CELL AND GENE THERAPY

Gene therapy is the introduction, removal or change in genetic material — specifically DNA or RNA — into the cells of a patient to treat a specific disease and it has been studied for more than 40 years. The transferred genetic material changes how a protein — or group of proteins — is produced by the cell.

Cell Therapy is the transfer of cells into a patient with the goal of improving or curing a disease. Some cell therapies are routine, like blood transfusions. One approach is gene-modified cell therapy, which removes the cells from the body, then a new gene can be introduced, or a faulty gene can be corrected.

Increased progress in Cell/Gene therapies has been observed due to the promising opportunities for the mitigation, treatment or cure of many rare diseases as FDA has approved new gene therapy products in 2017 as it was a pivotal year:

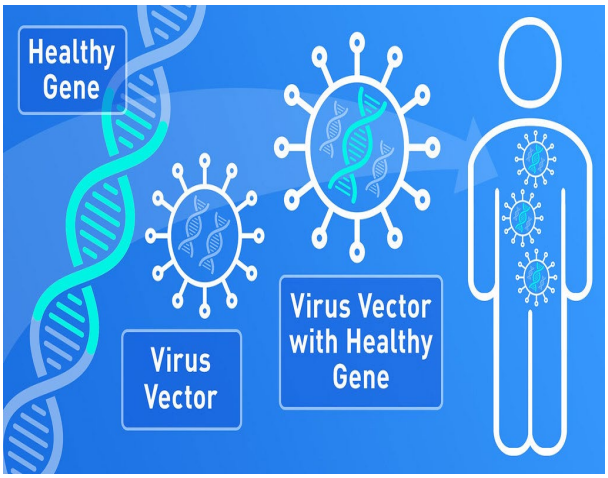
1. August 2017, the FDA approved Kymriah (by Novartis) the first gene-therapy product to treat a form of leukemia.
2. October 2017, a cell-based gene-based treatment, called Yescarta (by GileadKite Pharma), was approved by the FDA for a form of to treat adult patients with certain types of large B-cell lymphoma.
3. December 2017, the FDA approved Luxturna (by Spark Therapeutics), a genetically modified virus that ferries a healthy gene into the eyes of patients with an inherited form of vision loss born with retinal dystrophy, a rare condition that destroys cells in the retina needed for healthy vision.

The FDA has established its regulatory policy framework for these products within its regenerative medicine advanced therapy (RMAT) program. With the additional activity, CBER received more 150 INDs in 2018 for gene therapy products, bringing the total number of active INDs up to nearly 800 applications. This area is rapidly growing as evident from 97 RMAT designation requests, including 19 in the first three months of 2019, with 33 granted. The unique and complex CMC issues set these products apart from traditional biologic products. These novel therapies involve unique development challenges due to unknown safety profiles, complex manufacturing technologies and the use of cutting-edge testing methodologies. The regulators are welcoming a science and risk-based approach to the control strategies used to ensure quality and safety. Syner-G Pharma Consulting has experience in the areas of gene/cell therapies and science and risk-based CMC strategies and can help sponsors develop their approach with product development and interactions with the agency.

The FDA has suggested that sponsors discuss their programs with them very early in the form of an INTERACT (CBER INitial Targeted Engagement for Regulatory Advice on CBER product) meeting. EMA has a similar program of Advanced Therapy Medicinal Products (ATMPs) and this program is for medicines for human use that are based on genes, tissues or cells. Most recently at the end of March 2019, A European Medicines Agency panel recommended a conditional marketing approval for a gene therapy from Bluebird Bio Inc as a genetic blood disorder treatment.

Key CMC areas for regulatory considerations during early development of Cell/gene therapies:

- Safety Concerns which could affect sourcing continually evolve as more information is obtained in a rapidly emerging field
- Smaller batch sizes (impacts the ability to test, characterize and evaluate the stability of products using typically acceptable biologic criteria)
- Analytical test methodologies need to be validated/qualified much earlier specifically for potency/efficacy concerns directly related to the effectiveness of these therapies
- CMC Changes and Comparability, the ability to perform comparability can also be impacted by the typically small batch sizes seen



FDA is trying to direct sponsors as CBER's Office of Tissues and Advanced Therapies also released 10 new guidance documents in 2018, including six new draft guidance documents on gene therapy and a recently finalized guidance on expedited programs for regenerative medicine. One of the guidances released for comment was directed at early stage Gene Therapy CMC issues and it provided recommendations regarding CMC information required to assure product safety, identity, quality, purity and strength (including potency) of the investigational product (IND).

Syner-G has experience in supporting CMC regulatory activities for gene/cell therapy products. We are here to help sponsors at this crucial moment in the development of their gene/cell therapy products and help sponsors provide these effective medicines to the patients that need them.