quickest and most feasible path to approval via clinical trials.

The FDA is keeping up with the rapidly changing scenario in the development of gene therapies. The FDA is adjusting its policies and structure to meet the requirements of a clinical trial for gene therapy. For instance, 50 clinical trial reviewers were hired by the FDA to review the increasing number of gene therapy applicants (as of 2020).

At present, gene therapy trials are ongoing for the following rare diseases:

- Human Immunodeficiency Virus
- Sickle cell anemia
- Choroideremia
- ADA-SCID

CONCLUSION :

Due to the RMAT designation by FDA, clinical activity with regard to development of gene therapy, is expected to continue to increase. A **Regenerative Medicine Advanced Therapy (RMAT)** term was added by the FDA to the 21st Century Cures Act on December 13, 2016. **Incentives are provided by FDA for pharmaceutical companies to pursue gene therapies. These incentives include recurrent and regular interactions with FDA and the possibility to deliberate intermediate endpoints or outcomes for clinical trials of gene therapies.**

Clinical efficacy of gene therapy has been determined for various rare diseases, using different vectors. The advancement in technology is unparalleled in current times. Yet, there is a lack of treatment for **more than 90% of rare diseases. Undoubtedly, gene therapy is a viable treatment option to cure rare diseases as these diseases are genetic in nature.** Gene therapy is the future of treatment of rare diseases and a step to eliminating prevalence and incidence of rare diseases in the population.

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APPENDIX:

Abbreviations:

AAV	Adeno-associated virus
ADA-SCID	Adenosine deaminase-severe combined immunodeficiency
ALL	Acute lymphocytic leukemia
AMT	Amsterdam Molecular Therapeutics
ATMPs	Advanced therapy medicinal products
CAR-T	Chimeric T cell receptor
CDFA	China State Food & Drug Administration
DLBL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
FDA	Food and Drug Administration
FIX	Clotting factor IX
GSK	GlaxoSmithKline
HSC	Haematopoietic stem cell
HSCT	Haematopoietic stem cell transplant
IV	Intravenous therapy
LPL	Lipoprotein lipase
LPLD	Lipoprotein lipase deficiency
ODA	Orphan Drug Act
RPE65	Retinal pigment epithelium 65 gene
R&D	Research and Development
RMAT	Regenerative Medicine Advanced Therapy
SMN	Survival motor neuron