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WHITE PAPER

Gene Therapy Manufacturing: Ensuring Manufacturing Success

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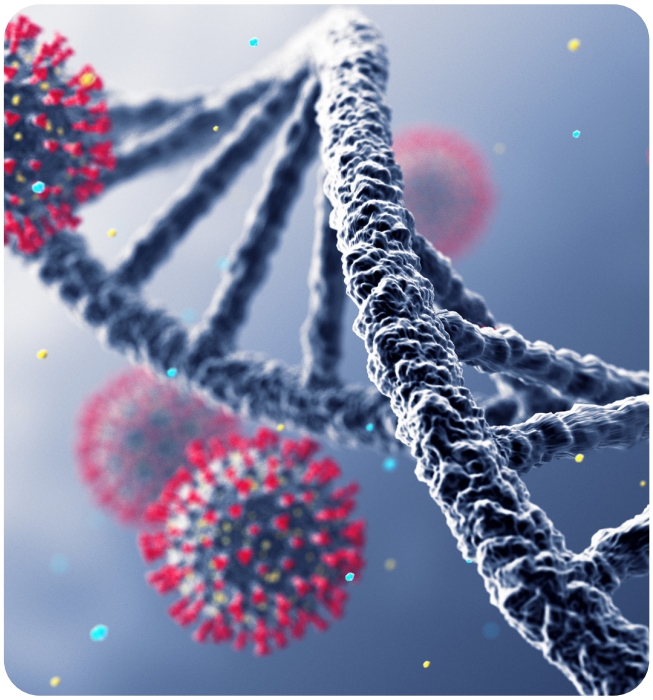
Gene therapies are an emerging and exciting space in the biotech world, with the potential to positively impact patient lives all over the industry. Many gene therapy companies are currently working on novel therapeutics for previously untreatable diseases. With the unique potential to restore the function of a gene, gene therapy may allow patients to manage otherwise challenging diseases without the need for ongoing treatment. As pioneering gene therapies move through development, manufacturing, qualification, and ultimately regulatory approval, we've gained a better understanding of the development pathway. This allows companies to make informed strategic plans that circumvent hurdles and pitfalls in the development process.

Background

In general, gene therapies employ techniques that modify a patient's genetic material for the purpose of treating a genetic disorder or pathology. Multiple approaches can be utilized for gene therapies, including adding new copies of a gene that is not functioning appropriately, replacing a defective gene or replacing a gene that was completely absent. Under the umbrella of gene therapy is gene editing, which involves using techniques that modify the patient's existing genes, resulting in a change in the genome. All of these novel approaches offer potential therapeutic intervention for diseases where none existed before. It is an exciting field. By virtue of the novel nature of the field, there is significant complexity regarding development paths and manufacturing.

Gene Therapy Platform Overview

There are broad and varied approaches to accomplish delivery of gene therapies. Described below are some of the more common platform approaches to gene therapies.



01

Viral Vectors

A viral vector is used to insert a target gene or DNA sequence into a patient's or donor's genome. Lentiviral vector (LVV), adeno-associated viral vector (AAV), and adenovirus are a few common examples. Vectors are often modified for safe handling (i.e. not inducing viral load in host) and are designed to be stable and easily quantifiable to ensure consistency during manufacturing.

02

CRISPR/Cas9 and Other Gene Editing Technologies

CRISPR is an acronym for “Clustered, Regularly Interspaced, Short Palindromic Repeats”, and refers to a recently developed gene editing technology that removes specific sequences and replaces DNA in a highly targeted manner. CRISPR technology allows for gene edits to be made in a very specific location compared to viral vector platforms, which insert in less targeted locations. CRISPR uses two different types of molecules, guide RNA and a nuclease (gene editor, typically Cas9) to modify a target gene.

CRISPR is not the only method of gene editing. Rare-cleaving endonucleases also have the ability to make targeted genome modifications. A few examples of rare-cleaving endonucleases include zinc-fingered nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and meganucleases (MNS, or homing endonucleases).

