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Elevated Insights

Right from the start:

Successfully managing the life cycles of cell and gene therapies

By Mike Paglia, Chief Operating Officer ElevateBio BaseCamp

The development of cell and gene therapies (CGTs) is highly complex and challenging. While incredible strides have been made in the field, this area of the biotech industry is still maturing, especially when it comes to manufacturing. Because we're just starting to see the first wave of cell and gene therapies reach commercialization, managing the entire life cycle of CGT product development is still a very specialized skill.

Along with specific technical challenges of CGT process development and manufacturing, CGT life cycle management involves complex supply chains, traceability systems and analytics to guarantee safety and navigating the CGT regulatory environment. The cost of failure is also quite high in terms of additional expenditures, lost time, and patients' lives that may hang in the balance.
All of these factors underscore the importance of correctly managing the life cycle of a CGT product the first time around, by knowing upfront what's needed for regulatory approval and then developing the product to meet those needs from the start. But the challenges of "getting it right, right from the start" are more than just technological. Success depends on having both the right processes across the life cycle and the right people to develop and execute those processes. Having one but not the other is a recipe for failure.

Process in the CGT product life cycle

The life cycle of a CGT product starts with procurement of materials, including reagents and cells from donors or patients for autologous products, and extends through dose administration for clinical use. All along that complex supply chain, many different controls must be in place to define, characterize, test and validate the materials. A key element in the supply chain is traceability, which is the process of keeping cellular materials segregated, safe, and well identified from their sourcing through manufacturing and into the patient, and it requires very specific systems and analytics. Traceability is especially critical for autologous cell therapies. When a patient's blood sample comes to the manufacturing facility and the starting cells are isolated from that sample, it is necessary to ensure the right patient's cells are modified in the right way – to generate the needed CGT – and then sent back and administered to that same patient. Lack of certainty anywhere along that chain of custody creates a major safety concern: administration of the CGT product to the wrong patient will induce an immune response (rejection) that could severely sicken the patient.

Securing the CGT chain of custody is highly important, but so are the analytics needed to identify and validate the cells along that chain. For example, in-house release testing methods for an autologous therapy must be able to correctly identify the original patient's cells, even after they have been genetically modified. The chain of custody also includes logistical components, such as training hospital staff to receive and administer the cells.

All of these factors come into play when navigating the complex regulatory environment, which is the primary hurdle that CGT companies face, especially on the manufacturing side. A CGT company must be in constant communication with the U.S. Food and Drug Administration (FDA) to get the Agency's input and feedback. When a company does submit an IND for an autologous CGT product, the FDA's top questions are always, "What is your traceability matrix?" and "What is your control around the traceability for the product?"

Materials used for CGT manufacture are defined, tested and regulated very differently than materials for other drug products. Regulations for each CGT material differ among regulatory agencies around the world.

Therefore, knowing the domestic and global regulatory environment, especially from a CMC perspective, is critical to success. If the CGT team hasn't lived this life cycle approach to CGTs and their regulation, it has to start from scratch; and without someone who has that hands-on experience, the learning curve is very steep.

The importance of getting it right the first time

In addition to managing the life cycle components described above, it's also necessary to understand how each of those components ties into manufacturing, and how to make critical development decisions around them, early on the development of a product. Whether the issue is raw materials, developing a process or gaining regulatory approval, waiting to think about these things until the product is approaching the clinic – or even after it has completed clinical testing – makes it harder to introduce the necessary changes later.

The main regulatory hurdle for CGTs is not getting FDA to accept an IND; the agency does accept INDs based on how products have been characterized for Phase 1 testing. The real hurdle comes later, when a company has to conduct process performance qualification (PPQ), which is the characterization and validation required to produce commercial batches of CGT product.

If the PPQ hasn't been worked out before submitting the IND and entering the clinic, then later clinical development and commercialization will be an uphill battle. The company will have to demonstrate comparability between the previous (IND-related) and newer (approval-related) processes; otherwise it will not be able to use the data generated throughout clinical development to seek regulatory approval. If comparability cannot be shown, the company may have to repeat clinical trials using the new PPQs.

In fact, one of the main reasons the FDA puts products on clinical hold relates to CMC activities or deficiencies, such as lack of comparability. Therefore, a CGT company must anticipate where its product will need to be at the commercial end of the life cycle and develop the product with those needs in mind from the outset. Doing this may involve more work on the front end of the cycle, but it ultimately results in lower costs and development burdens downstream – both of which accelerate the commercialization of the CGT product.

Building the right team

People are just as critical to successful CGT product development as the processes. If a CGT company has one but not the other, the potential for failure is high, because developing and implementing processes correctly requires a team with experience and know-how across the entire life cycle. Putting together the right team comes down to recruiting, hiring and, above all, retaining the right people.

Given that the CGT sector is still in the early stage of growth, the talent pool is quite limited, and it's practically impossible to staff an entire company only with people who have CGT expertise. But finding the right people is achievable by viewing people's backgrounds and experiences through the appropriate lenses rather than strictly seeking CGT experience.

To be sure, at any CGT company there are some roles where it is essential to have people with prior CGT experience in order to accelerate development. These include such roles as managing technical operations across the entire life cycle and developing the specialized electronic systems for traceability. However, there are other roles that can be filled by people who don't have any CGT experience but do have transferable skills. The key is educating and training those people to redeploy their extensive expertise for CGT applications.

This redeployment approach can work well for many, but not all, potential CGT employees. For example, it's hard to teach someone who has "lived" small molecules throughout their entire career how to reapply that knowledge to CGTs; whereas for people who have worked with proteins, enzymes, and antibodies, the transition to CGT comes more naturally.

In the end, the real challenge in assembling the right CGT team isn't hiring people; it's retaining them, because the still-limited pool of CGT is highly sought-after and competitive as the field continues to grow. Therefore, the key to keeping an experienced team on board is offering them a variety of products, projects, roles and opportunities, so that they remain happy, excited and fulfilled.

How the ElevateBio model gets it right

At ElevateBio, we have everything it takes to get CGT development and manufacturing right the first time: an infrastructure for the entire product life cycle; a world-class team of drug developers and operators who can get the job done successfully; and a diverse and growing portfolio of innovative CGT products. Having all three – infrastructure, people and product diversity – in one place benefits us in several ways.

First, because we don't have to line up CDMOs, we can control our own timelines which saves us time and money.

Second, we have a great deal of talent under one roof; this promotes rapid knowledge transfer among team members and gives us the flexibility to assign our people to multiple products, platforms and technical areas.

Third, we anticipate our employee retention will be higher than conventional CGT companies precisely because we can offer people a wide variety of opportunities within one organization, and we believe this variety will continue to draw additional talent to us.

Together, these benefits translate into an ability to accelerate the development of affordable CGTs and deliver them to as many patients as possible.

The CGT sector continues to grow at a rapid pace. There are now many sophisticated CGT companies and a host of exciting new technologies, from electronic traceability systems to robotics, that are advancing how CGT products are developed and manufactured. However, all of the technology and automation in the world will not guarantee success without having the right processes and the right people in place across the whole life cycle of a CGT product.

References

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