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What gene therapy manufacturers can gain from collaboration

In this article, Neil Almstead, Chief Technical Operations Officer at PTC Therapeutics, shares his view on why collaboration is key to streamlining manufacture of gene therapies.

IN RECENT YEARS, the biopharmaceutical industry has found itself at a crossroads – being able to offer advanced and truly innovative treatments, such as gene therapies, but facing the complex challenge of creating manufacturing standards for the biotechnology sector from the ground up. Solving this issue will improve industry best practice, increase public confidence and create a more efficient pathway to patients; but it necessitates enhanced collaboration between companies.

Challenges in gene therapy manufacturing

The biotech industry is facing a bottleneck in product manufacturing, with more than 1,000 gene therapies currently being developed as potential clinical candidates,[1] and not nearly enough capacity in manufacturing facilities to accommodate them. Growth has been rapid since Europe's first gene therapy approval in 2012,[2] and the first US Food and Drug Administration (FDA) approval of a gene therapy in 2017.[3] Any sector would struggle to keep up with expansion of this speed, but the inherent difficulty of working with and producing biologics adds another layer of complexity.

At PTC Therapeutics, we have opened a gene therapy manufacturing Center of Excellence. We started this process by examining our manufacturing practices, and asked ourselves: where are the bottlenecks and what can we do to speed up the process from start to finish? It became clear that a level of control was required to ensure our products were manufactured to a high quality in a timely manner, especially given the intense regulatory scrutiny of pharmaceutical products and facilities.

Building expertise through collaboration

Success in the pharmaceutical and biotechnology industries requires a comprehensive understanding of your organisation's strengths and weaknesses. No matter the strength of your company, or the experts within it, there are always opportunities to learn from each other and improve. At PTC, working with contract manufacturing organisations (CMOs) was incredibly beneficial, as we gained insight from external expertise from different areas – you cannot work independently in this industry and assume you will be successful.

As an organisation, we produced the initial findings for our commercial product for Aromatic l-amino acid decarboxylase (AADC) deficiency, and how to manufacture it. However, as we moved further through the process we were supported by many different organisations.

Preparing and qualifying a multi-use facility

As we considered the goals and intentions behind our own Gene Therapy Center of Excellence, it was clear that one of the most important aspects would »

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be the ability to control our own destiny. If we could manufacture our own products, there would be less need to accommodate the timings and practices of third parties, greater assurance of quality and resource effectiveness, and even the potential to save money and time. When an opportunity presented itself to lease and convert a facility formerly used to manufacture early-phase clinical drug substances for monoclonal antibodies, it was too good to pass up.

As we wanted our manufacturing facility to be compatible for both clinical and commercial use, the first step was building a well-rounded understanding of guidance and internal validation standards across the industry. For our purposes, this primarily included the International Committee on Harmonization Q8, Q9 & Q10; ASTM E2500 The Standard Guide for Specification, Design, and Verification of Pharmaceuticals and Biopharmaceuticals Manufacturing Systems and Equipment; and the European Medicines Agency (EMA) Eudralex Part 1. Our qualification strategy used ASTM E2500 as the standard guide.

Throughout the qualification process, our cross-functional teams performed risk and gap assessments, ensuring that all relevant parties were aware of new and changing regulatory requirements. Considerably more focus had to be applied to data integrity, microbial control strategy and facility operations, as well as the intricacies of transitioning the facility from clinical drug substance manufacturing to a commercial-ready facility for both drug substance and drug product.

Qualifying our facility for multi-use was challenging, especially when considering the differences in scale, product quality attributes, and limited process data between commercial and clinical products. However, collaboration between our internal team of experts as well as external design and engineering consultants meant we were more able to balance the provision of flexibility for the unknown parameters, with ensuring tighter controls of the specifications for our first two anticipated programmes.

Collaboration is key to streamlining manufacturing practices

To streamline the manufacturing process, businesses must collaborate to build a widely accepted standard of best practice. Between the rapid expansion of gene therapy manufacturing and individual proclivities of much of the pharmaceutical and biotechnology industries, this will be a difficult task; yet it is one we must commit to. I propose several ways in which we can work towards this goal:

1. **Learn from your CMOs.** No company can do everything themselves, and to try to do so would be an inefficient drain on valuable resources and time. Working and communicating with external organisations on their areas of expertise can help you and your company recognise and fill your own knowledge gaps.
2. **Work with peers on understanding best practice.** With an ever-changing regulatory process, understanding the path to approval and the regulations to follow is a full-time job. Someone may have a better way of doing something, and if they are able to share that with you it is not just the companies that benefit, but patients as well.
3. **Streamline your processes.** There are eleven gene therapy products that are currently approved by the EMA,[4] – all of which use different manufacturing processes. Similarly, as with monoclonal antibodies, we can share what works best and develop a far more streamlined manufacturing process that goes cross-platform, across different products and different companies.
4. **Encourage employees to join technical groups.** Biologics manufacturing is

complicated. Having people who are members of different organisations and technical groups means that colleagues can network and share information more widely, bringing new expertise in, which can greatly improve speed and quality across the manufacturing process.

Currently, there is very little knowledge sharing, in part due to organisations feeling that it is either proprietary or information they do not wish to share; yet doing so would speed up product development and help patients receive treatment faster. We as an industry need to think about how to encourage and facilitate this.

There is also a benefit in giving manufacturing production lines a more seamless transition from one product to the next and sharing knowledge on best practice will speed this up. At PTC, we have hired people from different backgrounds with different expertise and connections. This has allowed us to work collaboratively with not just external organisations, but also build our own internal network of experts.

Gene therapies cannot be created in a vacuum – the complex nature of producing these therapies has led to challenges in accessing facilities and delays in production across the pharmaceutical industry. If manufacturers can come together to create mechanisms for collaboration and knowledge transfer, treatments will have a more efficient route to patients, and companies will not need to reinvent the wheel at every turn.

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With a career spanning more than 20 years with PTC Therapeutics, Neil Almstead has served in several executive positions since 2000. He initially came aboard as the company's senior vice president, research and chemistry, manufacturing and controls. From there, he assumed the role of executive vice president, research, pharmaceutical operations and technology. Today, Neil oversees the manufacturing and supply chain for the small molecule and gene therapy programmes as PTC's Chief Technical Operations Officer.

