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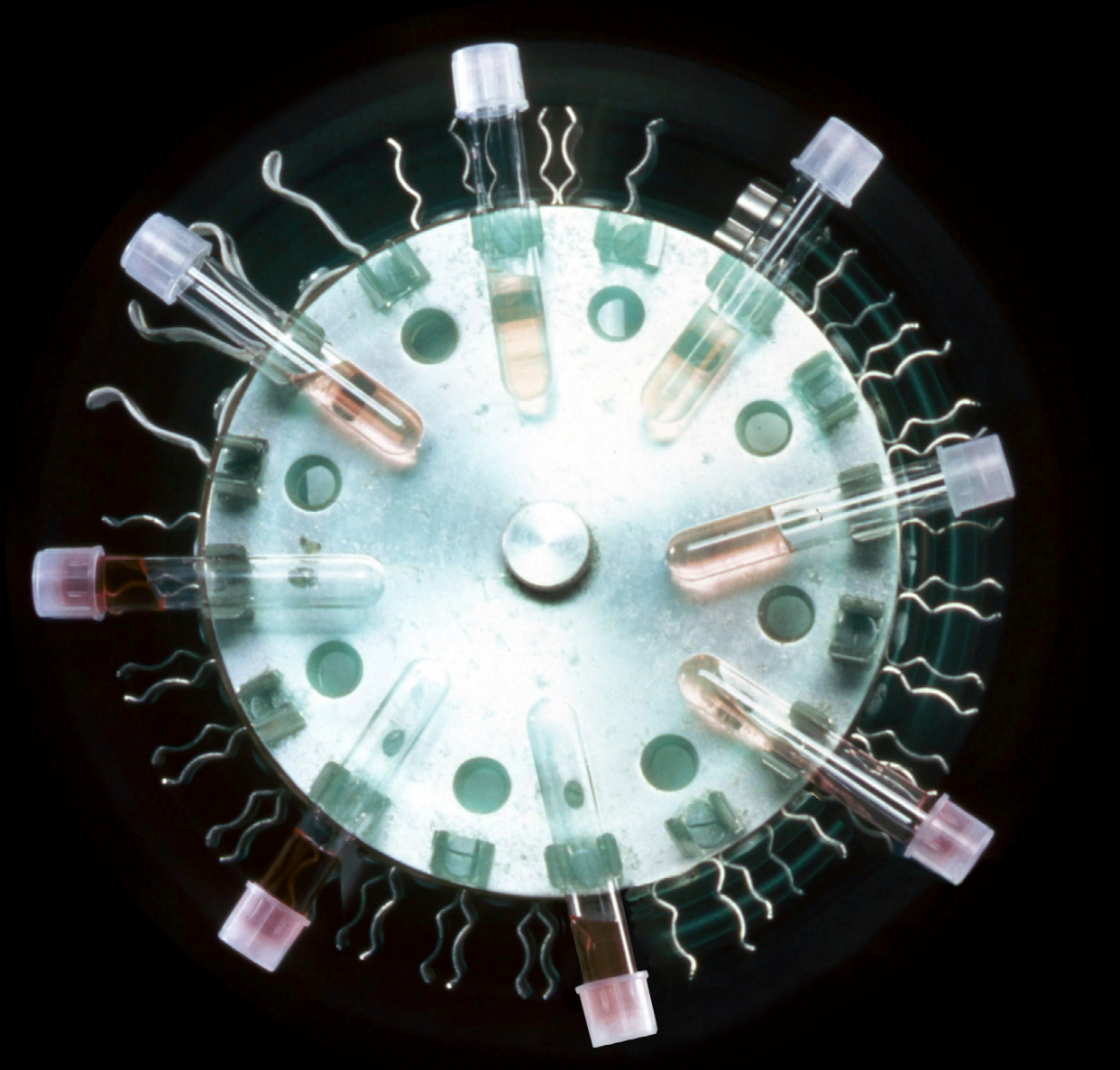


Advancing advanced therapies

A Belgian Recipe for an Innovative Ecosystem

MAKING AN IMPACT THAT MATTERS since 1845

October 2024

Our three key takeaways

1

Rapid pace of scientific innovation drives broader utilization for advanced therapies (beyond rare diseases) and higher feasibility to adopt in clinical practice (reducing COGS to improve affordability)

2

Yet, an advanced therapy ecosystem with the right level of funding and maturity across the value chain (e.g., manufacturing, logistics, talent, etc.) is a must for patient access and outcomes (i.e., enabling quality and performance of advanced therapies at commercial scale).

3

Belgium has all the right ingredients to tackle the challenges in the supply chain and establish itself as the biomanufacturing gateway to Europe, building on specialized logistics, multi-disciplinary academic centres, access to biomanufacturing infrastructure, novel funding schemes and innovative healthcare system in the heart of Europe

Contents

Advanced therapies are growing in potential and complexity

The growing importance of advanced therapies lies in their potential to revolutionise the treatment of underlying cause of diseases that have been historically challenging to address. These innovative therapies – including gene therapy, cell therapy, and tissue engineered therapy – offer the prospect of targeting diseases at a molecular level, leading to more personalised mechanism of action, with a better safety and effectiveness profile. Furthermore, the availability of personalized diagnostics, thanks to improved affordability, supports the integration of these innovative therapies in the clinical workflow, driving improved patient outcomes.

Advanced therapies in a broad term means innovative biologics (such as antibody-drug conjugate or radioligand therapies), upcoming generation of vaccines using new delivery method, and advanced therapy medicinal product (ATMP which includes cell therapy, gene therapy, and tissue engineering product). For the later, the potential is lifesaving (i.e., gene therapy can cure rather than treating the patient) and the economic upside is very promising (Deloitte 2024, return on pharmaceutical innovation[1]).

The sources of innovation for advanced therapies stem from a diverse range of scientific and technological advancements. These include breakthroughs in genetic engineering, such as gene editing techniques like CRISPR-Cas9, which enable the modification of genetic material with a potential for several medical applications (e.g., hemoglobinopathies, chronic infections, chronic inflammatory conditions).

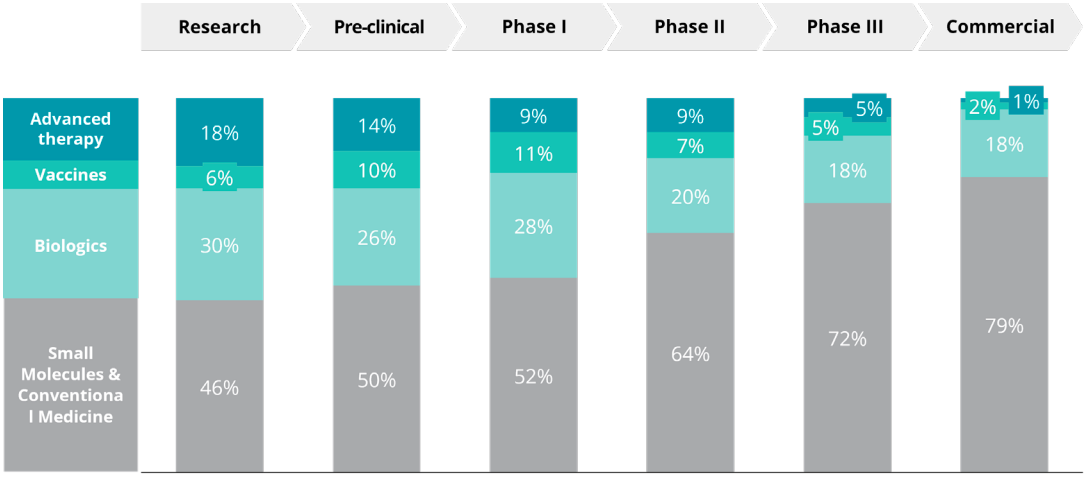
The field of cell therapy, including the use of stem cells and engineered T-cells, has provided novel avenues for treating previously incurable conditions.

