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5 Key Challenges in the Development of Cell & Gene Therapy

We see the headlines every day, the loss or delay of a promising cell or gene therapy (CAGT) because the technology was not executed correctly, the study was not fully thought through, the patient population was not defined precisely enough, or funding ended because needs were not fully understood. "They should have known better" is the first thing that people often think.

Frequently, the excitement of creating the next cure for a rare disease or the idea of evolving treatment options was the driver for the development of new CAGT products. There was an unmet need, but the program lacked the correct support to enable the treatment.

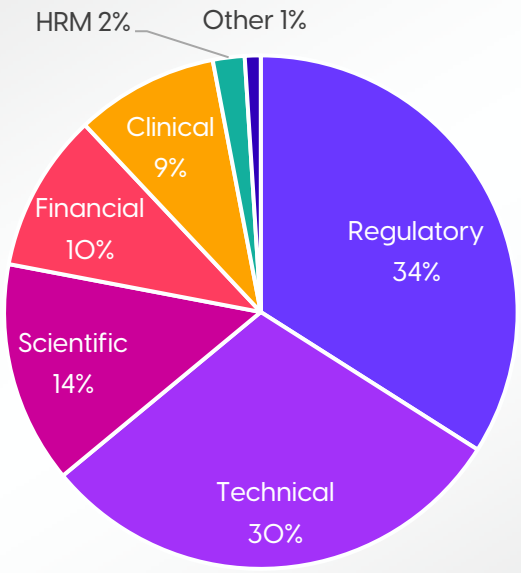
To help you on your road towards a regulatory sound and successful CAGT program, it's important to consider the top reasons for failure, so you can better prepare. **According to research, 97% of product failures fall into five categories:**

1. Regulatory
2. Technical
3. Scientific
4. Financial
5. Clinical

Let's explore each in more detail and discuss how organizations can improve chances for approval and marketing of their CAGT product.

Reported Challenges

Survey of 271 CAGT/ATMP developers



Mol Ther Methods Clin Dev, 2018 Oct 11;11:121-130
Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe; Renske M.T. ten Ham, Jarno Hoekman, Anke M. Hövels, Andre W. Broekmans, Hubert G.M. Leufkens, and Olaf H. Klungel; Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University

Given their impressive therapeutic potential, the development of Cell and Gene Therapy (CAGT) products, also known as Advanced Medicinal Therapy Products (ATMPs), is an extremely exciting endeavor but has also been shown to be challenging. The manufacturing of these innovative products is complex and expensive. Clinical development generally involves rare conditions, where establishing benefit/risk will likely be based only on a low number of patients, and developers should have a good understanding of the regulatory and data requirements for approval. In addition, the expectations from payers on data quality are very high, as these products aim for reimbursement at a very high price. Financing these high cost/high risk projects is an additional difficulty, mainly for start-up and small biotechnology companies.

Regulatory Hurdles

Regulators have the responsibility to scientifically review and approve the use of medicinal products, and this is a big challenge for CAGT products as a rush to cover high unmet needs generally exists. In this respect, approval is often pursued before data on long-term efficacy is available and the safety characterization is complete. Consequently, regulators need to make decisions on benefit/risk based on limited information. Agencies have published multiple guidelines, however these provide only a general framework, as there are no "one size fits all" nonclinical and clinical development programs. Sponsors are encouraged by regulators to seek regulatory advice when starting to work towards the first-in-human (FIH) data packages, and indeed agencies have created different programs to meet with developers and provide scientific advice.

To support sponsors on this journey, ProPharma has built the Cell and Gene Therapy Center of Excellence, which includes a multidisciplinary scientific team of regulatory consultants, with strong nonclinical, CMC, and clinical backgrounds and extensive experience in the development of CAGT products. The team can guide you to customize and accelerate your development plan with consideration of the state of the art for similar products, either approved or under development. At ProPharma we consider that early and continued communication between sponsors and regulatory agencies is key for successful CAGT product development. Therefore, our experts can facilitate any type of interaction with global regulatory agencies, including INTERACT, ITF, PRIME, Breakthrough Therapy designation, and pre-IND or general Scientific Advice meetings.