03

Non-Viral Vectors

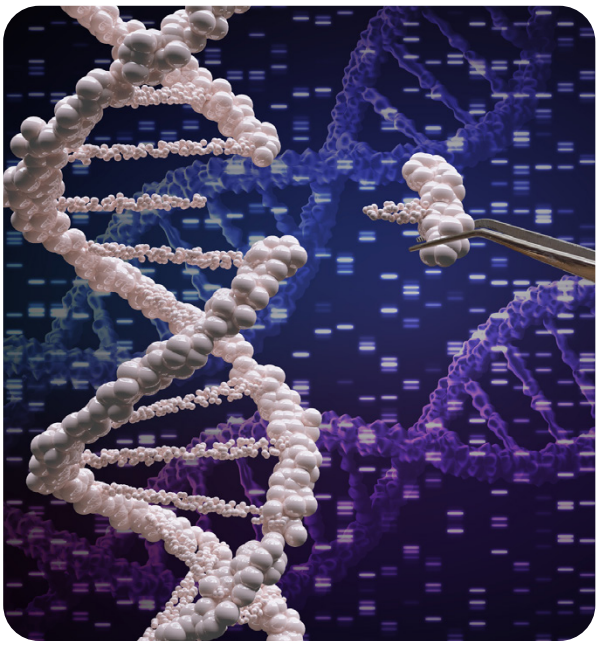
Non-viral vectors, such as transposon systems, are another method of gene therapy delivery. Transposons are DNA sequences that have the ability to be translocated within host cell chromosomes, create or reverse mutations and act as a gene delivery system.

Commonly used transposon systems are Sleeping Beauty™, piggyBac™, and TcBuster™. Sleeping Beauty™ has been used in ex-vivo gene delivery to stem cells for both immunotherapies and regenerative medicine.

04

Oncolytic Viruses

Oncolytic viruses are used in various types of immunotherapy. Herpes simplex virus type one can be modified to produce an immune response and production of immune cells. Imlygic® is one approved oncolytic virus therapy for the treatment of melanoma.



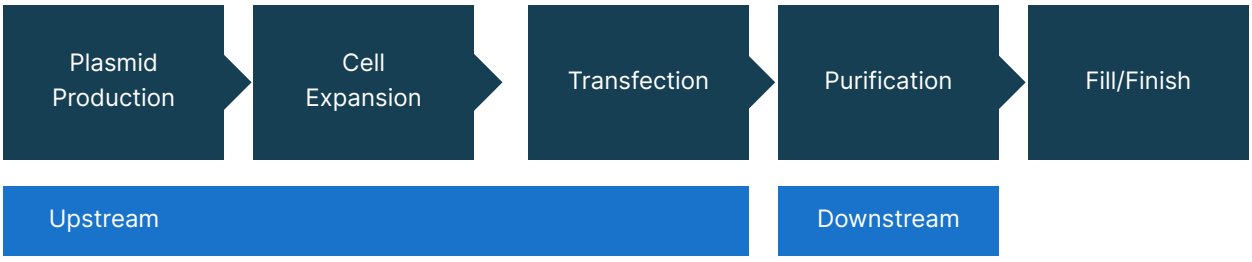
Overview of Manufacturing for Gene Therapies

Manufacturing processes for gene therapies have some significant technical and regulatory challenges to consider. The processes are often more complex than other types of pharmacological manufacturing, and additional safety testing is required to ensure less risk to patients. This is especially true in viral vector manufacturing which requires typical sterility testing but also replication competent viral testing (RCL). RCL tests have a longer turnaround time and add to the total time to product release for viral vectors.

Adherent vs Suspension Cell Culture

Viral vectors and other types of gene therapies are difficult to scale and have decreased efficiency when compared to protein and antibody manufacturing. Most organizations begin development with adherent cell culture methods, as these are easier to produce on a small scale initially and have lower startup costs than suspension methods. Suspension methods provide a much higher yield, less chance for contamination, and less overall lot to lot variability than adherent methods. However, suspension methods have much higher startup costs and require more time to implement. Purchasing bioreactors can take several additional weeks due to long lead times for equipment, as well as the time required to install and validate equipment.

Typical Viral Vector Manufacturing Process Example

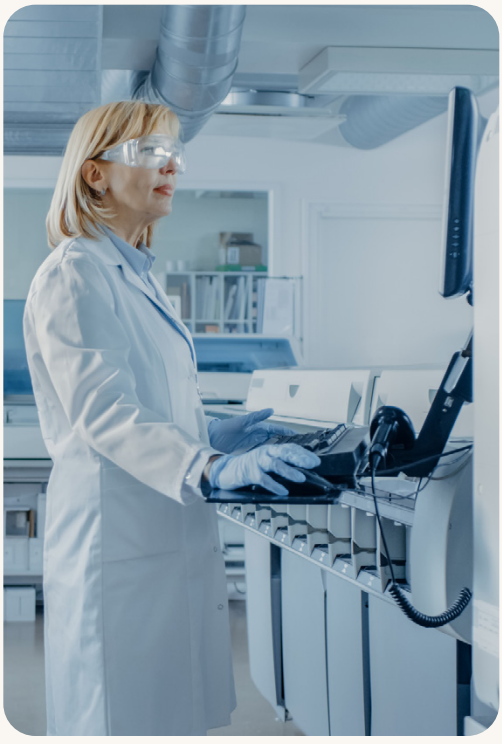


When planning for a new gene therapy program, it is critical to bring in an experienced, cross functional team to plan for manufacturing success.