And advancements in bioprocessing, biomaterials, regenerative medicine, and bioinformatics have also contributed to the evolution of advanced therapies, offering new possibilities for addressing unmet medical needs.

This diversity of innovation underscores the multidisciplinary nature of these therapies, from genetics, cell biology, immunology, and bioengineering to foster the development of transformative therapies.

The increasing investment and research focussed on these advanced therapies highlight their potential to drive substantial advancements in the pharmaceutical and biotechnology sectors, ultimately introducing paradigm shifts in medicine (figure 1).

Figure 1: Advanced therapies are driving innovation in the pharmaceutical sector[4].



Current market is in majority small molecule products with a growing contribution of biologics.

Considering the total pipeline from discovery, and taking attrition into account, we foresee a future where **small molecules will remain important**, but life saving **innovation will come from next generation biologics** and **advanced therapies.**

Demystifying advanced therapies: European Medicines Agency (EMA) definitions and basic concepts.

Innovation and complexity in advanced therapies comes from the combination of starting material, type of modification and delivery method or platform (figure 2) which allows us to better understand different advanced therapy types and adjacent therapies, such as radioligand therapy and mRNA vaccines (figure 3).

Advanced therapies are medicinal products based on genes, cells, or tissue engineering. They can be classified into three main types according to the European Medicines Agency[2]:

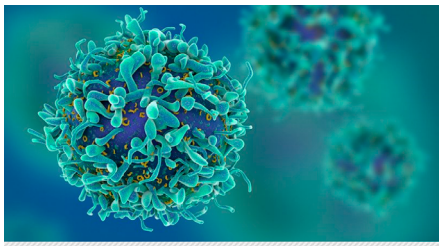
1. Gene therapy medicines contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They function by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from diff erent sources.

2. Somatic-cell therapy medicines contain cells or tissues that have been manipulated to change their biological characteristics, or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose, or prevent diseases.

3. Tissue-engineered medicines contain cells or tissues that have been modified so they can be used to repair, regenerate, or replace human tissue.

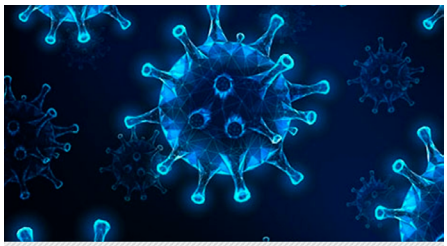
In addition, so-called combined advanced therapies may contain one or more medical devices as an integral part of the medicine. An example is cells embedded in a biodegradable matrix or scaffold.

Figure 2: Simplifying advanced therapies into basic concepts.



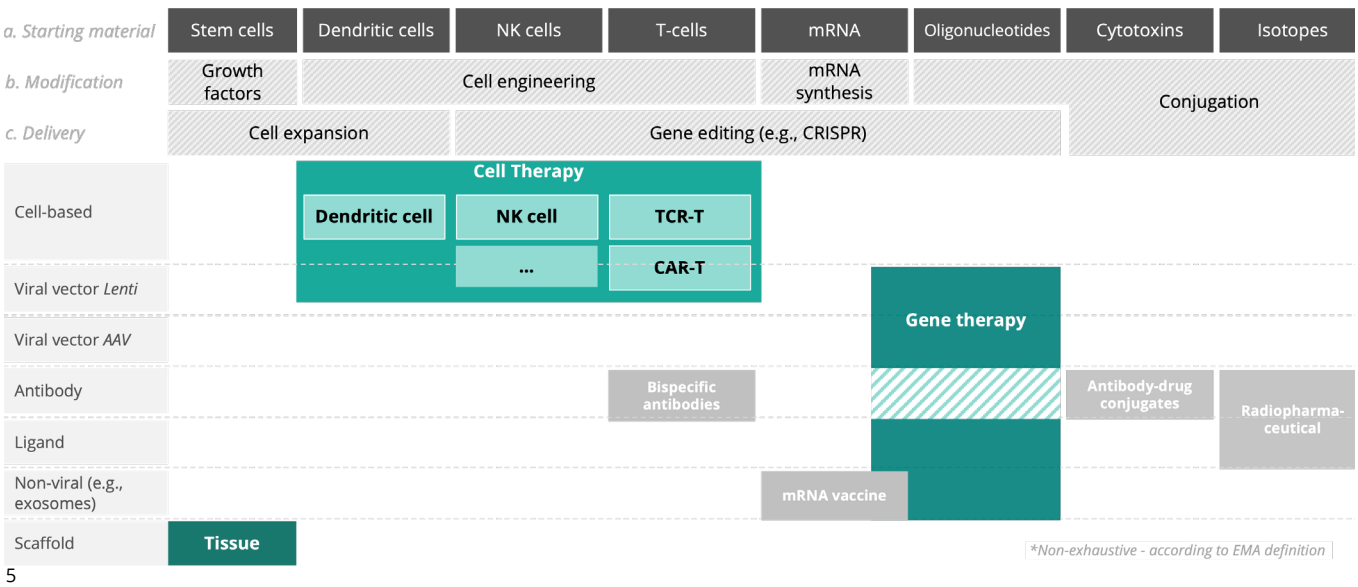
The **starting material** are the building blocks of advanced therapies. These are the biological substances or cells that form the foundation for the therapy. Different types of cells or molecules can be used depending on the intended therapeutic effect.

The **modification technology** used are the modalities that allow for customization of the therapy by altering or engineering the starting materials to enhance their therapeutic effect.



The **delivery platform** is what gets the therapy to the target. These systems and methods are used to transport the therapeutic agents into the patient's body.

Figure 3: The position of advanced therapies in the complex evolving landscape of next-generation therapies.



Advanced therapies come with their own set of challenges and unique specificities.

The key differences with conventional medicines such as small and large molecules are:

- Potentially irreversible action: advanced therapies often have the potential for irreversible action, meaning their effects may be long-lasting or permanent, compared to conventional medicines where the effects may be reversible or temporary.

- Complex evidence generation: advanced therapies typically require new protocols to generate evidence due to their novel mechanisms of action and the need to demonstrate long term safety and efficacy vs. more established evidence pathways for conventional medicines. The health economic models for advanced therapies rely on clinical trials with a higher uncertainty, resulting in challenges to interpret long term economic benefits.

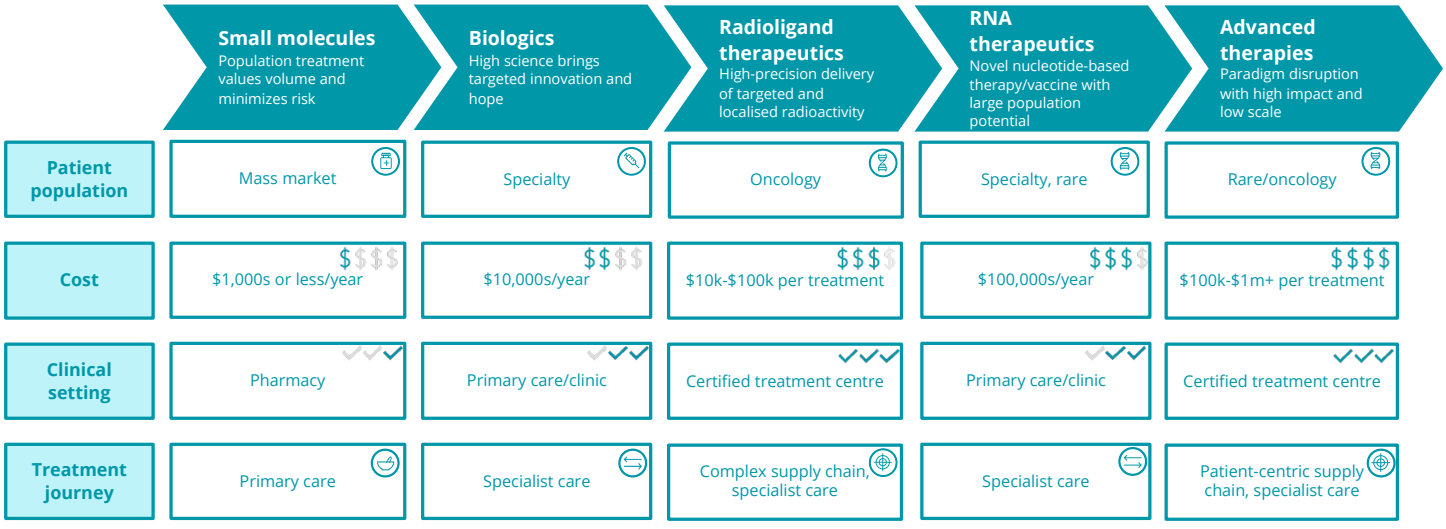
- One-off high upfront cost: advanced therapies often involve a one-off high upfront cost due to their personalised nature and complex manufacturing processes.

