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Whitepaper

# Maximising Investor-Readiness: The Critical Role of Regulatory Affairs Input in Early-Stage Cell and Gene Therapy Development


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# Summary

# Abstract

Cell and Gene Therapies (CGTs) represent some of the most innovative and promising advancements in modern medicine. However, the complexity of their development, combined with an evolving regulatory environment, presents significant challenges. For developers seeking investment for their product development, early and informed regulatory input is crucial to mitigating risks and increasing confidence in the product's pathway to market.

This white paper highlights the critical role of regulatory affairs in the early stages of CGT development, focusing on how a robust regulatory strategy can be a powerful tool for securing investment. Key areas explored include the value of integrating regulatory planning into investor pitches, the importance of demonstrating a clear regulatory pathway, and the role of consultants specialised in CGTs. These insights underscore how early regulatory input, when leveraged effectively, can reduce uncertainty and enhance the attractiveness of a CGT development project to investors.

# Introduction

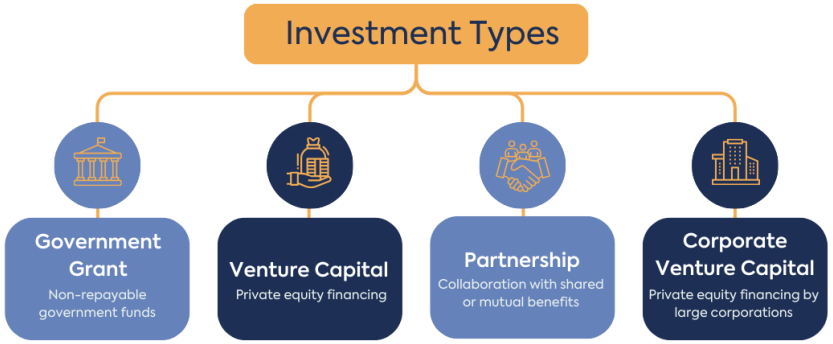
Cell and Gene Therapies (CGTs) promise to revolutionise the treatment of previously untreatable diseases. To date, approximately 40 cellular and gene therapies have been approved in the US [1], and in the EU, approximately 25 Advanced Therapy Medicinal Products (ATMPs) have been approved [2,3]. This is set to increase based on the number of medicines in clinical development, with over 300 and 900 clinical trials ongoing across all Phases in the EU and US, respectively [4].

However, CGTs' groundbreaking potential come with unique regulatory hurdles due to their novel mechanisms of action, long-term safety concerns, and ethical considerations. This complexity combined with high development costs can create significant uncertainty for investors, making a sound regulatory strategy indispensable in early-stage development.

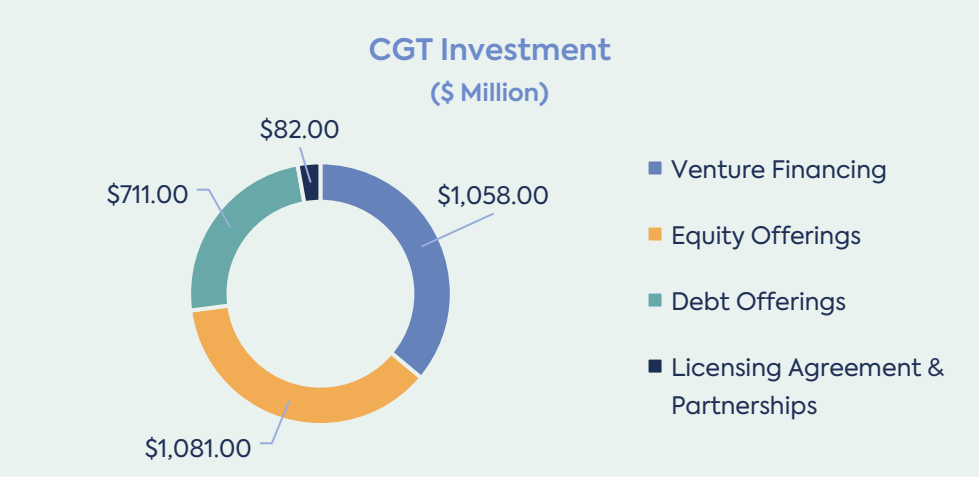
The regulatory environment for CGTs is fast evolving, as agencies like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) work to keep pace with these innovations. Developers must show potential investors they have a thorough understanding of their product and a robust plan to navigate the ever-changing regulatory and commercial landscape, ultimately sharing the strategy for return on investment. This whitepaper focuses on the importance of regulatory input in the preliminary stages of product development of CGTs to strengthen the pitch to potential investors.

