Developing Advanced Therapies: Considerations for Internal Versus External Manufacturing

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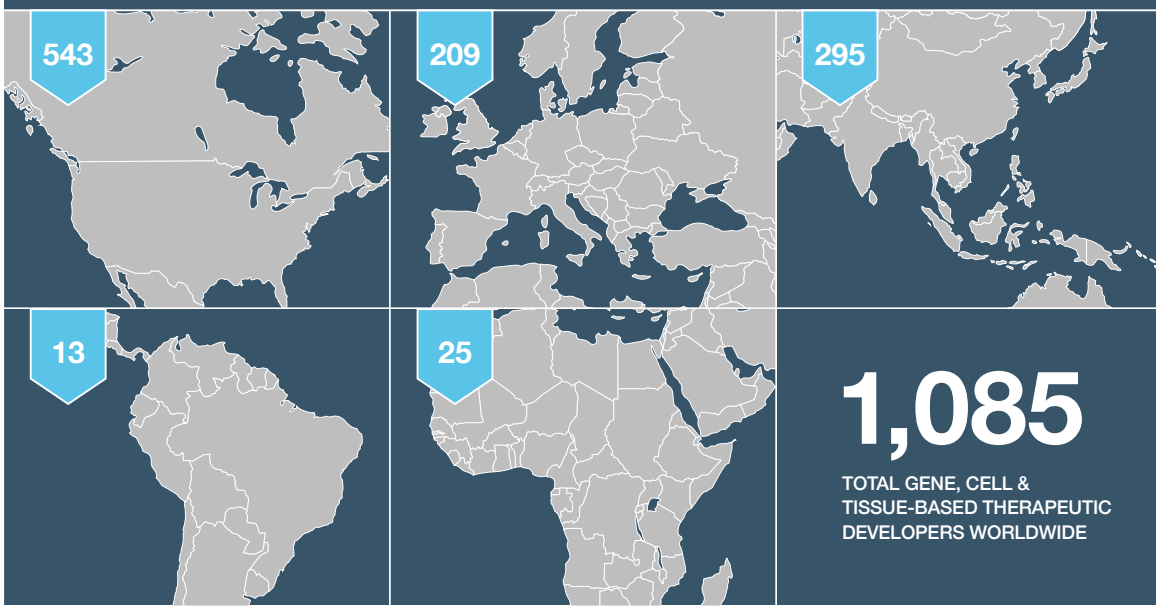
Considerations for Internal Versus External Manufacturing

Due to their complexity and cost, developers of cell and gene therapies face unique manufacturing hurdles. Determining the right approach to manufacturing is crucial when bringing these advanced therapeutics from clinical to commercialization. Recently, Precision for Medicine co-sponsored a webinar with Informa Pharma Intelligence, bringing together high-profile leaders in the cell and gene therapy space to discuss key considerations for cell and gene therapies. The combined expertise of these four panelists in their respective fields of investment management; manufacturing and technical operations; global pricing; and commercialization, advocacy, and legislation provided a distinctive perspective on how to approach manufacturing and other roadblocks at every stage of development.

Current State of the Cell and Gene Therapy Sector

The regenerative medicine sector is growing at an exponential rate. A recent briefing given by the Alliance for Regenerative Medicine found that there are currently over 1,000 regenerative medicine and advanced therapy developers (see Figure 1).[1] Most of these developers are located in the U.S., but there are meaningful clusters in Europe and a growing number of developers in Asia.