Therefore, a different approach is required in the healthcare sector

The move towards more complex therapeutic interventions marks a significant shift in the healthcare landscape (figure 4). This evolution highlights a transition from conventional treatment methods to more sophisticated, targeted approaches. It includes the rise of personalized medicine (e.g., individual cancer vaccination based on tumor profiling), and innovative treatment strategies (e.g., combined therapies) that address diseases at a molecular level, enabling more precise and effective care. For advanced therapies specifically, as examples, patient enrolment often requires specific eligibility criteria due to the personalized nature of these therapies. Scheduling and order fulfilment are critical as these treatments are often time-sensitive and involve complex logistics, including handling and delivery of the therapy itself. Moreover, a close connection with the technology developer throughout the process is required to ensure compliance, communication, and proper administration. Follow-up care is more intricate due to potential side effects and the novel nature of the treatments, demanding more frequent monitoring. Additionally, there is a need for specific training for healthcare providers to safely administer the therapy, as advanced therapies often involve cutting-edge techniques that require specialized skills.

In summary, as therapies become more innovative and personalized (e.g., biologics, RNA, and advanced therapies), patient populations become more niche, costs rise, and clinical settings, treatment journeys become more specialized and complex.

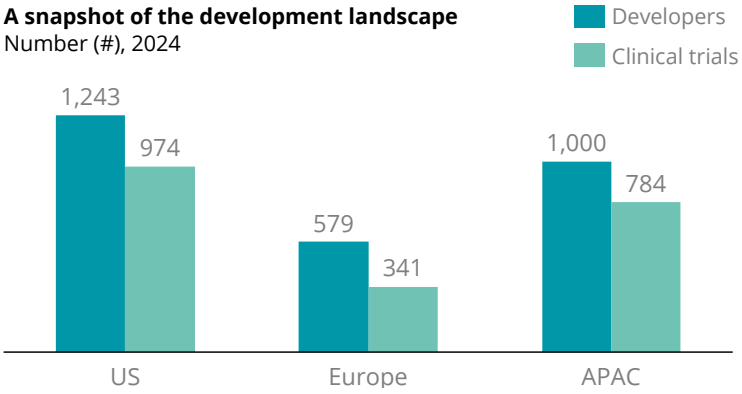
Figure 4: Advanced therapies require a different healthcare approach.[3]



The landscape is evolving quickly

Fast growing and geographically expanded clinical pipeline.
The advanced therapy pipeline is rich with innovations aimed at treating previously untreatable conditions, like genetic disorders and certain cancers. We see a promising pipeline: 10 to 20% of drug products in early-stage clinical trials are advanced therapies (figure 1). The global increase in clinical trials of cell and gene therapy specifically underscores the increasing speed of translational research for advanced therapies (figure 5). Notably, the increase in clinical trial activity in APAC, positioning it second after the U.S. in terms of volume. This year, eight new approvals are anticipated, with autoimmune diseases emerging as a key therapeutic area after oncology. Recent breakthroughs include the remission of three patients (two men and one woman) with severe autoimmune conditions, following treatment with bioengineered and CRISPR-modified immune cells[4].

Figure 5: Clinical trial landscape and value proposition of advanced therapies.[5]



- **Expecting 8 and 6 possible approvals** in US and EU respectively
- **APAC emerging** as a key player
- **Expansion** in other indications (e.g. autoimmune)

A promising horizon combined with ...

Cell therapy

Provides a durable and effective treatment option that can offer hope for many patients who are in later stages of cancer.

Increasingly demonstrating superior safety and efficacy in comparison to the standard of care.

CAR-T' success is spurring innovation that can provide new therapeutics options.

... a life saving value proposition

Gene therapy

Devastating, often deadly diseases: average life expectancy targeted by approved GT is <40y – half of the normal lifespan.

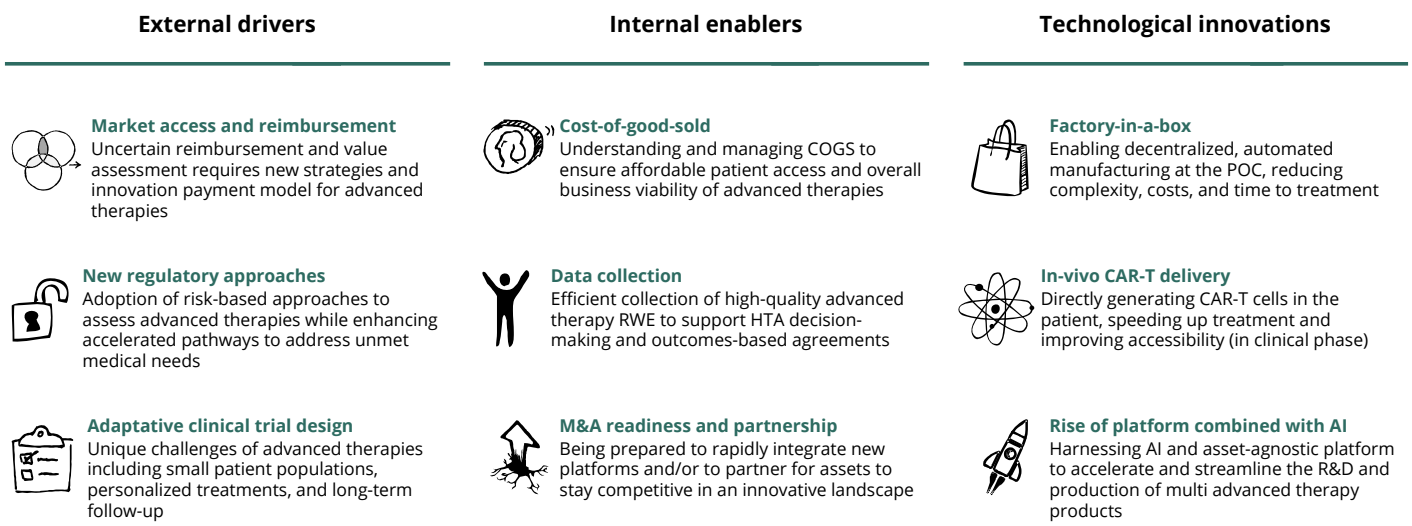
Highly effective: orphan GTs are 3,5x times more likely to be approved once entering in ph1.

Target expensive diseases: ~$5 to +20mio estimated lifetime cost.

Drivers shaping the advanced therapy landscape.

The advanced therapy environment is driven by a selection of key trends (figure 6).[4]

Figure 6: External forces, internal enablers and technological innovations shaping the advanced therapy landscape.