# Regulatory Strategy For CGTs as a Tool to Secure Investment

Opportunities to raise capital for research and development (R&D), early phase non-clinical and clinical studies are typically through government grants, venture capital (VC), corporate venture capital (CVC) and partnerships with startups, research institutions and pharmaceutical companies.




In Q3 2024, there was a $2.9 billion investment in CGTs, of which approximately $1 billion was through venture financing. This is an increase from the $662 million venture financing in the same quarter of 2023. Importantly, the total investment from Q1 to Q3 of 2024 is higher than the total 2023 sector investment, $14.2 and $11.7 billion, respectively.




(Source: https://alliancerm.org/data/ Q3 2024 data)

As CGTs are more complex and have fewer regulatory and commercial precedents than traditional medicinal products they could present a riskier investment, therefore having a well-defined plan to address the unique regulatory and commercial requirements specific to advanced therapies is crucial. A strong investment pitch should clearly outline a well-defined route to market, and should include a regulatory roadmap and commercial strategy, along with mitigation plans for risks associated with clinical and regulatory delays.

It is important to highlight the market opportunity by addressing the unmet medical need the medicinal product will fulfil, timings for early engagement with regulatory agencies to minimise development risks and plans to leverage from regulatory designations and fast-to-market registration routes for early access to patients.

## Market Opportunity

In recent years, we have seen the development and approvals of groundbreaking CGTs addressing unmet medical needs by targeting cancers, rare diseases and genetic disorders. Such as the recent FDA approval of Kebilidi® for aromatic L amino acid decarboxylase (AADC) deficiency, a rare genetic disorder affecting the nervous system and EMA approval of Durveqtix® for severe haemophilia B a rare genetic blood clotting disorder.

A good investment pitch will cover the patient need, market size, and strategy for commercialisation. Investors will be looking to understand the landscape of medicinal products within the target indication and population, such as the existence or lack of alternative treatments, as well the level of potential benefit the new medicinal product offers compared to existing treatment.

The definition of an unmet medical need is generally similar across regions. For example, in the EU, unmet medical need is defined in Article 4, paragraph 2 of EU Regulation 507/2006 as '*a condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected*'[5]. In the US, according to the Guidance for Industry – Expedited Programs for Serious Conditions it is defined as *'a condition whose treatment or diagnosis is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs)'*[6].

By conducting thorough market research and identifying potential competitors, developers can highlight the innovative aspects of their products and present their unique value proposition. This is further strengthened, by engaging in early dialogue with regulatory agencies to determine if their medicinal product has the potential to address an unmet medical need.

## Early Engagement with Regulatory Agencies

Like traditional medicines, early engagement with regulatory agencies is beneficial for advancing and de-risking the development of CGTs. For these innovative products, early interactions are especially important as they allow developers, who are often Small to Medium Enterprises (SMEs), to discuss early development topics and introduce new technologies unique to their medicinal product, which are in some cases not in scope or clearly covered in regulations and guidelines. Agencies can provide guidance and clarity on their expectations from a non-clinical, clinical and quality perspective. They can also provide advice on regulatory topics and the legal basis for the marketing authorisation application (MAA).

