REGULATORY CONSIDERATIONS

IN GENE AND CELLULAR THERAPY DEVELOPMENT

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THE GENE AND CELLULAR THERAPY LANDSCAPE

Gene and cellular therapy holds the extraordinary potential to transform global health care. As a result, the gene and cellular therapy pipeline has grown tremendously. There are currently more than 1,800 active and recruiting gene and cell therapy trials globally. Furthermore, by 2030 more than 60 United States (US) approvals of gene and cellular therapy products are projected, with more than 500,000 patients anticipated to be treated with these therapies.[1]

TYPES OF GENE AND CELLULAR THERAPIES

Plasmids utilized in the gene and cellular therapies are usually artificial and designed in a laboratory to introduce foreign genetic material into another cell. Due to their artificial nature, these plasmids are commonly referred to as "vectors" or "constructs". In these therapies, foreign genetic materials are introduced into a patient in order to treat a genetic disease. A delivery system called a vector is used to introduce genetic material into cells. The two most commonly used vectors are viral and non-viral vectors. Viral vectors are genetically engineered viruses that deliver foreign genetic material into cells using their viral genome. Non-viral vectors are chemical vectors such as inorganic particles including; lipid-based, polymer-based, and peptide-based vectors that deliver foreign genetic material into cells.

There are several different forms of genomic alterations including gene therapy, cellular therapy, and gene editing. Gene therapy is the introduction, removal, or change in the genetic material Deoxyribonucleic Acid (DNA) or Ribonucleic Acid (RNA). A vector delivers a new functioning gene or genetic material into a cell using an inactive virus. Genetically modified cell therapy involves the removal of cells from the patient and uses a vector to deliver a new functioning gene into cells. These genetically modified cells are then reintroduced to the patient. Gene editing consists of the removal, disruption, or correction of faulty elements of DNA within a gene. Gene editing uses highly precise technology to modify cells.

FACILITATING THE PATHWAY TO THE PATIENT

Gene and cellular therapies are eligible for expedited programs. These programs are focused on the pre-submission phase and as such increase collaboration and consultation between regulators and sponsors prior to submission of a dossier. These programs can reduce at least two years off of a new drug development timeline. The standards for approval don't change, but what changes is how the benefit/risk evaluation is done. If a therapy shows a high benefit in earlier stages, there may be more acceptance of a risk. Sponsors still have to do the required studies, but there may be post-marketing commitments to prove that the earlier data still holds up. Expedited review programs require a much faster, more adaptable research and development process, because products will move into Phase III development very quickly.[2]

The Orphan Drug Act was signed into law by President Reagan in 1983 to treat diseases affecting fewer than 200,000 people. An orphan drug designation offers; 7-year marketing exclusivity to sponsors, 25% federal tax credit for expenses incurred in conducting clinical research within the US, a Prescription Drug User Fee Act (PDUFA) fees waiver, and eligibility to receive regulatory assistance and guidance from the Food and Drug Administration (FDA) in the design of an overall drug development plan. As many gene and cellular therapies currently under development target orphan diseases, the small patient populations require considerations of alternative trial designs and statistical techniques, such as single-arm study design with historical controls that can maximize data from a small and potentially heterogeneous group of subjects.[3]

GENE AND CELLULAR THERAPY CHALLENGES

The diversity and complexity of gene and cellular therapy products also pose challenges to the product characterization and testing programs. There are few industry standards and reference materials for the manufacturing of these products. Manufacturing is often done on a small scale or in patient-specific lots where there may be considerable lot-to-lot heterogeneity. Gene and cellular therapy products often have a limited shelf-life and stability, which makes strategies for product testing, storage, and shipping highly product specific.

Quality raw materials may be difficult to obtain due to the need to use human and animal-derived materials, the biological complexity of the materials, and variable lot-to-lot performance characteristics. Import and export requirements for starting materials, clinical samples, and finished products can slow down efficient product development. There are also constraints in manufacturing that have an impact on product development including

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the high cost of raw materials, long lead times, and upfront investment requirements. Available production capacity for viral vectors has been limited by the increase in the number of therapies being developed and the expanding sizes of target populations. The limited capacity of existing GMP facilities results in long wait times for clinical trial material and increased cost of goods. The complexity of these therapies leads to unique manufacturing challenges. Critical quality attributes (CQAs) are not well established for many of these products, and it is often difficult to demonstrate a link to clinical outcomes. Expedited clinical and regulatory pathways to submission and approval put pressure on chemistry, manufacturing, and controls (CMC) timelines to be completed faster for these therapies than for traditional medicinal products.