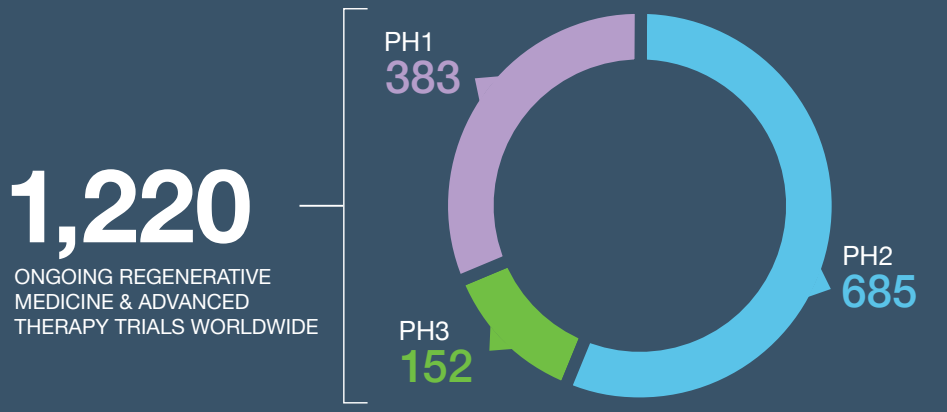
Figure 1. **Regenerative Medicine and Advanced Therapy Developers by Geography**



1. Alliance for Regenerative Medicine. The Alliance for Regenerative Medicine Cell & Gene State of the Industry Briefing, January 13, 2021. Available at https://alliancerm.org/arm-event/sotibriefing/

The clinical trial pipeline has been growing at an incredible pace over the past few years, with over 150 phase 3 studies underway (see Figure 2). With more than 1,200 clinical trials ongoing worldwide, there has also been a shift in development focus. The preponderance of late phase trials are in gene therapy, but cell-based immuno-oncology therapeutics currently dominate phase 1 studies. While research in rare diseases—including rare cancers—continues to be robust, development work around more prevalent conditions such as cardiovascular diseases is on the rise.

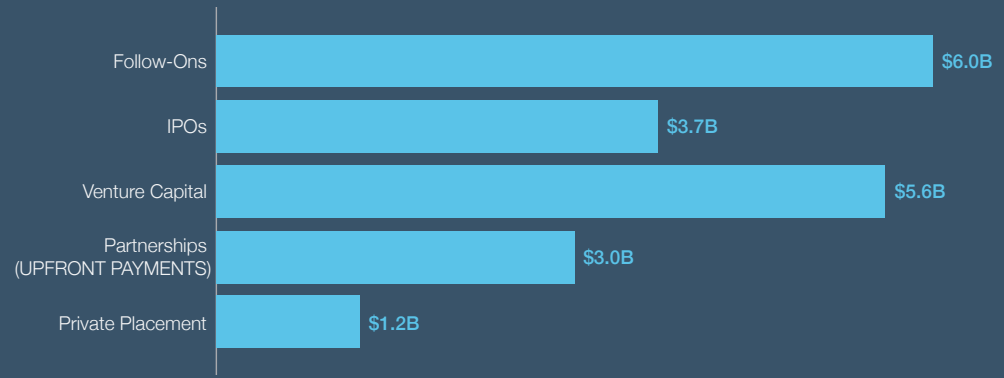
Figure 2. **Ongoing Advanced Therapy Clinical Trials Worldwide**



The late-stage clinical pipeline continued to advance

An incredible amount of capital has been put to work to finance R&D in the cell and gene therapy sector. In 2020, nearly $20 billion was invested in companies developing advanced therapies. Performance in the IPO market has also been remarkable, testifying to the profound impact these treatments can have on patient lives (see Figure 3).

Figure 3. **2020 Cell and Gene Therapy Financing by Type**



The intersection of genomic information with big datasets has enabled investment management groups to better evaluate the probability of successfully translating cell and gene therapies from the bench to the bedside. The combination of biological insight and biomarker innovation has made it possible to validate targets and detect efficacy signals earlier in the development process.

Key Considerations for Manufacturing

When asked about their biggest manufacturing hurdle, the webinar audience identified the issues below:

- Lack of experience or shortage of talent
- Inadequate supply of raw materials
- External vendor management

Much of the complexity involved in cell and gene therapy manufacturing lies in process development. Process development for advanced therapies requires a different mindset—rather than building molecules and shipping them to wholesalers for scale up, cell and gene therapy developers need to provide an end-to-end service that is integrated with the health system. As service providers, these developers need to collaborate with more external stakeholders and build those relationships early on in the manufacturing process to ensure that Good Manufacturing Practice (GMP) requirements are met at every stage of development.

