Global expedited programs for cellular and gene therapies

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Cellular and gene therapies hold tremendous promise for addressing some of the most problematic diseases, including those currently without treatment options and rare genetic conditions. The goal of the article is to provide a review of global expedited regulatory pathways and best practices for the successful implementation of them. The author recommends developers of these therapies work with regulators from the earliest stages of development. Interactions with regulators on how to design the product development program could facilitate the approval process and expedite delivery of treatment to patients in need.

Keywords – advanced therapies, rare diseases, regulatory dossiers, regulatory frameworks

Introduction

There are three programs in the US designed to promote product development – fast track, breakthrough therapy, and regenerative medicine advanced therapy (RMAT designations.[1] The EU offers the priority medicines (PRIME) designation, and Japan offers the Sakigake designation.[2,3] As a product proceeds successfully through clinical development, all three countries offer programs to expedite the review of BLAs or marketing applications. In the US and Japan, these programs are called priority review, and in the EU, the program is known as accelerated assessment. As with the programs that promote product development, these expedited review programs have specific requirements and features. The US (accelerated approval), EU (conditional marketing approval) and Japan (conditional and term-limited approval) also offer conditional approval mechanisms for expediting the registration pathway of promising therapies. It is important for any expedited registration pathway that confirmatory studies are conducted in a timely manner after conditional approval has been granted. As regulatory authorities continue to issue new guidelines that assist with the interpretation of the regulations, it is critical for sponsors to stay current with evolving regulatory standards and best practices.

The cellular and gene therapy landscape

Cellular and gene therapies hold the extraordinary potential to transform global health care. As a result, the cellular and gene therapy pipeline has grown tremendously. There are currently more than 1,800 active and recruiting trials globally. Furthermore, by 2030 more than 60 US approvals of cellular and gene therapy

products are projected, with more than 500,000 patients anticipated to be treated with these therapies.[4]

Types of cellular and gene therapies

Plasmids used in cellular and gene therapies are commonly artificial and designed in a laboratory to introduce foreign genetic material into another cell. In these therapies, foreign genetic materials are introduced to a patient 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 nonviral vectors. Viral vectors** are genetically engineered viruses that deliver foreign genetic material into cells by using their viral genome. Nonviral 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 therapies, 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

Cellular and gene therapies are eligible for expedited programs. These programs are focused on the presubmission phase and, as such, increasing collaboration and consultation between regulators and sponsors before submission of a dossier. These programs can reduce a new drug development timeline by at least two years. Regulators allow for more uncertainty in their benefit-risk evaluation with a promising agent that is eligible for an expedited pathway. 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 postmarketing commitments to prove that the earlier data still hold up. Expedited review programs require a much faster, more adaptable research and development process because products will move into phase 3 development quickly.[5]

An orphan drug is a pharmaceutical agent that is intended to treat a rare medical condition, which is typically a disease or disorder that affects a small number of people. Due to the small market size, the cost of developing an orphan drug can be prohibitively expensive, making it difficult for developers to recoup their investment. In response to these challenges, governments around the world have implemented programs to incentivize the development of orphan drugs. Although not an expedited program, orphan drug designation, which is granted by regulatory agencies such as the FDA, EU, and Japan, is defined as a drug intended to treat a rare disease or condition.[6-8]

When a drug receives orphan designation in the US, EU, and Japan regulators provide valuable benefits such as fee reductions, scientific advice, and a period of market exclusivity. Market exclusivity is a key benefit of orphan drug designation and typically lasts for 10 years in the EU and Japan, and seven years in the US. During this period, the drug developer has exclusive rights to sell the drug, which helps recoup the

investment in development costs. However, there are variations in the criteria for orphan drug status between regions. In the US, developers of orphan drugs can also benefit from grants, additional meetings with the FDA, and waived fees for certain applications. In the EU, the indication an orphan drug addresses must be rare and debilitating or life-threatening, and the drug must apply to not more than 5 patients in 10,000. In the US, the condition must be rare, the reason for treatment must be explained, and the condition must affect fewer than 200,000 people. Japan requires that the patient population an orphan drug addresses be smaller than 50,000 patients. In addition, the European Medicines Agency (EMA) requires preclinical or clinical data to support the drug's treatment, diagnosis, or prevention story, while the FDA only requires a rationale for the orphan status of the drug. Overall, developers of orphan drugs can benefit from understanding the nuanced differences in orphan drug designation frameworks across regions. By doing so, they can strategically navigate regulatory pathways and capitalize on the available benefits to advance their life-saving treatments for rare diseases. [6-9]