External drivers:

The clinical trials required for advanced therapies present unique challenges. **Novel trial designs for advanced therapies (advanced therapy)** that address small patient populations, individualised treatment, and the need for faster approval are revolutionising how these personalised treatments are developed and tested. For example, adaptive trial designs enable real-time adjustments to dosage and patient selection, based on early data which is crucial for therapies like CAR-T. Basket trials test gene therapies across different diseases that share a common mutation, while platform trials evaluate multiple treatments simultaneously, such as various gene-editing approaches for conditions like sickle cell disease. Additionally, synthetic control arms leverage historical data instead of placebo groups, as seen in rare genetic-disorder trials like spinal muscular atrophy, making them more efficient and ethical. These innovative approaches ensure that advanced therapies can be evaluated quickly and effectively, speeding up patient access to life-saving treatments.

Meanwhile, **regulators are increasingly adapting their frameworks** to accommodate the unique challenges posed by advanced therapies, emphasising risk-based assessments and accelerated pathways to expedite the approval process for treatments targeting unmet medical needs. For instance, the FDA's Breakthrough Therapy Designation allows for more frequent interactions between sponsors and regulatory bodies, enabling faster development for therapies like Zolgensma, a gene therapy for spinal muscular atrophy. Zolgensma received approval within three years due to its critical nature in addressing a severe, life-threatening condition. Similarly, **the EMA has implemented the Priority Medicines (PRIME) scheme**. It provides early and enhanced support for the development of therapies that address significant unmet medical needs, facilitating quicker market access for innovations like Luxturna, a gene therapy for inherited retinal dystrophy. It is expected that in the future focus on potency assays (standardization of methods and requirements), flexibility in GMP and GMO classification, and ease of patient registry set-up for the post surveillance data needs will continue to improve.

The **uncertainty surrounding reimbursement and value assessments** for advanced therapies highlights the need for innovative payment models. These therapies often target small populations with personalised treatments, so traditional models may not suffice. For example, since therapies like CAR-T cell treatments can cost $100-500k, there is a growing need for outcome-based payment models, where reimbursement is contingent upon the therapy achieving specified clinical outcomes, thereby ensuring that payers only pay for effective treatments. Additionally, subscription models or annuity payments are being explored, allowing healthcare systems to pay a flat fee over time for unlimited access to a therapy, as discussed for gene therapies for haemophilia. These innovative approaches aim to balance the high upfront costs of advanced therapies with the value they provide to patients, promoting equitable access to potentially life-saving treatments while addressing the financial sustainability for healthcare providers and payers.

Internal enablers:
To ensure the affordability and sustainability of advanced therapies, companies must prioritise reducing the **cost-of-goods-sold (COGS)** while maintaining business viability. This is particularly challenging given the complex and often labour-intensive production processes for advanced therapies, such as manufacturing CAR-T cells, which requires meticulous handling of patient-derived cells, gene modification, and extensive quality control. For instance, by adopting automated manufacturing and process optimisation techniques, companies like Novartis have been able to streamline their production workflows, significantly reducing operational costs. Moreover, leveraging data analytics to monitor and improve supply chain efficiencies can support further minimisation of costs. As companies navigate these complexities, focusing on COGS reduction is essential not only for making therapies more accessible to patients, but also for ensuring these innovative treatments can be produced profitably and sustainably in the long term.

Data collection, particularly through real-world evidence (RWE), is a critical enabler for the success of advanced therapies, as it supports informed decision-making for health technology assessments and outcomes-based agreements. For instance, collecting RWE on patient outcomes enables manufacturers to demonstrate the long term effectiveness and safety of their products, facilitating negotiations with payers for reimbursement. By leveraging RWE, companies can provide compelling data that illustrates the value of their therapies in real-world settings, ultimately helping to secure market access and optimise reimbursement strategies. Data collection capabilities to enable a successful development include biomarker development and validation, understanding of the disease often necessitating earlier partnerships with universities, earlier and frequent engagement with regulatory authorities and payers to inform clinical trial design the ability to design, implement patient registries.

Merger and acquisition (M&A) readiness is crucial for companies in the sector, as it enables them to swiftly integrate new platforms or form strategic partnerships to stay competitive in a rapidly evolving landscape. An example is Bristol Myers Squibb, which purchased Celgene to enhance its advanced therapy portfolio and access cutting-edge technologies. By being M&A-ready, organisations can capitalise on emerging innovations, expand their capabilities, and better address the growing demand for advanced therapies, ensuring they remain at the forefront of this dynamic industry.

Technological innovations:

Factory-in-a-box (FiB) systems enable decentralised, automated manufacturing at the point of care (such as automated closed-loop system of a size of a microwave). This reduces complexity, costs, and transportation delays – accelerating the time-to-treatment for patients. It is especially critical for personalised therapies (where timing is crucial) and helps extend access to regions with limited infrastructure. By automating the manufacturing process, FiBs minimise human error, improve consistency, and reduce labour costs, making these expensive therapies more scalable and affordable. Moreover, FiBs allow rapid production of patient-specific therapies, such as autologous cell therapies, where a patient's own cells are modified and returned. Finally, the modular nature of FiBs permits flexibility in scaling production and adapting to various therapy types and patient needs. Manufacturing at point-of-care brings many challenges, which force companies to take a more "in-between" approach consisting of decentralized manufacturing hub close to multiple hospitals. These challenges include managing IT systems, coordinating material inflow, and ensuring consistent training. IT infrastructure must ensure data accuracy across multiple sites, while materials need timely delivery and quality control. Standardized training and certification across sites are crucial for maintaining production quality. Finally, defining ownership of release steps, like quality checks, can be complex and requires clear coordination to avoid delays.

In-vivo CAR-T delivery involves generating CAR-T cells directly within the patient's body, a significant leap forward in accessibility and speed during the clinical phase (first trials started this year). New technologies, like CRISPR/Cas9 and base editing, are being tested in clinical trials for in vivo gene editing. This allows direct gene modification in the patient's body, as opposed to ex vivo modifications (where cells are edited outside the body and then infused back into the patient). Adeno-associated viruses and lipid nanoparticles are common delivery mechanisms, but there's an ongoing search for improved delivery vehicles to reduce immunogenicity and improve efficiency.

The rise of platform technologies combined with artificial intelligence (AI) is accelerating research and development by streamlining the production process across multiple advanced therapy products. This helps address the complexities and reduces the time required to bring these therapies to market. Advanced therapies often require highly customised, small-batch manufacturing processes. AI-driven automation is increasingly important for 1) process automation: AI can optimise workflows in the production of advanced therapies, reducing human error and increasing throughput; and for 2) quality control: AI can analyse production data to ensure that therapies are being manufactured to the highest quality standards, detecting deviations before they become problematic. This is critical for scaling therapies from small trials to broader patient populations while maintaining high quality. In a broader way, digital innovation combined with data insights are significative accelerators in R&D of advanced therapies where the landscape is evolving so fast and the competition is dense.

As the field of advanced therapy continues to evolve, a **second wave of innovation** that goes beyond the current predominant focus on oncology is developing. While therapies like CAR-T have revolutionised cancer treatment, emerging technological advancements are paving the way for expanding therapeutic areas beyond oncology, into conditions such as genetic disorders, neurodegenerative diseases, and autoimmune disorders. As the technology matures (e.g., with the next generation of CAR constructs leading to less toxicity and better efficacy[7]) it signals the potential to broaden the scope of transformative therapies across a wider range of diseases. This diversification will significantly impact the future landscape of advanced therapies, offering hope to more patients.

In summary, the advanced therapy landscape is experiencing rapid evolution, driven by external market factors and regulatory pressures, internal operational strategies, and groundbreaking technological innovations. These elements collectively push the field toward a more streamlined, efficient, and accessible future for advanced therapies.