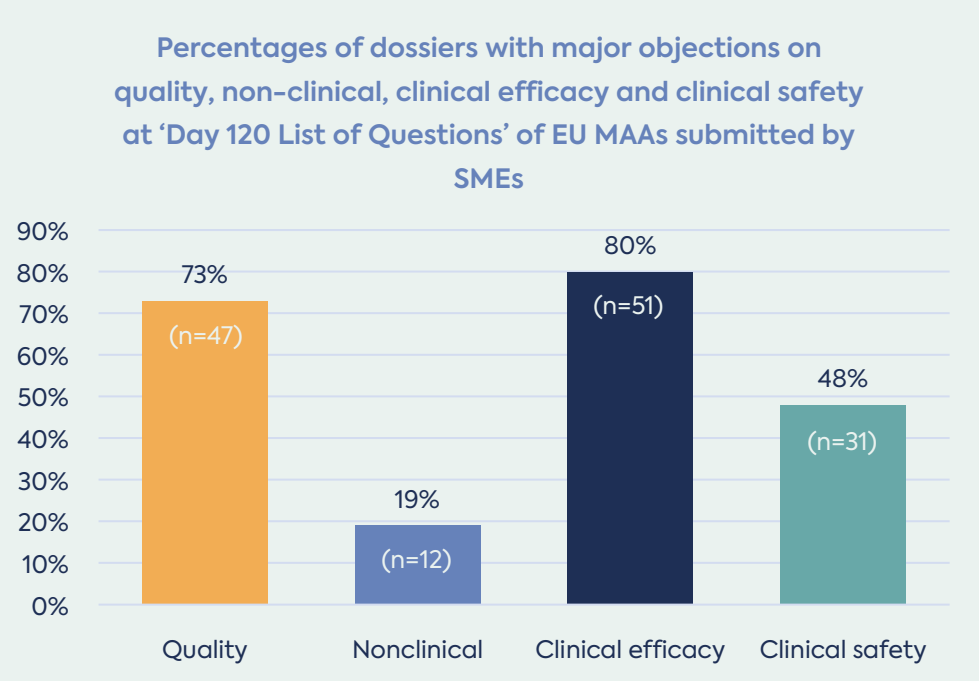
Agencies such as the EMA, the Medicines and Healthcare Products Regulatory Agency (MHRA) and the US FDA offer early interaction opportunities to developers. The EMA Innovation Task Force offers very early dialogue between the agency and developers of innovative medicines and novel technologies, an opportunity to discuss scientific, technical and regulatory topics. The MHRA offers a similar forum for early dialogue through the Innovation Office. The US FDA INTERACT (INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs) is a forum for early dialogue before the pre-IND meeting between sponsors and the FDA Center for Biologics Evaluation and Research (CBER) or Center for Drug Evaluation and Research (CDER) on innovative medicinal products to discuss how to approach

non-clinical, clinical and quality product development for novel medicines. These early interactions are free of charge.

| Region | Agency Meeting | Eligibility |
|---|---|---|
| EU | Innovation Task Force | No prerequisite |
| UK | Innovation Office | No prerequisite |
| US | INTERACT | Preliminary non-clinical proof-of-concept data with the intended clinical product is required. |

As developers progress through their product development, they may also seek Scientific Advice from the Agencies at specific development milestones, such as prior to commencing and/or after the completion of clinical studies. The EMA also offers the opportunity to request Advanced Therapies Medicinal Product (ATMP) classifications to confirm if a product is an ATMP according to the EU definition in Article 2 of Regulation (EC) No 1394/2007, this can offer benefits such as eligibility for PRIME and expedited marketing authorisation assessment (see 'Regulatory Designations and Fast-to-market Registration Pathways for CGTs'). It is also possible to request ATMP certification in which the EMA conducts an early evaluation of product quality and non-clinical data, this is available to SMEs only and can help developers address gaps before filing a marketing authorisation application.

