Commentary: Miguel Forte

A business model for cell and gene therapy

Cell therapy is as old as blood transfusion and bone marrow transplantation where cells were used, unmodified, as replacement therapies. Today cell and gene therapies are intrinsically connected. This is because the cells used as therapeutic agents are mostly functionally conditioned to deliver a therapeutic objective. This is almost always through gene engineering.

Over the last couple of years, the adoption and investment into cell and gene therapy products has been below expectations if we consider the potential benefits of these agents, but understandable if we look at the business model. The value proposition cannot be only based on good science and clinical efficacy. It needs to be based on valid models for patient access with clarity on the concept. Manufacturing, cost-of-goods, clinical convenience, and anticipated product launch must be present in the minds of any product developer from the initial stages of translation. As science becomes a product, the market vision, anchored in the target product profile (TPP), should aim to be an integrated business model with the goal of serving the patient.

It is time for a new classification of cell and gene therapy (CGT) products based on the integration of clinical science, manufacturing and supply chain requirements, and the associated business models. This could give clarity to product characteristics, development, delivery, opportunities for business development, and commercialisation. It would also increase patient access and deliver commercial success. Today we see three types of cell and gene therapy products: *allogeneic, ex-vivo autologous, and in-vivo products*. At this stage it is difficult to project the relative positioning of these three approaches except to say that they will bring significant value to patients.

The *allogeneic CGT product* uses different cell types engineered for a therapeutic purpose. Under this model, cells will less and less be sourced from donors but will be sourced from cell lines, like iPSCs, and primed or engineered for a therapeutic function. The cells therefore are a 'raw-material' or a therapeutic tool, using the optimised engineered cell function for a specific effect. These products are off-the-shelf, allogeneic cells which are very likely to be manufactured centrally with a corresponding, traditional, supply chain. These cell/gene therapy products, and the corresponding business model, will be close to the traditional pharma commercial model. Improvements in sourcing and manufacturing in this traditional business model will enable easy patient access, good return on investment, and commercial success. These products will be the paradigm for cell therapy using bio-engineered cells through optimal cell sourcing and optimal cell function, coupled with an optimised cost-of-goods. This is an understandable business model which could lead to patient access and benefit.

For *ex-vivo autologous CGT products* the patient cells are manipulated, mostly genetically engineered *ex-vivo*, and returned to the patient for an enhanced and targeted effect. The product here tends to be defined as the cells returned to the patient and their characteristics. But one could also consider the product as the manufacturing process itself. This opens some interesting possibilities for the manufacture and delivery of the product including decentralised and eventually even bedside manufacturing. We may have to evolve the models for this approach including development and regulatory issues. Some regulators seem prepared to move to this paradigm. Coupled with autonomous manufacturing devices, this could democratise treatments, bringing them closer to the patient at regional and hospital level. This model could help ensure patient access while raising returns for multiple public and private players. The clinical value of this approach has already been extensively documented.

Under the *in-vivo CGT product approach*, the cell therapy activity is 'manufactured' and achieved inside the patient. The gene engineering leading to a therapeutic function such as correcting a genetic mutation, is delivered to the patient directly through a vector, either viral or non-viral. Thus, the cells are changed inside the patient. Here, the product is the vector and the genetic payload. This approach is also aligned with the traditional pharma model of centralised production, off-the-shelf availability, low cost-of-goods and clinical convenience. As data emerges and experience increases in managing these *in-vivo* therapies we will see them become mainstream. This would provide significant clinical value to large populations and attractive returns on investment.

Therapeutic strategies for cell and gene therapies must be based on an understanding of their unique characteristics and how they can be optimised. This is not just the biological effect, but how the products are produced, delivered and used. Product development must be done with an end in mind, focusing on feasibility, scalability, automation and cost, together with clinical convenience and ease of use. Understanding the business and commercialisation models and launch objectives from the start, will help all stakeholders to confidently invest, guide, and support the industrial translation process.

Developers of the *allogeneic* and *in-vivo* cell and gene therapy products, aligned with the traditional pharma business models, will become significant industrial players in the field, targeting large populations. Together with the clinically proven *autologous* CGT products with alternative business models, large patient populations will benefit. Overall, this three product perspective, with its corresponding business models, should bring clarity to the industry. In turn, this clarity should build confidence in cell and gene therapies leading to higher investment, commercial success and above all, value to patients with unmet medical needs.

This article was written by Miguel Forte, president of the International Society for Cell and Gene Therapy.