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Navigating Challenges and Best Practices for Regulatory and Clinical Success in Cell and Gene Therapies

Push the Boundaries of Clinical Research with Tigermed

> "Achieving success in cell and gene therapy development requires not only innovation but also a comprehensive strategy that addresses clinical, operational, and regulatory challenges. At Tigermed, we are committed to supporting our clients through this complex landscape to bring life-changing therapies to patients worldwide."
>
> --- Dr. Jiansong Yang, CSO and Head of CGT Business Unit, Tigermed

The cell and gene therapy (CGT) sector is experiencing explosive growth and innovation. In late 2023, the first CRISPR-based gene-editing therapy, **Casgevy**, received FDA approval, signaling a significant advancement in medical science. This momentum continued into 2024 with the FDA's accelerated approval of **Tecelra** in August, the first engineered T-cell therapy for a solid tumor cancer in the U.S.

Globally, over 4,000 CGT therapies are currently in development, with 31 gene therapies and 68 non-genetically modified cell therapies already clinically approved. These advancements offer immense hope for patients but also present complex challenges for sponsors. Navigating these challenges effectively is crucial for achieving regulatory approval and clinical success.

4,000+
over 4,000 CGT therapies are currently in development

31
31 gene therapies already clinically approved

68
68 non-genetically modified cell therapies already clinically approved

The Expanding CGT Pipeline: More Than 4,000 Therapies in Development

Of the 4,000 CGT therapies in development, gene therapies constitute over half of this pipeline, and CAR-T therapies remain predominant among genetically modified cell therapies. Oncology and rare diseases are the most common therapeutic areas, with oncology representing a majority of **54%** in CGT development for rare conditions.

Recent Approvals

The CGT field is rapidly evolving, with several notable therapies approved across different regions, highlighting the global impact of these innovative treatments. These include:

Tecelra (Afamitresgene Autoleucel)

- **Developer**: Adaptimmune Therapeutics
- **Indication**: Unresectable or metastatic synovial sarcoma in adults
- **Approval**: U.S. FDA accelerated approval in August 2024
- **Significance**: Marks the first engineered T-cell therapy for a solid tumor approved in the U.S., offering a new treatment option for synovial sarcoma patients after over a decade.

Casgevy

- **Developer**: CRISPR Therapeutics and Vertex Pharmaceuticals
- **Indication**: First CRISPR-based gene-editing therapy
- **Approval**: Received FDA approval in late 2023
- **Significance**: Represents a milestone in gene-editing therapies, paving the way for future CRISPR-based treatments.

Carvykti (Ciltacabtagene Autoleucel)

- **Developer**: Legend Biotech and Janssen Biotech (a subsidiary of Johnson & Johnson)
- **Indication**: Relapsed or refractory multiple myeloma
- **Approval**:
  - **U.S.** : FDA approval was received in 2022 for patients who have received at least four prior lines of therapy.
  - **China** : Approved by China's National Medical Products Administration (NMPA) in August 2024 for patients who have received at least one prior therapy.
- **Significance**: Carvykti is one of the first CAR-T cell therapies approved for multiple myeloma in the U.S. and China, demonstrating global progress in CAR-T therapy development.

While recent approvals highlight the exciting potential of CGT therapies, the road to regulatory success is still fraught with challenges, especially in manufacturing. These hurdles can slow approvals and keep life-changing treatments from reaching patients as quickly as hoped.

Manufacturing Challenges Continue to Hinder CGT Approvals in 2024

Despite the remarkable advancements, manufacturing remains a significant hurdle for sponsors seeking regulatory approval. The complexity of CGT manufacturing processes, combined with stringent regulatory requirements, often leads to delays, increased costs, and, in some cases, complete response letters from regulatory agencies.

Such is the case for some sponsors seeking approval for their CGT therapies this year. One company received a complete response letter from the FDA requesting additional Chemistry, Manufacturing, and Controls (CMC) information, specifically concerning validation requirements for certain manufacturing and release testing methods. Another company also received a complete response letter this year, with the FDA requesting more CMC information from the drugmaker.