Cellular and gene therapy challenges

The diversity and complexity of cellular and gene 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. Cellular and gene 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 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 facilities with good manufacturing practice 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 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 control 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, and the expressed transgene. Additionally, the level of viral replication in nontarget cells/tissues, insertional mutagenesis or oncogenicity, vector bio distribution and transgene expression levels post administration should be assessed.

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 helps guide the design of the initial clinical trial. Additional animal studies may need to be performed during late-phase development after clinical trials have been initiated. For example, an assessment of developmental and reproductive toxicity, which can usually be conducted concurrently with phase 3 trials.

Cellular and gene 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 1, 2, and 3 trials into phase 1/2, phase 3, and postapproval trials are 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, cellular and gene 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 1 cellular and gene 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 1 study, is that sponsors can assess for 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 cellular and gene therapy products simultaneously to multiple subjects within a given dose cohort. To allow for 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 2 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 1 studies. Phase 2 data are critical for informing the design of the phase 3 trials, which are intended to provide substantial evidence of effectiveness and safety. Some of the important knowledge that can be obtained from phase 2 studies include information

that can guide the selection of a study population that would be appropriate for enrollment in phase 3, dose and dosing regimen exploration, optimization of study procedures, refinement of the concomitant medication regimen, the treatment effect for the phase 3 primary endpoint, and the product bioactivity.

As many cellular and gene 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.[9]

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 the gene or protein expression. There are regional differences in vector-specific study duration recommendations for long-term followup. 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 EU. The unknown durability for cellular and gene 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 benefit-risk profile.

To support the evaluation and regulation of cellular and gene 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 cellular and gene 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.[7]
To date, there is no harmonized international standard for regulating cellular and gene therapy products. However, the US, EU, and Japan have established regulatory frameworks for these products. In the FDA and its Center for Biologics Evaluation and Research, there is an Office of Tissues and Advanced Therapies. In the EU, in addition to the EMA's Committee for Medicinal Products for Human Use, there is the specialized Committee for Advanced Therapies that covers cellular and gene therapies. In Japan, under the Pharmaceuticals and Medical Devices Agency and the Ministry of Health, Labor, and Welfare, there is an Office of Cellular and Tissue-based Products.[10]

Confidentiality commitments (CCs) and memorandums of understanding (MoUs) are tools whereby 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 a CC-MoU activity. Clusters are forums in which the FDA and other regulatory authorities discuss specific areas of mutual interest. The Advanced Therapy Medicinal Products Cluster is specific for cellular and gene

therapy products. This cluster exists as a three-way interaction between the FDA, EMA, and Health Canada.

International activities regarding regulatory convergence specific for cellular and gene therapy products include FDAs participation in the International Pharmaceutical Regulators Forum's (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 and the Asia-Pacific Economic Cooperation 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 Council for Harmonization), as well as organizations seeking standardization of technical and scientific approaches for specific topics (e.g., International Organization for Standardization and the American Society for Testing and Materials International). The development and use of national and international standards for cellular and gene 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 cellular and gene therapy products utilizing the same vector can be compared.

Expedited programs and accelerated approvals

Regulators experienced with cellular and gene therapies have adopted requirements and practices that are unique to the development of these products. For example, both the EMA and the FDA have developed many guidelines and guidance documents specific to cellular and gene therapy products.[3,13] 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, early 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 nonconfirmatory 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 cellular and gene therapies include fast track, breakthrough therapy, and RMAT in the US, 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 is accelerated assessment.[1-3,8,10,13]

These countries also offer expedited commercial registration pathways. With these pathways, it is possible that only the first of two pivotal trials needs to be conducted or that a surrogate endpoint can be used as the

efficacy endpoint for a pivotal study 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.[8,10,13]