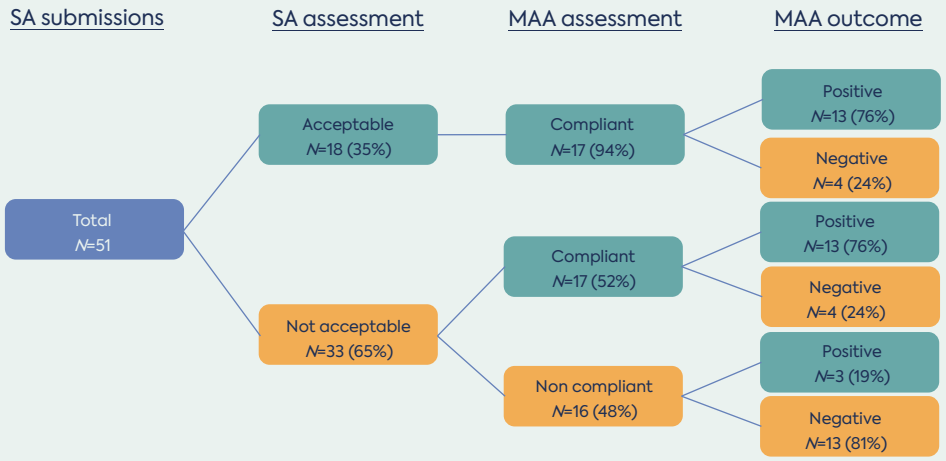
An analysis of MAAs submitted by SMEs between 2011 and 2015, showed major objections in clinical efficacy, clinical safety and quality were observed in 80%, 48% and 73% applications, respectively [7]. Common quality major objections seen in MAAs submitted by SMEs are related to issues with manufacturing process development and validation, characterisation data of drug substance and drug product, batch-to-batch inconsistencies and GMP compliance [8]. Major objections seen in clinical efficacy are related to the robustness of the pivotal study, selected population and validity of endpoint measurement [7].




*(Source Amaouche et al. 2018)*

Engaging early with regulatory agencies is a strategic advantage for CGT developers, as it allows the identification and management of potential risks and increases the probability of a positive MAA outcome. A focussed analysis by Hofer et al. (2018), of 51 orphan products that received scientific advice (protocol assistance) before MAA during 2008 and 2013, showed that almost 80% of those who obtained and followed scientific advice received a positive opinion compared to 19% of those who did not follow scientific advice.

**The use of scientific advice and MAA outcome; based on the analysis of the evolution of clinical trial designs from the scientific advice request to MAA outcome**




*(Source Hofer et al. 2018)*

Established lines of communication with regulators and early scientific advice can increase investor confidence by ensuring alignment on clinical trial design, quality control and safety endpoints.

## Regulatory Designations and Fast-to-market Registration Pathways for CGTs

As CGTs tend to address areas of unmet medical need, there is scope to leverage from regulatory designations and expedited assessment pathways. Products targeting rare diseases may be eligible for Orphan Drug status (see whitepaper on 'How to Successfully Apply for Orphan Designation in the EU and How to Maintain It'[11]). CGTs may also be eligible for designations such as Regenerative Medicine Advanced Therapy (RMAT), Breakthrough and Fast-track designations in the U.S., Priority Medicines (PRIME) in the EU and the Innovative Licensing and Access Pathway (ILAP) in the UK. These regions also offer expedited registration routes such as accelerated assessment and priority review in the EU/UK and US respectively, and opportunities to file a new drug application when comprehensive clinical data is not yet available at the time of filing, through conditional marketing authorisations and accelerated assessment in the EU/UK and US, respectively.