Advanced therapies require early assessment of commercial viability. Although the clinical trials landscape is booming, investor's appetite is slowing down (figure 7). The commercial viability of the business case for advanced therapies is becoming more and more critical to raise funds and convince investors to support the technology.

In 2023, investments in the sector fell significantly compared to 2021's record level, due to rising inflation, interest rate spikes, and market volatility. Companies now face difficulties raising capital, and investors are increasingly cautious, favouring clear development paths and late-stage projects over early-stage, higher-risk ventures.

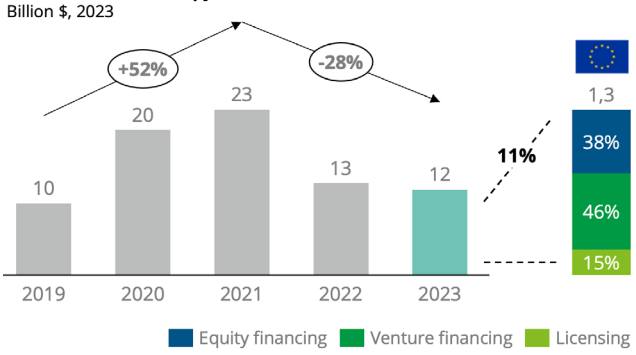
Despite the investment decline, there is still optimism for long term growth. Innovations in advanced therapies, such as CRISPR-based treatments and breakthroughs in rare diseases, continue to fuel interest. Investors are now more selective, looking for opportunities in precision medicine, AI, and technologies with strong clinical or regulatory potential.

This shift in funding trends reflects a broader transformation in the biotech sector, where emerging therapies are positioned to play a critical role in future drug development.

Figure 7: The investment landscape is slowing down.[11,12]

Advanced therapy investments have now entered a downturn

Global advanced therapy investments
Billion $, 2023



- **Significantly less funding is entering the sector** as venture investors prioritise technologies with lower risk and simpler market entry paths.
- **Europe is only covering 10%** of total investment in advanced therapies, the majority being through venture and equity financing.

The business case should be a priority in advanced therapy board rooms

Top 3 decision drivers of investors

1. **Technology platforms with a focus on gene editing**, induced pluripotent stem cell–derived cell therapies, and natural killer cells.
2. **Management experience** is crucial for navigating regulatory challenges and successfully commercialising therapies.
3. **Significant clinical data** influences investor confidence and market adoption.

Top 3 barriers for investment

1. **Competition from other drug modalities** having a proven track record, established market share, and familiar regulatory pathways.
2. **Manufacturing and scale-up** which requires ensuring consistent product quality and managing operational costs.
3. **Complex clinical development** due to the specific nature of trials for rare diseases.

- **The key challenge for advanced therapies is proving commercial viability**, as both investors and Big Pharma hesitate to commit, exemplified by a recent US-based biotech **shutting down programmes despite significant funding.**

Because improving commercial viability is key for the sustainability model of these therapies, development of **asset-agnostic platforms** can be a **way to de-risk investment**. These platforms are flexible systems designed to support development and manufacturing of a wide range of therapies, regardless of the specific product or technology being used[8]. They provide standardized processes, tools, and technologies that can be adapted to different advanced therapy products, enabling faster scaling, and streamlined production. By not being tied to a specific asset, they offer versatility in handling various therapeutic products under one system. These platforms are playing a critical role in mitigating the risks associated with the complex development process. At the end, they help lower costs, increase scalability, and ensure regulatory compliance, attracting more stable investment in this rapidly growing field.

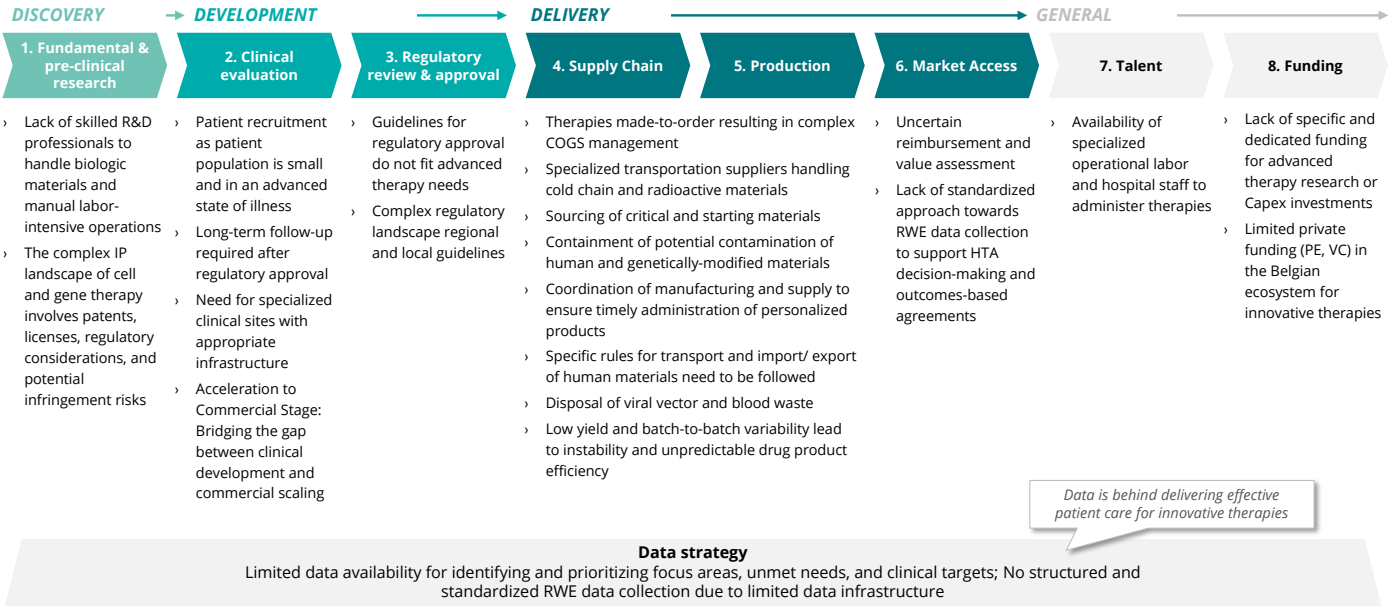
Governments could play a crucial role in de-risking advanced therapies by providing targeted funding and support for high-risk, early-stage ventures. As private investors become more cautious, favouring late-stage projects with clearer development paths, there is a gap in funding for innovative but riskier therapies. Government intervention, through grants, tax incentives, or public-private partnerships, could encourage continued innovation by reducing the financial risk for companies. By offering easier access to funding for high-risk projects, governments can stimulate breakthroughs in advanced therapies, ultimately accelerating the development of life-saving treatments.

12

Advanced therapies require a tailored ecosystem

Advanced therapies bring unique challenges along the entire value chain. Shortage of skilled R&D professionals, complex intellectual property (IP) laws and complex patient recruitment due to small size and state of illness (e.g., late-stage cancer) already pose a burden on R&D from the start of the value chain. In addition, the need for long term follow-up after regulatory approval, outdated regulatory guidelines which do not fit advanced therapy product and technological complexities put commercialization at risk. Also supply chain faces multiple challenges, such as specialized transportation, sourcing of materials, and containment of contamination risks, along with production variability and batch-to-batch instability. Market access is hindered by uncertain reimbursement and the lack of standardized data for value assessment. More broadly, the sector struggles with a shortage of specialized talent, especially in hospitals, and limited funding for early-stage innovations (riskier). Finally, there is a lack of structured data collection across the ecosystem and stakeholders to inform decision-making and optimize outcomes for the patient (figure 8).

