INTERVIEW

Gene therapy is having a monumental year: how can the industry keep up with supply?

Lauren Coyle, Commissioning Editor, *Cell & Gene Therapy Insights*, talks with **Suman Subramanian**, Head of Commercial Operations, Catalent Cell and Gene Therapy, to discuss the major achievements in the gene therapy market in 2023, with a focus on reliable manufacturing processes and strategies to enhance predictability while reducing waste in gene therapy manufacturing.

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Q Can you discuss the key milestones achieved in the gene therapy market in 2023 and how these advancements have impacted the therapeutic landscape?

SS: Gene therapy is experiencing unprecedented growth, surpassing expectations, especially in the post-pandemic era. The past 2 years have served as a testament to this growth, marked by a significant number of approvals. In 2023, notable approvals included that of ELEVIDYS for Sarepta and ROCTAVIAN™ for BioMarin, each representing distinct drugs that have the potential to shape the industry. ELEVIDYS addresses muscular dystrophies, catering to a substantial patient population with a high demand for the product. ROCTAVIAN targets hemophilia A, making it equally significant in its therapeutic impact.

These approvals are shaping the future trajectory of gene therapy. Current estimates indicate that the market continues to grow at a double-digit rate, steadily approaching the

US$20–30 billion mark. The gene therapy space is indeed an exciting and dynamic field to be a part of at this point in time.

Q What supply chain strategies have proven effective in addressing accelerated timelines associated with gene therapy development?

SS: One of the most common inquiries we receive from new clients revolves around accelerating timelines when engaging with a CDMO. The biggest factor that impacts timelines in the gene therapy space, given its time sensitivity, is material procurement and analytical work. Post-pandemic, the focus on materials and supply chain has intensified due to significant lead times and challenges in procuring products.

Most CDMOs and innovator companies have increasingly adopted the strategy of standardized materials and specifications. Although the gene therapy market is not entirely commoditized, certain elements can be standardized. Moving towards standardized materials and specifications is crucial. This approach allows for different fulfillment strategies such as maintaining stock for certain materials. By maintaining a certain safety stock and swiftly pulling materials when needed, we can substantially reduce the material requirements' impact on the overall timeline, thus reducing the overall program risk.

Another important challenge in the gene therapy supply chain is material movements within the facilities. Establishing and implementing more traditional methods, such as trying to establish a supermarket approach for 'just-in-time' materials, is essential. In the bioprocessing industry, certain materials require just-in-time delivery, limiting their storage time at ambient temperatures. Having certain tools in place to precisely track when the materials are needed is critical. These strategies are proving to be efficient and will likely continue to play a significant role as the gene therapy space expands.

Q Focusing on the challenges in developing reliable and scalable manufacturing processes for gene therapies, what strategies or innovations can be implemented to ensure a robust manufacturing pipeline?

SS: The most important aspect is addressing standardization and the adoption of a platform process. Regulatory agencies, including the US FDA, have already indicated the importance of innovators, manufacturers, and CDMOs embracing a platform process. This approach provides a more predictable and streamlined manufacturing environment. Currently, platform processes have not reached the peak of where they need to be, and there is significant interest from clients moving towards the platform process.

The reasoning behind a platform process lies not with the amount of DoEs attempting to achieve the end goal, but with trying to perfect an improvement in the overall process. The focus is on directing energy into certain critical DoEs, based on experience and history, that have proven to be the most effective.

Another important consideration is equipment. Avoiding the creation of multitudes of equipment trains that complicate the process is crucial. A predefined equipment train will allow for easy integration into the platform. Equally important is not tying the equipment

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train to a specific scale, which has remained a challenge in the industry. Multiple equipment trains with different scales can be offered, giving clients flexibility, but also remaining within the confines of being a platform process.

Lastly, enabling partnerships within the industry remains indispensable. Taking a product from a gene to the clinic largely relies on multiple partner collaborations, each contributing unique expertise, both in-house and external. Understanding how to work with partners and establish relationships to predefine your service level expectations, certain test timeframes during production, and establishing information upfront with clients is paramount.