### *Designations:*

| | | |
|---|---|---|
| **EU** | **PRIME** | Enables early and enhanced scientific and regulatory support from agencies, including the EMA and Health Technology Assessment (HTA) organisations. |
| **UK** | **ILAP** | Allows for collaboration with the MHRA and HTAs, and accelerated time-to-market, to facilitate patient access to medicines. |
| **US** | **RMAT** | Allows for early FDA engagement, expedited development and reviews, restricted to regenerative medicines, including cell and gene therapies. |
| **US** | **Breakthrough** | Intended for medicinal products that demonstrate substantial improvement over available therapies. |
| **US** | **Fast-Track** | Allows for expedited reviews and frequent agency meetings/rolling review. |

RMAT and Breakthrough designations have similar benefits such as frequent Agency interactions, eligibility for priority review and accelerated approval. The main difference is that RMAT is specific to advanced therapies, and that a developer does not need to demonstrate substantial improvement on clinical endpoints over available treatment, as would be needed for Breakthrough designation.

*Expedited Registration Pathways:*

| | | |
|---|---|---|
| EU/UK | Accelerated Assessment | Expedited review process for medicinal products expected to be of major public health interest, particularly therapeutic innovation. |
| EU/UK | Conditional Market Authorisation | Approval of a medicinal product based on less-comprehensive data, with the commitment to conduct confirmatory studies. |
| EU/UK | Authorisation Under exceptional circumstances | Approval of a medicinal product where it is not possible to provide comprehensive data as little data exists or is difficult to obtain, such as rare diseases. |
| US | Priority Review | Expedited review process in comparison to the standard review. |
| US | Accelerated Approval | Approval of a medicinal product based on surrogate endpoint in a clinical trial, with the commitment to conduct confirmatory studies. |

These designations and registration pathways enhance market potential, offering additional years of market exclusivity and making them highly attractive to investors. A roadmap from the non-clinical phase through to regulatory filing, highlighting key development milestones, timings of agency interactions, designation applications and health technology assessments, will provide investors with an overview of the expected timelines for their return on investment.

### Market Access for CGTs

CGTs face unique market access challenges, including high up-front prices for one-off, potentially curative treatment compared to traditional medicines, where cost is spread over years for chronic treatment. Manufacturing costs are often high and long-term efficacy and safety profiles difficult to predict. Performing a health technology assessment (HTA), engaging patient advocacy groups and getting the payer perspective will help understand the market dynamics and demonstrate the economic value of the product developed.

Identifying potential barriers to market access and reimbursement early in development allows for the proactive development of mitigation strategies to address these risks. A developer who can present a clear strategy for market access, including payer engagement, reimbursement models, and evidence of cost-effectiveness, will be more likely to attract investment.

The EU HTA Regulation (EU Regulation 2021/2282) was adopted in 2021 to harmonise the clinical evaluation of health technologies across member states (MS) and improve efficiency by reducing the duplication of assessment across HTA bodies. The regulation is coming into effect in January 2025 and advanced therapies will be subject to Joint Clinical Assessment (JCA) at the time of MAA filing, see blog on 'HTA Regulation: Cross-functional Collaboration to Target Success'[12].

## Clinical and Technical Challenges During CGT Development

Investors need to see how developers plan to mitigate risks associated with clinical development, product quality, and commercial-scale manufacturing to demonstrate the product is ultimately commercially viable.

### Clinical Development Complexity

The clinical development complexity of CGTs often lies in the requirement of clinical trial designs with innovative endpoints to demonstrate safety and efficacy, and the long-term follow-up due to potential delayed adverse effects, as outlined in the EMA Draft Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products. A comprehensive design and implementation plan for these studies, together with long-term follow-up

obligations, is critical for building investor confidence in understanding financial costs for the lifetime of the product. Investors need clear timelines for clinical development and regulatory submissions in a pitch deck, which can be more challenging than traditional products. Showing investors how these timelines will be managed and the potential for interim approvals or early access programs can strengthen their confidence in your project.

Preclinical to clinical transition can also be a challenging process. Regulatory agencies often require specific safety studies due to the novel nature of these products. Patient and environmental safety is of high concern for gene- and cell-based therapies. Agency feedback on data requirements can be sought through scientific advice, which ensures that the study design and objectives support efficacy and safety claims. It also helps avoid unnecessary studies, which can be unethical for medicines intended for rare diseases and/or cancer.