Manufacturing Challenges

For CAGT products, the commonly complex manufacturing often requires a high degree of customization. Assuring high quality of the starting materials, developing a process with high consistency and efficacy, identifying critical quality attributes, designing and validating a suitable potency assay, or choosing the proper release specification margins are only some of the many aspects that manufacturers need to address. A key parameter is demonstrating comparability among the different batches used during development. Such batches are generally produced using a manufacturing process that has been developed in parallel to the non-clinical and clinical studies, and often required major changes, mainly to allow scalability. Other challenges faced for the manufacturing of autologous products pertain to the high heterogeneity of the patient´s starting material, the control of single patient product batches and the urgency of the manufacture (ideally with vein-to-vein times of 2-3 weeks). These aspects pose additional challenges to the manufacturing process of autologous products, where there is only one chance to succeed in creating the patient´s specific product.

Our experts at the Cell and Gene Therapy Center of Excellence can support CMC development covering multiple aspects as required by developers (both industry and academia) or manufacturers (CDMOs or hospitals). Among others, we have thorough expertise in process development (viral vectors and cell-based therapies), process validation, analytical method validation, design and qualification of manufacturing devices, and preparation and review of CMC modules.

Additionally, ProPharma offers full planning to design new manufacturing sites and ensure that the site is licensed to legally manufacture products to treat patients. Our process modeling team has developed validated methodologies which provide the confidence that manufacturing challenges can be overcome with GMP and ISO standards compliant solutions. ProPharma has worked with multiple hospitals and research institutions to develop qualified spaces for effective CAGT manufacturing, which included collaborating with all the major equipment suppliers in multiple roles from equipment design, production, to qualification and validation. Moreover, we have a thorough expertise in auditing different types of GMP facilities for all relevant quality and regulatory standards.

Clinical Challenges

A major challenge for the clinical development of CAGT products is that a positive benefit-risk ratio should be demonstrated based on limited data from a small group of patients, often less than a hundred.

Critical issues that should be considered for the successful completion of CAGT clinical trials include:

- Identifying the correct patient population, assuring consistency within these often-small patient populations and, where not possible, understand the heterogeneity of the sample (i.e.: genetic profile, severity of the disease, natural history, etc.);
- Selecting efficacy endpoints with demonstrated clinical value that support early access to the patients and reimbursement. In this light, Patient Reported Outcomes (PROs) are expected to be the subject of extensive discussion among regulators and Health Technology Assessment (HTA) bodies;
- In-depth safety monitoring, timely signal detection and development of management guidance for eventual new toxicities, as it is well known that CAGT products may have serious side effects both in the acute and long-term settings.

At ProPharma´s Cell and Gene Therapy Center of Excellence, we can design and support the most innovative designs for the successful clinical development in bespoke populations, including natural history studies, synthetic control arms, virtual models or long-term follow-up studies, as well as the corresponding statistical analyses plans. With our extensive experience in a broad range of therapeutic areas, including rare diseases, we support protocol design (including selection of efficacy outcomes), perform outreach and identification of patients, and conduct timely detection of inclusion limiting factors. Additionally, as ProPharma strongly believes in the power of Real-World Data (RWD) to support the lifecycle of CAGT products, our team is ready and capable to collect, analyze and discuss this data. Moreover, we have digital solutions to enable decentralized models of clinical trials.

Market Access

Beyond regulatory approval, when a company has launched a new product, pricing and reimbursement needs to be established and is the next major hurdle to cross for CAGT products to be accessible to patients. Market access is about getting the right treatment for the right patient at the right time, and at the right price. The price of a product comes from an agreement, very often negotiated, between manufacturers and payers. Payers make the final decisions on what drugs they will cover. A part of this process is reimbursement. Reimbursement relies on demonstrated clinical and economic benefits compared to already available therapies. HTA bodies are responsible for assessing the medicinal product's clinical effectiveness, cost-effectiveness, relative efficacy and budget impact. Demonstrating clinical and cost-effectiveness for CAGT products is very challenging, as high short-term costs combined with limited efficacy and effectiveness data creates uncertain cost-effectiveness and, consequently, heterogeneity in requirements as set by the HTA bodies. For the Marketing Authorization Holder (MAH), the ideal outcome after regulatory approval is to achieve the optimal price with maximum reimbursement for the approved target population. However, in reality there is always a trade-off between price and reimbursement level, target and selected patient population, and prescription and funding procedures.