PRECLINICAL AND CLINICAL STUDY CONSIDERATIONS

For gene therapy products, an appropriate preclinical testing program should evaluate the potential for adverse immune responses to the *ex-vivo* modified cells, the vector, the expressed transgene, level of viral replication in non-target cells/tissues, insertional mutagenesis or oncogenicity, vector biodistribution and transgene expression levels post-administration. For cellular therapy products, there may be a heightened concern of tumor or ectopic tissue formation, toxicity or mechanical failure associated with the resorption or degradation of a scaffold component, and unknown donor cell fate (i.e., survival, phenotype, distribution, and proliferation following administration). These concerns should be evaluated as part of the preclinical testing program. Information obtained from preclinical studies help guide the design of the initial clinical trial. Additional animal studies may need to be performed during late phase development after clinical trials have initiated. For example, an assessment of developmental and reproductive toxicity, which can usually be conducted concurrently with Phase III trials.

Gene and cellular therapies often demonstrate early signs of clinical efficacy resulting in accelerated development programs. The typical paradigm of clinical trial requirements is shifting for these therapies, for example consolidating the Phase I, II, and III trials into Phase I/II, Phase III, and post-approval trials is becoming common. With the rapid advances in these therapies, as well as the early efficacy data frequently obtained for these products, regulators are more open to discussions about innovative clinical trial designs.

Establishing quality, safety, and efficacy data necessary to support a favorable benefit/risk profile requires an understanding of the following challenges; correct dose estimation, routes of administration, small patient populations for rare disease applications, the development of manufacturing processes and associated quality standards, and a potential lack of established clinical endpoints. In addition, gene and cellular therapies have varied potential and some theoretical, long-term risks, such as immunogenicity and tumorigenicity, as well as a potential for loss of expression over time.

Most Phase I gene and cellular therapy studies enroll subjects who have the disease or medical condition. The reason for this is that there is an unfavorable benefit/risk for administering these products that carry the risk of long-term adverse events (AEs) to healthy volunteers. Therefore, in addition to evaluation of safety, the primary objective of a Phase I study is that sponsors can assess preliminary evidence of bioactivity on characteristics of the disease or condition which then can guide the subsequent clinical development program. A single administration dosing regimen is used in most First in Human (FIH) studies until there is an understanding of toxicity and duration of activity of the product, since risk due to repeated dosing of these products might not be acceptable. In the absence of preliminary safety data, FIH studies should not administer the gene and cellular therapy products simultaneously to multiple subjects within a given dose cohort. To allow for an intersubject and intercohort monitoring, FIH studies often stagger the administration of the product to sequential subjects to allow for detection of acute and subacute AEs.

Phase II studies should be designed to provide safety, efficacy, and feasibility data that can further investigate hypotheses that are generated from the data collected in Phase I studies. Phase II data are critical for informing the design of the Phase III trials, which are intended to provide substantial evidence of effectiveness and safety. Some of the important knowledge that can be obtained from Phase II studies includes; information that can guide the selection of a study population that would be appropriate for enrollment in Phase III, dose and dosing regimen exploration, optimization of study procedures, refinement of the concomitant medication regimen, the treatment effect for the Phase III primary endpoint, and the product bioactivity.

GLOBAL REGULATORY PERSPECTIVES

It can be challenging for companies to receive agreement from regulators in different global regions on a proposed novel or surrogate endpoint for clinical studies that could include changes to gene or protein expression. There are regional differences in vector-specific study duration recommendations for long-term follow-up. These include; different timelines, study requirements, and regulatory pathways. For example, environmental risk assessments requirements for genetically modified organisms vary with each member state in the European Union (EU). The unknown of durability for gene and cellular therapy products could be addressed by collecting long-term data through disease registries. The safety and efficacy data available before the approval of these products may be limited, therefore regulators typically require patient follow-up and disease registries to build long-term efficacy and safety data supporting the product's risk/benefit profile.

To support the evaluation and regulation of gene and cellular therapy products, regulators globally either stretch the boundaries of their existing medicinal product regulations or design and implement new regulations. Most countries belong to the first group and do not have regulations specific to gene and cellular therapies. Instead, regulation for these products typically captures them as a subset of products under existing legislation, for example biologics. Many countries do not have the research and medical capabilities necessary for the development of regulatory frameworks that would support the timely and efficient introduction of these therapies, leaving many patients without access to them.[1]

To date, there is no harmonized international standard for regulating gene and cellular therapy products. However, the US, EU, and Japan have established regulatory frameworks for these products. In the US Food and Drug Administration and its Center for Biologics Evaluation and Research (CBER), there is an Office of Tissues and Advanced Therapies (OTAT). In the EU in addition to the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use, there is a specialized Committee for Advanced Therapies that covers gene and cellular therapies. In Japan, under the Pharmaceuticals and Medical Devices Agency (PMDA) and the Ministry of Health, Labor, and Welfare, there is an Office of Cellular and Tissue-based Products.[4]