### Manufacturing and Scalability

Manufacturing and scalability considerations should also be part of the pitch deck: CGTs often require complex manufacturing processes, and regulatory agencies require detailed validation of these processes. Investors will want to see that the developer has accounted for regulatory hurdles related to manufacturing scalability and quality controls. A regulatory strategy outlining these considerations provides greater predictability in development timelines and outcomes and, therefore, reduces the risk of product failure and financial wastage.

### Product Supply Chain

The supply chain for CGTs can be complex and commercial considerations need to be assessed in the early to mid-phases of product development. Developers need to plan the sourcing of raw materials, product transportation including cold-chain management, and the documentation for distribution, whilst maintaining a chain of custody (COC) and chain of identity (COI), ensuring the product reaches the intended patient for treatment.

The transportation of CGTs can be quite costly due to their sensitivity to environmental conditions and the need to reach patients on time. Cold chain management is often required as CGTs typically need to be stored and transported at temperatures between -80°C to +4°C to maintain their quality. A monitoring system and contingency plan for potential disruption in the cold chain is essential to ensure that all Qualified Person (QP) released batches make it to the patient; therefore, having a good partnership with specialised distributors that follow Good Distribution Practice (GDP) can support readiness for clinical trial and commercial operation.

Companies must ensure compliance with local and international regulations governing the shipment of biological products, such as obtaining necessary permits and adhering to specific packaging and labelling standards. Ensuring compliance with GMP and other regulatory standards requires extensive documentation throughout the supply chain. This includes maintaining records of raw material sourcing, manufacturing processes, and distribution logistics.

## The Role of Regulatory Input in CGT Development for Investor-readiness

Early regulatory input is valuable to navigate the evolving and highly complex regulatory frameworks of CGTs. Regulatory requirements can vary across regions and shift as new scientific data emerges; therefore, having the support of regulatory consultants who specialise in CGTs during product development can help de-risk the overall regulatory strategy and increase the probability of regulatory success. CGTs often require intricate manufacturing processes, which must meet stringent regulatory requirements; experienced consultants in Chemistry Manufacturing and Controls (CMC) can guide developers through gap analysis against relevant national, regional and international regulations, ensuring compliance with Good Manufacturing Practices (GMP), which is critical for regulatory approval.

Overall, consultants can guide and support developers with agency interactions, designation requests, expedited approval applications, and pre-empt risks based on precedent experience. Support models can be flexible, ad hoc, or more integrated/embedded, ensuring developers receive tailored expertise as required.

## Conclusion

The cutting-edge science and ever-evolving regulatory landscape of CGTs make early and continuous regulatory input not only important but essential.

For developers seeking to attract investment, the aim is to show a robust plan for advancing the medicinal product from the laboratory to patients. The proposal to potential investors should demonstrate regulatory foresight and outline plans to navigate development risks. Therefore, including regulatory consultants in the very early development phase and in the preparation for investor presentations will help strengthen the proposal to investors.

DLRC has supported several cell and gene therapy developers and SMEs and has extensive experience with agency and HTA interactions in the EU, UK and US. As a chosen partner, DLRC can support your regulatory strategy and readiness for investor presentations.

## About DLRC

DLRC is an award-winning consultancy team of more than 80 highly qualified, experienced regulatory professionals operating from our offices in the UK, Germany, and US. With a deep commitment to excellence, we are dedicated to helping clients navigate the complex regulatory landscape of the life science industry. We develop and execute innovative phase-appropriate regulatory strategies, providing comprehensive support from early development to post-licensing activities for medicinal products and medical devices. Our team comprises consultant experts in nonclinical, CMC, clinical and MedTech from pharmaceutical, medical device and regulatory agency backgrounds. We have proudly served companies of all sizes and backgrounds in various regulatory jurisdictions.

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