Figure 8: Challenges across the advanced therapies value chain.



Delivering advanced therapies require a patient-centric model. The manufacturing and supply of advanced therapy products present complex, high-cost, and customised challenges tailored to the specific treatment journey (figure 9). This complexity arises from low-yield manufacturing processes involving cell culture, genetic modification, and extensive quality control testing for product purity, sterility, and stability.

The advanced therapy value chain is the determining factor for delivering on two moments of truth: product availability at the critical time and achieving the desired outcome. Drug discovery and approvals will continue, however if manufacturing and/or therapy delivery is prohibitively difficult or expensive, patients will likely not benefit.

7 key supply chain challenges

- **Unpredictable demand**: advanced therapies target rare and complex diseases and are most often second, third or even fourth line treatments. Consequently, the patient pool can be hard to predict. Additionally, individualized therapies are made to order, in contrast to the typical made-to-stock model in traditional biopharma, making demand and capacity forecasting complex.

- **Slot scheduling and capacity management**: especially for autologous therapies, a successful treatment requires careful coordination of available slots. There are two types of slots to be managed.

  – On one hand, the manufacturing slots, depending on the capacity to manufacture the final drug product.

– On the other hand, the apheresis pickup slots. The apheresis pickup slots are communicated to and selected by the hospitals and should link to the available manufacturing slots & capacity.

Depending on the selected apheresis pickup slot and reserved manufacturing slot, a large group of stakeholders need to be informed. This group includes logistics players who will ensure pickup and drop-off for the right patient, at the right place at the right time.

- **Scalability & automation of manufacturing processes:** the costly infrastructure, including specialised cleanrooms and robust cleaning systems, poses logistical and financial challenges. Long term competitiveness in manufacturing and supply beyond initial approvals necessitates standardisation of processes, quality controls, and the establishment of adaptable technology platforms to anticipate evolving technologies and regulations while maintaining compliancy.

- **Cold chain & time sensitivity:** advanced therapies are characterized by shorter shelf lives, which can be hours or days for some therapies. The ultra-low temperatures require shipment and storage solutions with dry ice or liquid nitrogen and constant, proactive temperature monitoring.

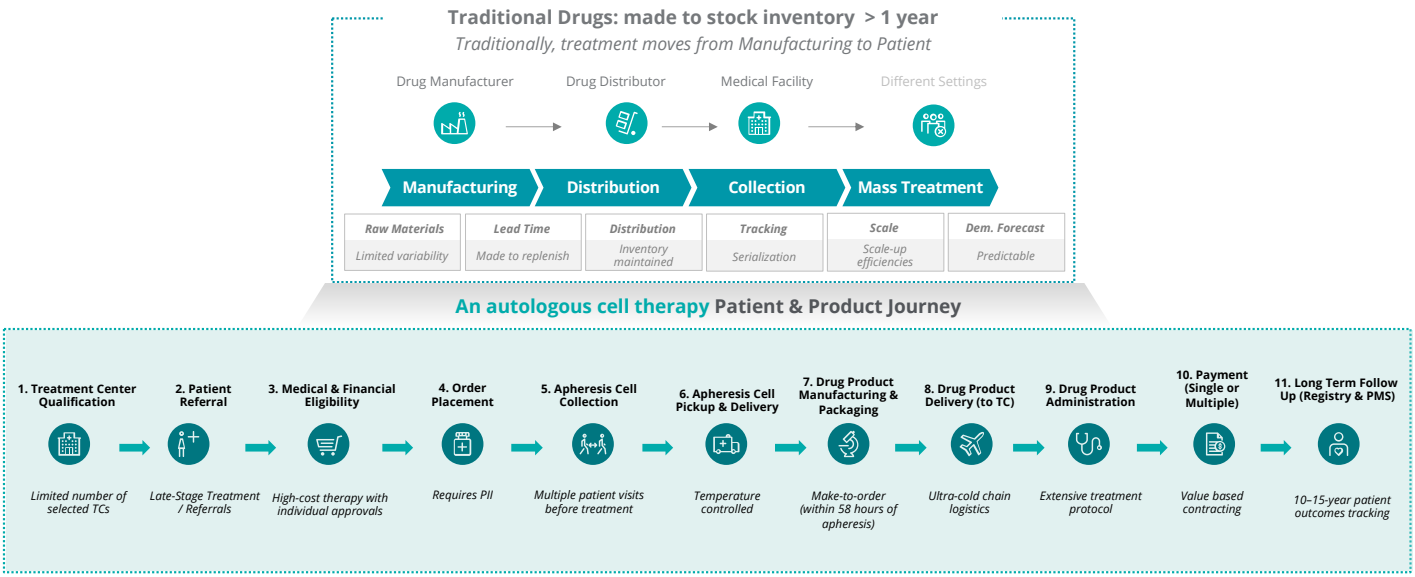
- **Redefined role for logistics players and affiliates:** the function of regional affiliates or operation companies, which traditionally play a fundamental role in the marketing, distribution, and payment of drugs sold in specific countries, is different. Given the customized nature of cell therapies, the small volumes, and the short turnaround times, regional affiliates are unlikely to play a role in distribution. Instead, direct-to-patient distribution will likely be centralized through manufacturing facilities or regional hubs.

- **Complex administration and management:** serious adverse events such as cytokine release syndrome (CRS) and neurotoxicity are possible with advanced therapies. This requires advanced administration protocols, additional training, and specialized clinical resources to manage patients and for short- and long term monitoring.

- **Need for digital enablement:** technology is critical to the success of advanced therapies, especially as they advance towards commercial launch. Some technology applications are unique to advanced therapies and need to be built; others, such as back-office support services technology, can be leveraged from existing biopharma technology infrastructure. Specific advanced therapy applications include those that can trace therapies through the make, order, and delivery process, support complex scheduling operations, track COI/C etc. There is a need to have tools that can digitally reflect the end-to-end patient journey, provide a differentiated and consistent end-user experience, and enable architecture to accommodate global regulations and market access requirements. The challenge today also lies in working towards standardization of systems and integrations to provide a more consistent and harmonized experience towards customers.

Figure 9: Autologous cell therapy journey.

Tradititional Drug vs. Autologus Cell Therapy Journey



Belgium is tackling these challenges through several initiatives across the value chain

- **DISCOVERY**

  - **Research Institutions** – There are many recognized research centres in Belgium. For example, the University of Leuven, which ranks among the top 50 universities globally, has dedicated centres for regenerative medicine and advanced therapy research, and recently invested €14 million into a new state-of-the-art production facility. The Vlaams Instituut voor Biotechnologie (VIB) is known for its cutting-edge research in biotechnology, with over 2,200 researchers working across multiple domains, including gene therapy. The de Duve Institute, part of UCLouvain, houses the Ludwig Cancer Research Institute which discovered the first cancer antigens serving as a fundamental basis of immunotherapy. This has led successful spin-offs such as iTeos pioneering next generation of biologics.

  - **Collaboration with industry** – Over 70 biotech companies are based in Belgium (figure 10), many focusing on advanced therapies, leading to innovative therapies like CAR-T cell treatments for cancers. 10% of European advanced therapy companies have their HQs in Belgium (figure 11).

  - **Government support** – Flemish health cluster MEDVIA received government funding of €6 million in 2021 and €8 million in 2022 to boost innovation in advanced therapies[9]. In Wallonia, the BioWin health cluster coordinates ATMP-PIT, a three-year project funded with €81 million to target advanced therapy medicinal products[10].

- **DEVELOPMENT**

  - **Favourable regulatory environment** –Streamlined application process for advanced therapies, with an average review time of around 60 days for clinical trial applications.