The high cost of manufacturing and commercialization comes from the costs of reagents, Good Manufacturing Practice (GMP) facilities, research and development, and other operational expenses. For example, manufacturing vector-based gene therapies can cost millions of dollars per batch, varying widely depending on the complexity and scale.

Expenses also compound when considering the level of scrutiny paid to CGT therapies by regulators. Sponsors are expected to provide comprehensive safety data and demonstrate the selectivity and efficacy of their investigational therapies. Ongoing concerns regarding the risks of genotoxicity from integrating vectors or gene-editing methods means more testing is required to prove drug safety.

Taken together, the exorbitant price tied to CGT therapies makes regulatory setbacks more costly for sponsors—and places even more pressure on getting it right the first time.

Operational Challenges in CGT Clinical Development

Alongside manufacturing and regulatory hurdles, sponsors face significant operational challenges when conducting clinical trials for CGTs. These challenges can impact timelines, budgets, and, ultimately, the development program's success.

Patient Recruitment and Retention

CGT therapies predominate the rare disease space as an excellent biological solution for genetic conditions. Identifying and enrolling eligible patients for rare diseases and small affected populations is difficult due to the rarity of conditions and strict inclusion criteria. Delays in recruitment can extend trial timelines and compound costs. Further, the target patient population may be geographically dispersed, requiring coordination across multiple sites and regions. This increases logistical complexity and resource requirements on the sponsor.

Complex Protocols and Treatment Regimens

CGTs often involve personalized treatment plans, posing unique challenges due to the need for individualized treatment plans. These therapies often require seamless coordination between manufacturing and clinical teams to ensure patient-specific products are produced, processed, and delivered on time. The complexity of aligning these processes can create logistical hurdles, particularly in managing the production schedule for each patient.

As a result, scheduling conflicts and extended wait times can arise, which may delay treatment and impact patient outcomes. The intricate nature of personalized CGTs means any disruption in manufacturing or coordination can significantly slow down therapy administration, making efficient planning and execution critical for success.

Long Follow-up Periods

Regulatory agencies frequently mandate long-term follow-up for CGT trials to monitor potential delayed adverse events, given the complexity and novel mechanisms of these therapies. This requirement ensures patient safety over time, especially for therapies that involve genetic modification or long-lasting cellular effects.

However, this extended monitoring significantly increases the duration and cost of clinical trials. Sponsors must allocate additional resources for long-term patient tracking, data collection, and regulatory reporting, which can delay the overall development timeline and strain budgets. These factors add complexity to an already challenging clinical trial process.

Regulatory Compliance and Data Management

Regulatory compliance in the CGT space is particularly challenging due to the constantly evolving landscape across different regions. Staying up-to-date with shifting regulations is crucial, as non-compliance can lead to significant setbacks such as trial holds, rejections, or requests for additional data. For sponsors operating globally, navigating these regulatory differences adds complexity to the trial process, increasing the risk of delays.

Ensuring accurate and timely data collection is critical, especially for trials involving complex endpoints and biomarkers. Inconsistencies or delays in data reporting can slow the analysis process and hinder submission timelines, ultimately impacting the trial's progress. Managing these data requirements efficiently is essential to avoid bottlenecks that could jeopardize the overall success of the development program.

Supply Chain and Logistics

Maintaining the integrity of patient-derived materials in CGT development is critical, and it relies on stringent chain-of-custody protocols. Ensuring these materials are correctly tracked from collection to administration is essential to preserve their quality and efficacy. Any breach in these protocols, such as improper handling or documentation errors, can compromise the therapy, potentially endangering patient safety and leading to delays or costly re-manufacturing efforts.

Many CGTs require cold chain logistics to maintain product stability during transportation and storage. Managing these temperature-sensitive therapies adds a layer of complexity, as even slight deviations can lead to product degradation. This raises logistical costs and heightens the risk of therapy failure, making precise cold chain management a critical aspect of CGT development and delivery.