Q Can you elaborate on the specific challenges in AAV development and manufacturing, and how the industry is working to overcome them?

SS: When looking at over 80% of the molecules pipeline, most clients within this space are small emerging biotech companies and this encompasses the demographic of our clients. Several of these challenges are coming up from an academic or a lab setting where there is not a lot of data to prove how these viral vectors can be scaled. Although there is a wealth of hypotheses and experiences behind the behavior of certain viral vectors and other biopharmaceuticals, inconsistencies and limited data remain.

There remains a lack of robustness in the process of transitioning molecules from the clinic to late-stage manufacturing, with GMP readiness being a consistent challenge. The documentation and adaptation of these processes hold the potential to move towards automation in the future.

While bioprocessing, specifically gene therapy, is not a fully automated process yet, standardization and moving toward a platform may enable some automation. Initiatives such as adapting to paperless technology and implementing e-batch records will enable advancements to overcome these challenges.

Q Integrated solutions from raw materials through commercial supply are crucial for gene therapy development. How can companies effectively plan early for a commercial-ready process, and what role does collaboration with experienced partners play in achieving this goal?

SS: Gene therapy manufacturing can be inherently complex, comprising of various processes, materials, and technologies. Clients want an end-to-end provider capable of guiding their gene or sequence from inception to the clinic. Companies that can provide the end-to-end

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supply plan, or as we call it, an integrated supply plan, play a pivotal role. It entails seeking the starting material and strategizing from day one to the endpoint, such as the clinical setting.

Clients are actively looking for partners who simplify the supply chain and who can assemble various pieces of the process together, while also taking accountability for bringing the product to the clinic. This approach simplifies the program governance, eliminating the challenges of dealing with multiple partners as well as simplifying structures, commercial models, and coordinating dates. It de-risks the entire supply chain and also reduces the complexity.

Q Further to that, how can a partner with commercial manufacturing experience contribute to the success of gene therapy development, both in terms of solidifying processes and navigating the regulatory pathways?

SS: The field is continually evolving with an emphasis on the regulatory landscape. Having the right partner who comprehensively understands the regulatory agencies' requirements, possesses familiarity with global expansion, and holds experience and state-of-the-art facilities is key. This is partly due to regulatory agencies and their guidelines undergoing frequent changes.

Experience in dealing with the FDA and international agencies, what they are seeking, understanding the audit requirements for facilities, and adapting specificities are all important considerations. Clients often overlook these aspects earlier in the process, leading to a bottleneck as they progress through filing, IND submission, and the later stages of clinical phases.

Having partners with extensive regulatory landscape experience and previous success in taking molecules through the regulatory approval cycle is indispensable. Establishing protocols with companies such as Catalent, who can bring valuable experience, is a critical aspect of ensuring success in gene therapy development.

Q Given the importance of supply chain management and delivering gene therapies to clinical trial locations, what specific needs and challenges should be considered and how can they be effectively addressed?

SS: Traditional methods of managing the supply chain and its various aspects remain in place but one key aspect that has an increasing importance is the focus on business continuity planning. Dual or multi-sourcing of critical materials is vital, not only from a commercial competitiveness in pricing standpoint but also to ensure the security of the supply chain.

Several emerging excipients and consumables are becoming new considerations in finding the right suppliers, for example suppliers with an existing Drug Master File, and securing

long-term partnerships are essential. Lessons learned from COVID-19 emphasized the importance of securing partnerships and establishing long-term contracts to help enable the right level of discussions with partners, ensuring service level expectations and lead times are met.

Another important consideration is storage capacity, as most gene therapy products are single-use and can take up significant space and consume substantial amounts of product for processes. Enabling strategic storage capabilities, both within and outside networks, allows swift product movement. Consideration also needs to be taken when looking at partners to help expand support for the patient and product needs.

Q How is the space evolving in terms of the ability to leverage platforms, for instance, in platform assay development? What are some of the keys to capitalizing on the benefits of this?

SS: The first considerations when discussing a platform are cost-effectiveness and reduced timelines due to the plug-and-play nature of a platform. Each time a platform is used, the redundancy and development are minimized, specifically in terms of analytical methods and associated documents.