Interestingly, regulators and HTA bodies now offer joint scientific advice to pharmaceutical and biotechnology companies to aid them in designing their clinical programs to maximize their CAGT products' possibilities for reimbursement. In Europe, this advice is provided in the context of the new EU Regulation (EU) 2021/2282 on HTA (HTAR), which came into force in January 2022 and is applicable as of January 2025.

ProPharma´s Cell and Gene Therapy Center of Excellence has the capabilities to support the CAGT product developer to access markets within Europe and the United States by understanding and addressing these hurdles. An overview of the different payment schemes, stakeholders, and historical agreements within this therapeutic area can be provided. Our team also has the capabilities to provide HTA writing support and dossier preparations for local reimbursement applications. We follow closely the HTA bodies' development of the health economic modeling and clinical evidence requirements within CAGT and can assist with the latest analytical updates within this area.

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Market Access, Cont'd.

Moreover, our Cell and Gene Therapy Center of Excellence is a unique partner to support early engagement with HTA bodies since our teams of clinical regulatory experts and market access specialists closely collaborate to help you streamline the development and launch of new therapies. We strongly support the concept that to accelerate patients' access to innovative CAGT products, a full alignment of the expectations from all stakeholders, including patients, clinicians, the pharmaceutical and biotechnology industry, regulators, HTA bodies, and payers, is required.

Financial Aspects

The financial aspect of the development of CAGT products presents a major hurdle, mainly because the production costs are very high. This is related to the aseptic manufacturing process, expensive raw materials, extensive supply chain, treatment characterization, comparability studies and multitudes of tests to demonstrate safety, efficacy, and sterility. Clients while in the early development phase of their product often ask us to help them create a financial plan which they can bring to investors to show when funding is required, how much funding is needed and what the benefit of the funding is. Specific questions will include when to invest in infrastructure versus investing in analytics, or other key packages.

Our understanding of the regulatory expectations, their associated processing costs, and timelines for results along with the 168 other work packages provide a listing of required initial studies, their associated financial burden and the decisions that the studies support as well as which answers signal which funding to release. Indeed, funding is critical to bringing products to patients who need them, and developers do not want to go back to investors for another funding round without demonstrating that initial investments demonstrated the respective value. Our Cell and Gene Therapy Center of Excellence works with you to ensure funding requirements are understood, utilized efficiently and results oriented. Based on our thorough understanding of the global CAGT landscape, our experience in supporting early development of these products plus our knowledge of lifecycle management in multiple therapeutic areas, ProPharma can help you develop a business plan which outlines the key milestones including funding requirements, value propositions, endpoints and next steps to take your product from benchtop to bedside.

In Conclusion

Overall, developing new CAGT products and placing them in the market to provide benefits to patients in need is an exciting but very challenging endeavor. At ProPharma´s Cell and Gene Therapy Center of Excellence we fully understand the many hurdles behind these developmental programs, and we partner with innovators to collaboratively solve strategic, scientific, and operational challenges during development. Our Research Consulting Organization (RCO) model acts as the umbrella providing deep scientific and technical expertise ensuring that as CAGT programs move forward, they are well supported and expertly advised enabling success against whatever challenge they face.

Partner with ProPharma's Cell and Gene Therapy Center of Excellence

If you are looking for a trusted partner who can develop the strategy, identify risks, and implement effective solutions for your livesaving therapy, ProPharma's Cell and Gene Therapy Center of Excellence is here to help. Our team of experts has the knowledge and experience to seamlessly integrate with your organization and provide ongoing support to ensure your success.

Contact us today to learn more about how we can help you streamline your development process and achieve your goals..

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