Site Training and Preparedness

Clinical sites are crucial for successfully administering CGTs, but they require specialized training to manage the complex procedures and regulatory requirements unique to these therapies. This need for training can limit the number of qualified sites available, potentially constraining trial execution and impacting patient access to innovative treatments. Operational readiness is vital; sites must have the necessary infrastructure and protocols to accommodate CGT-specific needs. Delays in site activation due to inadequate preparedness can hinder study timelines, making it essential to ensure that clinical sites are both well-trained and operationally equipped to optimize trial efficiency and advance patient care.

Finding the Right Path Forward for CGT Development

Navigating these operational challenges requires meticulous planning, robust systems, and experienced partners who understand the unique demands of CGT clinical trials. Working with a knowledgeable partner can significantly enhance a sponsor's ability to streamline clinical operations and mitigate risks.

Tigermed: Your Partner in CGT Clinical Development

Tigermed offers comprehensive solutions to address the operational complexities of CGT clinical trials.

- Work with an integrated team of experts
- Simplify patient recruitment and retention
- Ensure smooth, budget-friendly clinical trial execution
- Eliminate uncertainties in compliance, data management, and supply chain
- Get your trial sites ready

Work with an integrated team of experts

The Tigermed CGT team is an integrated group of professionals who work collaboratively to provide seamless support across all stages of clinical development, ensuring optimal outcomes.

Simplify patient recruitment and retention

Sponsors have access to an extensive network of over 200 experienced clinical sites with expertise in CGT trials. We provide customized plans to identify and retain patients, leveraging relationships with patient advocacy groups.

Eliminate uncertainties in compliance, data management, and supply chain

Tigermed has expertise in navigating regional regulatory requirements and ensuring compliance. Sponsors can also make use of our robust electronic data capture (EDC) systems and real-time data monitoring. We also have secure systems to track patient materials from collection to administration. This includes end-to-end cold chain logistics management to preserve product integrity.

Ensure smooth, budget-friendly clinical trial execution

Tigermed leverages specialized teams that are proficient in managing intricate CGT protocols. We assist sponsors with proven methodologies to keep trials on schedule and within budget.

Get your trial sites ready

Tigermed has customized training programs and operational readiness assessments to ensure sites meet all necessary requirements before activation.

Whatever your needs, Tigermed offers tailored, integrated services to streamline your clinical trials.

From early development to post-marketing, we provide services like CMC consulting, PK/PD studies, GLP safety studies, medical affairs, biometrics, and laboratory testing.

"Operational excellence is the cornerstone of successful CGT clinical development. At Tigermed, we provide tailored solutions that address the unique operational challenges of CGT trials, enabling our clients to advance their therapies efficiently and effectively."

--- Dr. Jiansong Yang, CSO and Head of CGT Business Unit, Tigermed

Summary

The cell and gene therapy sector is at a pivotal moment, characterized by rapid innovation and significant clinical advancements. Approvals like Casgevy and Tecelra underscore the transformative potential of CGTs and highlight the complexities sponsors face in bringing these therapies to market.

By understanding and addressing operational challenges, adopting best practices, and partnering with experienced CROs like Tigermed, sponsors can navigate the intricate landscape of CGT development more effectively and accelerate the delivery of life-changing therapies to patients.

Want to learn more?

Tigermed has a specialized GLP-1 team that can provide sponsors with tailored and integrated drug development solutions. We have you covered across the full lifecycle from preclinical to Phase IV clinical development.

Click HERE to schedule a meeting with us today, or join us at an in-person event HERE.

References

1. **Adaptimmune Therapeutics Press Release**. "Adaptimmune Receives U.S. FDA Accelerated Approval of Tecelra® (afamitresgene autoleucel)." August 1, 2024.

2. **Legend Biotech Press Release**. "Legend Biotech Announces Approval of Carvykti® (Ciltacabtagene Autoleucel) in China for the Treatment of Relapsed or Refractory Multiple Myeloma." August 27, 2024.

3.**CRISPR Therapeutics and Vertex Pharmaceuticals Press Release**. "CRISPR Therapeutics and Vertex Announce FDA Approval of Casgevy™ (Exagamglogene Autotemcel)." December 2023.