Confidentiality Commitments (CCs) and Memorandums of Understanding (MOUs) are tools by which the FDA can share confidential information with other international regulatory authorities. Parallel Scientific Advice (PSA) is an example of a CC/MOU activity. The PSA process involves the sponsor of a regulatory application seeking joint advice with the EMA and the FDA on a specific product. This interaction may also provide an understanding of the basis of scientific advice and an opportunity to optimize product development and avoid unnecessary replication of testing or divergence in testing methodologies. Clusters are another example of an CC/MOU activity. Clusters are forums in which FDA and other regulatory authorities discuss specific areas of mutual interest. The Advanced Therapy Medicinal Products (ATMP) cluster is specific for Gene and Cellular Therapy products. This cluster exists as a three-way interaction between FDA, EMA, and Health Canada.

International activities regarding regulatory convergence specific for gene and cellular therapy products include FDAs participation in the International Pharmaceutical Regulators Forum (IPRF) Cell Therapy Working Group and the IPRF Gene Therapy Working Group. These forums are open to all regulatory authorities. The IPRF allows participants the opportunity to share scientific knowledge and regulatory experiences. Regional initiatives such as the Pan American Health Organization (PAHO) and the Asia-Pacific Economic Cooperation (APEC) Harmonization Center promote the convergence of regulatory approaches for these products.

FDA standards development activities include participation in initiatives that develop international standards with the goal of harmonizing regulatory expectations internationally, e.g., International Conference on Harmonization (ICH), as well as organizations seeking standardization of technical and scientific approaches for specific topics, e.g., International Organization for Standardization (ISO) and American Society for Testing

and Materials International (ASTMi). The development and use of national and international standards for gene and cellular therapy products can facilitate product development and reduce time to market. For example, the development of standard reference materials can provide a mechanism by which gene and cellular therapy products utilizing the same vector can be compared.

EXPEDITED PROGRAMS AND ACCELERATED APPROVALS

Regulators experienced with gene and cellular therapies have adopted requirements and practices that are unique to the development of these products. For example, both the EMA and the US FDA have developed many guidelines and guidance documents specific to gene and cellular therapy products. Expedited pathways aim to shorten the development and review timelines for therapies that provide significant advantages over current treatments or are the only treatment option for serious diseases to deliver them to patients faster. Expedited pathways include designation programs that offer opportunities such as increased earlier communication with regulators to facilitate streamlined development.

Accelerated approval and adaptive licensing make use of different requirements, such as the use of surrogate endpoints and authorization based on non-confirmatory evidence that needs to be confirmed after commercialization. Accelerated assessment programs allow for shortened review times for marketing authorization applications. These programs allow for the use of preclinical data, either alone or in conjunction with clinical data, to support the designation request. They offer increased access to and feedback from the regulatory authority that grants the designation. Through frequent meetings, the sponsor and the regulatory authority can achieve alignment on study design and data requirements. Current expedited programs specializing in gene and cellular therapies include fast track, breakthrough therapy, and Regenerative Medicine Advance Therapy (RMAT) in the US, Priority Medicines (PRIME) in the EU, and Sakigake in Japan. If a product proceeds successfully through clinical development, all three countries offer programs to expedite the review of the marketing applications. In the US and Japan, these programs are termed priority review, and in the EU, the program called accelerated assessment.[2,4,5,6,7,8]

These countries also offer expedited commercial registration pathways. With these pathways, it is possible to only need to conduct the first of two pivotal trials or to use a surrogate endpoint as the efficacy endpoint for a pivotal study in order to receive conditional approval. An important component of any expedited registration pathway is that confirmatory studies must be conducted after conditional approval has been granted. In the US, conditional approval of drugs that treat serious conditions and that fill an unmet medical need can be granted based on a surrogate endpoint. In the EU, this is known as marketing authorization under exceptional circumstances and in Japan, the conditional early approval system is for conditional approval without a confirmatory study.[2,4,5]

The rapid expansion of the gene and cellular therapy pipeline in recent years offers the potential to treat diseases with unmet medical needs. The complexity of these therapies poses challenges to regulating them within traditional frameworks. Some countries have established separate regulatory frameworks for these products, but differences exist between them. Fostering convergence among countries with separate regulatory frameworks and allowing for the harmonization of these frameworks to include countries without such abilities to develop them will facilitate the path to more patients. Regulators that establish new dedicated frameworks for regulating gene and cellular therapies should consider expedited regulatory pathways that offer early engagement with regulators, innovative clinical trial design, and post-market confirmatory studies. Increasing the alignment of international regulatory pathways will be critical in facilitating the access to gene and cellular therapies to patients with unmet medical needs globally.

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