  - **Clinical research networks** – Belgium is part of the European Clinical Research Infrastructure Network (ECRIN), enhancing access to clinical trials across Europe. In 2020, the country conducted over 400 clinical trials specifically for advanced therapies. Today, Belgium is ranked #2 globally in clinical-trials-per-inhabitant for advanced therapies.

  - **Collaborative projects** – Belgian institute playing a significant role in advancing advanced therapies is VIB. VIB collaborates with other institutions on various projects, such as the GATE initiative, which brings together Ghent University, University Hospital Ghent, and imec. This platform focuses on speeding up the development of gene therapies, advanced cell therapies, and regenerative medicine, helping bring innovations from early research to clinical trials. Another example is a Belgian CDMO (Contract Development and Manufacturing Organization) who participates in the PAT4CGT project, funded by the EIC Pathfinder program. This consortium, which includes partners from six EU countries and Switzerland, focuses on improving the scalability and reliability of advanced therapy manufacturing through advanced process control technologies and automation.

  - **High-Throughput Experimentation Centre Ghent** – Located at Ghent University's Zwijnaarde science park, it received €5 million from the Flemish government.

- **DELIVERY**

  - **State-of-the-art facilities** – Belgium boasts over 25 GMP-certified production facilities for advanced therapies, including those operated by major companies like UCB, Catalent, and J&J.

  - **VIB Centre of Excellence for Manufacturing** – It received €500 million from the Flemish government to develop advanced therapy manufacturing and attract more players.

  - **Patient registries** – Belgian institutions are involved in initiatives like the European Rare Disease Registry, for better tracking of rare disease patients and facilitating targeted advanced therapy developments.

  - **Patient advocacy groups** – Organisations like Belgium's Rare Diseases Alliance advocate for better access to treatments and improved communication between researchers, healthcare providers, and patients.

  - **Health Data Authority** – With a first wave of government funding totalling €20 million, this federated national healthcare data centre is accessible to all stakeholders.

- **GENERAL**

  - **Public funding** – The Belgian government and regions allocate approximately €150 million annually to life sciences research, including advanced therapies. Programmes like the Innovative Medicines Initiative further enhance funding opportunities. Examples include:

    » Biowin, a PPP investment in cell & gene science (up to €30 million)

    » FIT, investing in identifying future advanced therapy needs (€500,000)

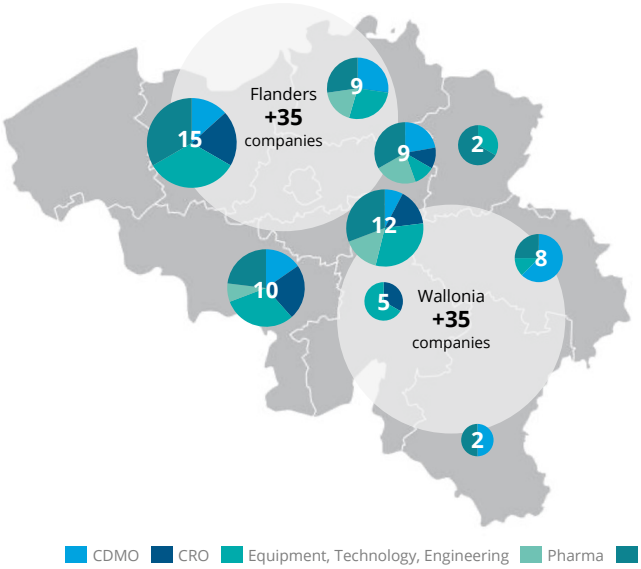
    » Medvia, a PPP investment in Flemish science projects (€8 million annually)

  - **Academic programmes** – Belgian universities offer specialised master's and doctoral programmes in biotechnology and regenerative medicine. For instance, the University of Ghent offers a master's in bioinformatics and biostatistics, crucial for gene therapy research. The University Libre de Bruxelles offers a master's in Entrepreneurship for Biotech and Medtech Ventures, essential to boost innovation in the field. Lastly, the EU Biotech Campus in Gosselies is preparing the future of biotechnology by providing training in data, AI, and biomanufacturing with leading advanced therapy players such as Takeda and Univercells.

  - ViTalent has state-of-the-art training facilities, including mock cleanrooms, which can also be used to train students with a targeted approach. ViTalent developed a training game focused on advanced therapy that is used to train students from institutions like AP, KdG, and Thomas More in GMP manufacturing (Good Manufacturing Practices) during the at.las Summer School. This initiative supports hands-on learning in an innovative environment, bridging the gap between academia and industry needs for skilled talent in advanced therapy production.

  - **Partnerships with EU Initiatives** – Belgium actively participates in Horizon Europe, the EU's key funding programme for research and innovation, with substantial allocations for advanced therapy research. The country has been involved in over 200 EU-funded life-science projects.

Figure 10: Overview of Belgium's advanced therapy landscape.



Ghent has, next to the most mature biotech ecosystem in general, also **a strong footprint in both cell and gene,** Illustrated by the recent **research and manufacturing developments** on Tech Lane.

Leuven ecosystem is built on **strong research assets and a history of both biotech and technology,** with significant investments in **gene therapy**.

Walloon Brabant ecosystem is pioneering **next generation of vaccines and biologics,** with strong innovation from universities, and recent strategic investment in **gene therapy.**

Charleroi is home to several **larger and international CDMOs/CROs**, with a strong **logistical hub** and presence of local biotech.

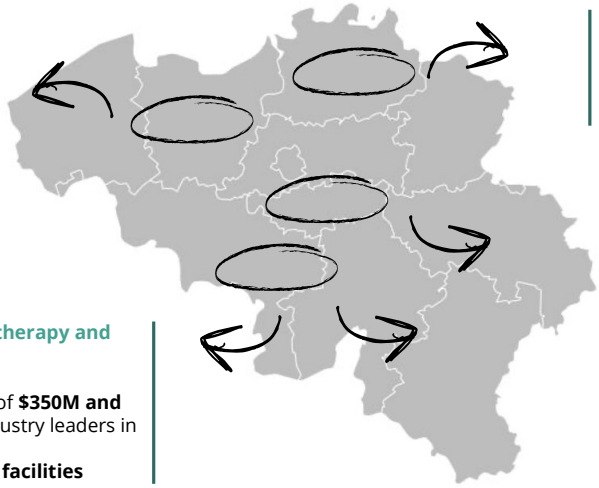
Antwerp is specialized in **vaccines/mRNA**, but also advanced therapies with **emerging biotech landscape**, presence of **large biopharma** and several recent investments in the province and close to the university.

Liege is an emerging area with facilities for advanced therapies connected to **investment funds and early-stage biotech**.

Figure 11: Success stories of Belgium in the advanced therapy sector.

10% **Of European advanced therapy companies have HQ in Belgium**

Supply EU market for commercial CAR-T
- **US Biotech, JV with a Belgian pharma**
- **State-of-the-art** cell therapy facility
- **Hundreds of jobs** created and +200-300 in the next years



Disrupt manufacturing innovation
- **Belgian biotech**
- **€125M and $14M acquisition** to accelerate access to next generation of advanced therapies – at **point-of-care**

Address rare diseases
- **Belgian biopharma**
- **State-of-the-art gene therapy** facility
- Acquisition of **university spin-off**
- **€300M+** investment, **17,000m²**

Supply EU market for cell therapy and plasmids
- **Belgian CDMO**
- 2 successive acquisitions of **$350M and $16B** bringing new US industry leaders in the country
- **Clinical and commercial facilities**

Supply global market for lentivirus
- **Belgian CDMO**
- **€725M** acquisition by a US-headquartered CDM(R)O

Figure 12: Non-exhaustive comparison with other advanced therapy ecosystems.