Significant planning is needed to determine how to scale bench top manufacturing to support clinical trials and, ultimately, commercialization. For developers considering in-house manufacturing, it is imperative to develop a long-term strategy for putting up a facility in a location with a strong talent pipeline, and then building an ecosystem and base of training to recruit and train that talent.

Make or Buy?

The business case analysis for internal versus external manufacturing will be unique for every cell and gene therapy product. Key considerations include:

- **Availability and cost of capital.** Most startup companies will need to buy because they cannot access sufficient capital at their early stage to make it on their own. Investment into manufacturing can also be done in phases as the product progresses through stages of development.
- **In-house technical capability.** Early-stage companies will need to hire or contract with the necessary talent to build out an in-house manufacturing capability.
- **Maturity of the science.** As the science matures, risk tends to decrease and confidence regarding scalability tends to increase.
- **Epidemiology of the indication of interest.** This provides insight on how much product will be needed at every stage of clinical development and upon commercial launch.

- **Stability of the supply chain for both GMP and non-GMP storage.** Does the company have the resources and infrastructure to mobilize and stabilize the supply chain? This includes management of a magnitude of raw materials and vendor partners.
- **Chemistry, manufacturing and controls (CMC) regulatory strategy.** With expedited approval pathways, important manufacturing decisions need to be made much earlier in data development than with traditional therapies. Interacting with the FDA early on in the development lifecycle and getting the agency's buy-in can be extremely useful.
- **Impact on cost structure.** While pricing is tied to the value delivered to patients and not manufacturing costs, it is important to consider how much is being spent on R&D versus marketing and other functions.

Developers must take a broad view of potential risks and strive to mitigate those risks up front. Even with a robust risk mitigation strategy in place, unforeseen circumstances may arise. One of the panelists provided an example of a developer who proactively ordered a freezer two months ahead of plan, only to learn that the lead time on freezers had increased due to COVID-19-related demand for cold storage. The delay in receiving the freezer would have potential downstream effects on the developer's ability to store raw materials they would be receiving, highlighting the importance of contingency planning.

Developers may consider performing process development work in-house and then transferring that technology to a contract development and manufacturing organization (CDMO). The success of this approach often depends on the creation of a partnership where a dedicated cross-functional group comprised of both developer and CDMO team members works together to ensure a seamless handoff.

If the capital and competency exist, having in-house manufacturing capabilities and facilities can be additive to enterprise value. It may also be a competitive advantage not only for developing a proprietary portfolio, but also for acquiring new assets to ultimately create economies of scale. Each business case is unique, however, and the landscape is constantly evolving. The decision to invest in manufacturing—whether it is building an in-house capability or locking in a long-term agreement with a CDMO—should be carefully discussed and debated with experts across the continuum to arrive at a best answer. Regardless of whether the decision is to make or buy, it is critical for developers to operate with a strategy.

Other Roadblocks

In addition to manufacturing bottlenecks, developers of cell and gene therapy may face other roadblocks.

- **Regulatory.** The infrastructure and framework for regulating advanced therapies is still a work in progress.
- **Reimbursement models.** Given the high cost of cell and gene therapies, there is a critical need for alternative payment models in key markets in the U.S. and Europe to make these treatments sustainable and affordable for both public and private payers. As advanced therapies for more common indications move closer to commercialization, there is increased urgency to develop innovative payment schemes that bring these products to the patients who need them. Non-profit groups such as the Institute for Life Changing Medicines are forging partnerships to support the advancement of cell and gene therapies in a manner that is cost effective for patients.
- **Patient access.** The patient perspective can get lost amidst the science. Developers are challenged to get patients more richly engaged in all aspects of drug development, including the identification of meaningful milestones and clinical endpoints. A nascent area of cell and gene therapy development is the forging of corporate partnerships focused on ensuring that these breakthrough treatments are available for all.

Conclusion

Cell and gene therapies are at the forefront of a therapeutic revolution. Stakeholders across the development lifecycle are enthusiastic about moving the science forward and making the leap from a treatment model to a curative model. In a rapidly evolving landscape, developers need to begin with the end in mind, factoring regulatory, manufacturing, reimbursement, and patient access considerations into their product development strategy.

To learn more and view our webinar in its entirety, download here.

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