In certain cases, it is essentially a plug-and-play scenario, resulting in a significant amount of time and rework being saved. This, in turn, has cost benefits passed on to clients, further reducing timeline risks due to the ability to execute specific processes with a specific platform, multiple times across several years.

On the analytics side, adopting platform assays involves adapting the client's gene of interest or other specific needs into an existing platform. This approach avoids the need to redevelop an entire assay, saving weeks or even months. Suitability assessments can be conducted to better understand the suitability of the platform within weeks of engaging the client.

Another significant aspect is the predefined and templated report summaries of how the assays and platforms perform. This not only helps to shorten the cycle of the work but also reduces the overall timeline and associated costs.

Q 'Right First Time' is a key aspect of the Catalent approach. Can you pick out some specific areas where this is particularly important?

SS: The concept of 'Right First Time' is not new to Catalent and has always existed in the industry, but it is evolving in various spheres of life sciences. In today's landscape, with more focus on platforms and standard processes, the expectation is to achieve accuracy the first time. Speed is of the essence to the market and not achieving 'Right First Time' could mean losing the race to the market.

The most important complexity is the tech transfer of a process. Whether it is transferring a process within a CDMO's network of facilities or from a client, it is a critical phase. Implementing an efficient protocol with defined stage gates for decision-making along with risk identification significantly reduces the risk and increases the chance of getting it 'Right First Time'.

Effectively measuring key performance indicators and metrics during the manufacturing process plays a vital role. Most manufacturing processes, whether platform or non-platform,

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can have predefined success criteria of what is expected, ensuring the right schedule, people, and talent at the right steps of the process. Regular stage gates, checkpoints, and communications greatly enhance the chance of success. Conversely, getting it wrong the first time can result in a ripple or cascading effect of losing a slot in the schedule that was meant for another program or another batch.

Q Finally, the focus on simplification of the manufacturing process includes minimizing unnecessary tweaks and reducing the number of supplier notes. Can you discuss some examples of successful simplification strategies in gene therapy manufacturing, and how they have positively impacted efficiency and reliability?

SS: Simplification always leads to more predictability, leading to less waste in the overall process and a significant improvement in the COG. COG is by far the single most important aspect looked at to scale programs, especially for rare diseases where batch yield may be limited.

Our continuous improvement teams play a pivotal role in identifying opportunities to simplify processes, eliminate waste, and cut redundancies. This focus on simplification not only has a measurable impact on the COG but also addresses areas where deviations in the process may occur.

Efficient application and enforcement of corrective and preventative actions are essential for maintaining the facility. Given the specificity of the area, historical data can help to identify potential deviations, ultimately reducing timelines, since the ability to manufacture correctly and release the product to patients is of utmost importance.

Manufacturing, along with effective documentation and reduced deviations all allow for the release of the product or disposition. Further, having trained operators within the organization to comprehend the nuances reduces delays and the associated risks of these complex operational aspects.

Predictable costs and lower contingencies are key considerations. Understanding the platform process, identifying waste, and utilizing tools such as enterprise resource planning and planning tools, contribute to predictable costs. This approach allows for an accurate estimate of program costs and minimal contingencies, ensuring that clients don't bear unnecessary costs later in the process.

BIOGRAPHY

SUMAN SUBRAMANIAN joined Catalent Cell & Gene Therapy Commercial Operations in 2022. In his role, he is responsible for integrating commercial strategy and fostering partnerships across the organization. Suman leads the BU commercial operations council/partnership to deliver best-in-class commercial performance. Before joining Catalent, he spent 6 years in various roles at West Pharmaceutical Services. During his time

there, he was tasked with integrating the world's largest API manufacturing facility into an existing supply network with over 3,600 supply nodes in Kalamazoo, MI and Puerto Rico.

Subramanian obtained a MSc in Pharmaceutical Systems Management from Rutgers, and Bioinformatics from the New Jersey Institute of Technology. In addition, he is fluent in speaking six languages and proficient in writing in them.

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AUTHORSHIP & CONFLICT OF INTEREST

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