A culture of innovation and entrepreneurship fueled with access to capital

- **Boston**: the global hub for biotech **innovation**, focusing in **genetic and rare disease** development (picture)
- **North Carolina**: a thriving cell and gene therapy hub with extensive **commercial manufacturing capacity** (100+ sites)

Home of clinical trials, highly skilled workforce and innovative incubators

- **Berlin**: Europe's largest university hospitals (picture)
- Largest **120k** labor pool
- Development of a **federal strategy for ATMPs** with a dedicated NNO
- **Translation of new research** into medical application (+80 hubs)

Interconnected innovation ecosystem supported by a flexible regulatory landscape

- **Basel:** "Health Valley", home of **largest PharmaCos** active in ATMPs
- **Regional programmes** to accelerate the development of **new Tx ventures**
- **Swissmedic** body is highly regarded for its **efficient** and **transparent** processes

Next generation of cutting-edge facilities to enable scalable production of ATMPs

- **Biopolis**: key national research institutes, **200k m²** built-up space, **€200+ mio** invested by the gov.
- "**Build and they will come**" approach
- **National** strategic plan 2025 allocates **€17B** for **innovation** in biomedical

One of Europe's most advanced ecosystem driven by innovation hubs

- **Home to over 90 organisations** focus in ATMPs
- **Catapult plays a pivotal role** in advancing the UK's ecosystem
- **Significant funding** of the government allocated (£600 million)

Example of strong collaborative network with a clear federal strategy for ATMP

- **Federal strategy 2030 to become a leader in advanced therapies**
- **+48 active** clinical trials in ATMP
- **+180% of employees** since 2018
- **One branding** increasing visibility and knowledge sharing

Inspirations from around us

- **Reinforce ambition** for **ATMPs by building capacity** – investors will follow
- **Propels innovation** with specialized **"tech-bio" hubs** to **increase technology platforms**
- **Streamline regulatory** and **ethical committee** processes for **ATMP** developers
- **Federal steers, regions boost, stakeholders operate** – with clear, transparent and **regularly updated ATMP strategic and tactical plans**

Relative comparison of the Belgian ecosystem.

	Belgium	Germany	United States	Switzerland	Singapore	United Kingdom	Sweden
Fast and Efficient Regulatory Framework	Belgium has a centralized, efficient, and fast approval process through FAMHP, particularly for clinical trials related to advanced therapy.	Germany's decentralized system makes the regulatory process more complex and slower.	FDA has a rigorous and lengthy process, increasing time and costs.	Swissmedic is highly reliable but timelines can be long.	Singapore is regulated well but lacks capacity for large-scale advanced therapy trials.	Post-Brexit, MHRA operates independently from EMA, adding complexity.	Sweden has strong support but not as quick as Belgium for approvals.
Cost Efficiency	Conducting clinical trials in Belgium is more cost-effective due to lower overhead costs and favorable tax incentives for R&D activities.	Higher operational costs in Germany for trials and research.	The U.S. is among the most expensive places for advanced therapy research, especially for startups.	Switzerland has some of the highest costs in labor and facilities.	Singapore is competitive but still more expensive for large-scale trials than Belgium.	R&D costs remain competitive but post-Brexit uncertainty can lead to higher complexity.	Sweden is slightly more expensive than Belgium for trials and manufacturing.
Collaborative Clinical Ecosystem	Belgium has world-renowned academic hospitals and a strong ecosystem for public-private partnerships in advanced therapy, making collaborations more streamlined and effective.	While Germany has prestigious institutions, the collaborative framework between academic centers and industry isn't as streamlined.	The U.S. has top institutions, but the scale and competition can slow down collaboration.	Switzerland's academic-industry collaborations are strong but more niche.	Singapore is a growing biotech hub but lacks depth in collaborative institutions compared to Belgium.	UK's clinical ecosystem is strong but faces post-Brexit uncertainties.	Sweden has academic hubs, but the scale and speed can't match Belgium's strong collaboration framework.

Belgium's concentrated ecosystem has all the right ingredients to tackle the challenges in the supply chain and establish itself as the biomanufacturing gateway to Europe (in a broader sense of next-generation biologics, vaccines and advanced therapies), building on its end-to-end value chain (from biopharma to specialized logistics), multi-disciplinary academic centres, access to biomanufacturing infrastructure, novel funding schemes and innovative healthcare system in the heart of Europe.

Recommendations for the ecosystem

Belgium's recipe is a combination of longstanding local deep knowhow with global connectivity from anchor companies.

"Think locally, Cooperate regionally, Ace globally".

We outline a strategic vision for positioning Belgium as the centre of excellence for advanced therapy in Europe. It identifies key areas of focus and provides recommendations for how Belgium can strengthen its ecosystem for development and commercialisation.

These are our five recommendations for becoming Europe's advanced therapy hotspot:

01. Make navigation easier

- Current need: the complex and fragmented advanced therapy landscape makes it difficult for partners – including startups, established companies, and research institutions – to find and collaborate with the right stakeholders.

- Recommendation: establish a collaborative platform that facilitates transparency and matchmaking within the ecosystem. This hub could streamline connections between different players, enhancing collaboration and innovation.

02. Focus on complementarity and collaboration

- Current need: improved synergy between various entities in the advanced therapy ecosystem, such as biotechs, academic institutions, and regulatory bodies.

- Recommendation: develop centres of excellence for specific technologies and platforms. They would act as collaborative hubs, providing resources, expertise, and infrastructure to foster advanced therapy innovation.

03. Invest in ecosystem assets

- Current need: growing demand for advanced therapies requires expanded infrastructure and resources to support manufacturing and development.

- Recommendation: invest in up-scaling biomanufacturing infrastructure accessible to the community of advanced therapy developers to ensure that Belgium can meet the production needs of emerging therapies, supporting both local companies and attracting international players.

04. Promotion and branding

- Current need: boost Belgian visibility and reputation within the global advanced therapy landscape to attract investment and talent.

- Recommendation: create a single brand for the Belgian advanced therapy ecosystem, ensuring coordinated marketing strategies that promote its strengths and capabilities to both domestic and international audiences.

05. Regulatory harmonisation

- Current need: a consistent and supportive regulatory environment, critical for the successful development and commercialisation of advanced therapies.

- Recommendation: develop a centre of regulatory excellence to streamline processes, providing a framework for seamless and flexible interactions with regulatory authorities. This would facilitate quicker approvals and encourage innovation.

By focusing on these strategic areas, Belgium can strengthen its position as a leading hotspot in Europe, fostering an environment that promotes innovation, collaboration, and investment. The recommendations aim to create a cohesive ecosystem that not only benefits local stakeholders, but also attracts global attention and participation in the evolving advanced therapy market.

Endnotes

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Thank you!

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MEDVIA
The innovation cluster for better health

BIOWIN
THE HEALTH CLUSTER OF WALLONIA

Contacts

Authors

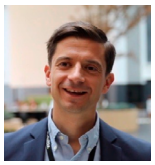
Kevin Missault
Life Sciences and Healthcare Strategy
Senior Manager
kmissault@deloitte.com

Olivia Claes
Life Sciences and Healthcare Strategy
Manager
olclaes@deloitte.com

Burçak Aydin
Life Sciences and Healthcare Strategy
Senior Manager
buaydin@deloitte.com

Charlotte Meuldermans
Life Sciences Supply Chain
Senior Manager
cmeuldermans@deloitte.com

Contacts



Pieter Sauwens
Life Sciences and Healthcare Strategy
Strategy Director
psauwens@deloitte.com

Marc Abels
Life Sciences and Healthcare Strategy
Partner
maabels@deloitte.com

Lieven Comeyne
Life Sciences Supply Chain
Partner
lcomeyne@deloitte.com

Michel De Ridder
Life Sciences Regulatory and Compliance
Partner
mideridder@deloitte.com

Deloitte.

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