Industry feedback

Bujar and colleagues did a study to assess the perceived value and impact of several expedited programs, including the US FDA's breakthrough therapy designation and fast track, the EMA's PRIME, and the Japanese Pharmaceutical and Medical Devices Agency's Sakigake. The study involved 11 companies, of which 10 had experience with both the FDA's expedited programs and PMDA's Sakigake, whereas 8 had experience with EMA's PRIME. The findings showed that companies experienced a higher degree of success with the two FDA expedited programs compared with the EMA and PMDA pathways. Specifically, all 10 companies that applied for FDA's expedited programs received the designation, compared with only 4 out of 10 companies for EMA and PMDA.[14]

Regarding the overall value for sponsors, the results show that expedited programs breakthrough therapy designation and Sakigake were perceived to offer the highest value, supported by comments indicating increased communication with agencies and the potential for accelerated development timelines. PRIME received a lower score due to the perception that not all assets are treated with the same urgency as they are with FDA's breakthrough therapy designation. FDA's fast track received the lowest but most consistent scores.[14]

Conclusion

The rapid expansion of the cellular and gene 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 cellular and gene therapies should consider expedited regulatory pathways that offer early engagement with regulators, innovative clinical trial designs, and postmarketing confirmatory studies. Increasing the alignment of international regulatory pathways will be critical in facilitating access to cellular and gene therapies to patients with unmet medical needs globally.

Abbreviations

AE, adverse events; **CC,** confidentiality commitment; **DNA,** deoxyribonucleic acid; **EMA,** European Medicines Agency; **EU,** European Union; **FDA,** [US] Food and Drug Administration; **IPRF,** International Pharmaceutical Regulators Forum, **MoU,** memorandum of understanding; **PRIME,** priority medicines; **PSA,** parallel scientific advice; **RMAT,** regenerative medicine advanced therapy; **RNA,** ribonucleic acid; **US,** United States.

About the author

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References

All references accessed and/or verified on 15 June 2023.

1. Food and Drug Administration. Expedited programs for serious conditions – Drugs and biologics. Current as of 25 June 2020.
2. European Medicines Agency. PRIME: Priority medicines. Last updated 6 June 2023. https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines
3. Ministry of Health, Labour and Welfare [Japan]. Strategy of Sakigake. Dated 17 June 2014. https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/140729-01-01.pdf
4. Food and Drug Administration. Designating an orphan product: Drugs and biological products. Current as of 8 July 2022. https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products
5. European Medicines Agency. Orphan drug designation: Overview. Last updated 8 March 2023. https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview
6. Ministry of Health, Labour and Welfare [Japan]. Overview of orphan drug/medical device designation system. Not dated. https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/orphan_drug.html
7. Drago D, et al. Global regulatory progress in delivering on the promise of gene therapies for unmet medical needs. Mol Ther Methods Clin Dev. Published online 5 April 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8099595/
8. Myshko D. Global expedited review. PharmaVoice. Published online 1 January 2017. https://www.pharmavoice.com/news/2017-1-global-expedited-review/612844/
9. Food and Drug Administration. Rare diseases: Common issues in drug development [guidance]. Current as of 16 April 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-common-issues-drug-development-guidance-industry
10. Kautz N. How to navigate global regulatory frameworks & expedited programs for gene therapy, development in the US, EU, & Japan. Premier Research website. Published online 21 December 2020. https://premier-research.com/blog-how-to-navigate-global-regulatory-frameworks-expedited-programs-for-gene-therapy-development-in-the-u-s-eu-japan/
11. Food and Drug Administration. Cellular & gene therapy guidances. Current as of 6 February 2023. https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances
12. European Medicines Agency. Guidelines relevant for advanced therapy medicinal products. Last updated 2021. https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products
13. Wang Y, et al. Regulatory pathways in EU, the United States, and Japan and health technology assessments for gene therapies. Value & Outcomes Spotlight. 2020;6(6):37-41. https://www.ispor.org/publications/journals/value-outcomes-spotlight/vos-

archives/issue/view/challenges-in-precision-medicine-aiming-to-align-data-value-and-costs/regulatory-pathways-in-EU-the-united-states-and-japan-and-health-technology-assessments-for-gene-therapies

14. Bujar M, et al. The qualitative value of facilitated regulatory pathways in EU, USA, and Japan: Benefits, barriers to utilization, and suggested solutions. Pharm Med. 2021;35:113-122. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7858039/

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