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Industry Polarized In Best Manufacturing Approach For Cell And Gene Therapy

Snapshot of industry manufacturing debate

by Shardha Millington

Ongoing debate emanates from industry players around the most efficient design of the manufacturing process for cell and gene therapies. The arguments surrounding outsourcing, centralizing, and standardizing processes will no doubt continue through into the near future.

As with any therapeutic, the design of the manufacturing process is central in being able to efficiently produce, and provide patients with, quality treatments. For cell and gene therapies (CGTs), however, the challenges in optimizing this process are unique due to the complex nature of the technology which is ever evolving and means dealing with high degrees of variability.

It's a topic which is comprised of a few recurring debates that can often polarize industry experts into different camps. Here, I will introduce some of the debates I have seen surface most frequently, and some of the arguments that have been put forward.

In House Versus Outsourcing

The question of whether a company should produce its cell and gene therapies using proprietary manufacturing facilities instead of outsourcing to CDMOs is important and can have big implications.

It was interesting listening to a Partner at the venture capital firm Forbion at the Advanced

Therapies Europe (ATE 2022) conference in London mention that you'll see companies building new infrastructure to support in-house manufacturing but lack sufficient pipeline to sustain it, leading to bankruptcy. With the great variability we see now in CDMOs, the suggestion was that, unless you have a particularly unique technology (such as a unique AAV vector), in-house manufacturing capabilities are not a necessity.

On the other hand, however, the originator and/or proprietor will know their own technologies and products the best, and while there are indeed many specialized CDMOs, their capacity also needs to be considered. In a conversation between *Hemant Dhamne,* head of process development for gene therapy products at King's College London and Emmanuelle Cameau, a strategic technology partnership leader in cell and gene therapy for *Pall Corp.*, it was mentioned that it can take up to 1.5 years to go from initiation to conceptualization.

Centralized Versus Decentralized

Possibly the most notorious debate on CGT manufacturing is the debate on whether manufacturing should be centralized to limited locations or decentralized to many locations. While centralized manufacturing provides good quality control and simplifies the provision of training and resources, on the other hand decentralizing manufacturing could provide the benefit of facilitating the production of fresh product and ease of access for patients, potentially negating the need for cryopreservation, for example.

For decentralized manufacturing to work however, as Jason Jones, until recently the chief business officer at OriBiotech, mentioned at ATE 2022, you need to consider who is *liable for ensuring consistency and co-ordination.* Siloing hardware and software components of manufacturing needs to stop, he said, because data handling across replicable facilities in a decentralized model is key.

It is helpful to put the different arguments in the context of two key issues the MHRA are aware of: standardization plus consistency, and staff plus training – i.e., whatever the solution or the chosen path, training programs and processes need to be deployed in the same way across multiple locations.

There is, of course, as mentioned when I spoke to *Terumo Corporation*'s director of scientific affairs, Dalip Sethi, a middle ground. Having regional bases for manufacturing, where perhaps you have core facilities in each country or region, could provide a "goldilocks zone" between the two options. There would still be a big training burden for the countries that adopt it, but it could work if you have the software controls in place to make sure processes are happening the way they should.

Standardization Versus Flexibility

The challenge that arises from how quickly new technology and iterations are introduced in the

CGT space, is how manufacturing processes can keep up with this while also reliably producing standardized and comparable products.

Standardization is extremely important for being GMP compliant. “As you move towards the later stage you want GMP compliant processing. These are very defined SOPs,” said Terumo’s Sethi. Automation can provide the key to this standardization and ensuring that across multiple locations the same SOPs are being followed.

Collaboration across companies is also vital to facilitating this: “A lot of effort is going on in the industry - now there's a lot of consortiums to bring that standardization on board.” Of course, besides aiding reproducibility, automation also has a positive impact on efficiencies and bringing down the cost of these highly expensive therapies by reducing the man-hours spent on each machine and allowing parallel processing.

When considering flexibility this is also where the concept of a modular manufacturing system comes in, facilitating this balance with standardization. In modular (as opposed to integrated) automation, when you are considering cells for example, the modification, isolation, and expansion steps are in different units, therefore “if you want to do a process optimization on your isolation, you can do it without thinking about expansion,” said Sethi. This introduces a level of flexibility in how you can tweak your process without affecting the whole system.

For each of these conversations, it is likely there is not one correct answer. However, gaining an understanding of the contributing arguments can help put the factors into perspective. It will be interesting to track how this develops across the course of 2023, and what new solutions will be brought to the conversation.

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