Listed below are some of the key considerations.

Manufacturing Facilities and Personnel

The first consideration when planning for a successful manufacturing process is the facility itself. Many companies, especially those in the start-up space, will choose a "virtual" model or contract development and manufacturing organization (CDMO) model for early clinical phases and beyond. There are, however, plenty of companies that will use their own facilities. "Cleanrooms on demand" have become more popular in recent years. These are clean room facilities or suites that are open to rent by a particular company or organization and allow access to a facility and equipment but a company can bring their own trained personnel rather than relying solely on a CDMO site for manufacturing personnel.



Keep in mind that it is usually best to look long term for facilities that are certified GMP, unless the product is for research use only or early phase. Transfer of the process to a GMP facility can have some challenges compared to development and GMP production at the same facility. **Here are some key factors or considerations when planning or evaluating a new manufacturing facility:**

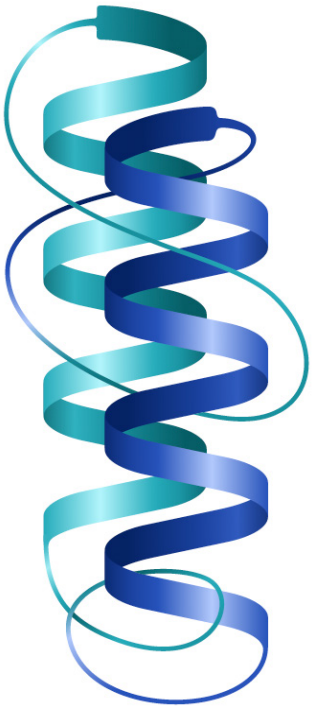
- Geographic location and qualification of site (inspection history, facility GMP certification, etc.)
- Appropriate HVAC system design to control for differential pressures, room temperature and humidity
- Planned personal and material flow from start to finish (including waste removal)
- Well-designed gowning areas
- Manufacturing labs or suites conductive to aseptic processing
- Dedicated suites per process or line clearance procedures as appropriate
- Central and controlled storage of raw materials and reagents
- Appropriate backup power for critical equipment
- Expansion capabilities for future scale-up if needed
- Previous experience in development as well as GMP production of comparable products
- Manufacturing schedules and slots aligning with necessary program timing, or with built in flexibility

Of course, it is impossible to manufacture anything successfully without the correct number of well-trained personnel. It is inevitable that personnel come and go over the lifespan of a project, making effective training plans essential. Employee turnover is generally higher at CDMO sites and site stability should be carefully considered when initiating a project. Water, pilot, and engineering runs are necessary process steps to not only ensure a process is working, but also as hands-on training opportunities. Periodic scheduled water runs are invaluable for new employees to train and/or troubleshoot complex manufacturing processes.

Reagents and Raw Materials

Almost all gene therapy products require starting materials in other biologic manufacturing areas (plasmids, mRNA, proteins, buffers, etc). This adds to the complexity of supply chain planning and makes it even more important to have contingencies to help mitigate any future supply constraints.

In the current climate of well publicized supply chain challenges, it is essential to plan contingencies when sourcing reagents and raw materials. Ideally, second and even third vendors are identified and qualified for all key manufacturing components and reagents. While this exercise can take considerable time, effort, and resources to complete, it has the potential of saving months (or more) of critical program time when the inevitable supply chain issue arises. Advanced supply chain planning and appropriate forecasting are necessary for project success, as well as minimizing financial impacts to the company. Changes in critical raw materials (plasmids, media, etc) can also result in changes in product quality and are therefore of regulatory and quality concern. Minimizing supply and raw material changes later in development makes for smoother regulatory submissions as well as time and cost savings in the change control process.



Cost and lead time are important factors when planning for all reagents and raw materials, and it is important to keep in mind the substantial difference in cost and lead time between GMP grade vs R&D grade raw materials and components. The earlier GMP grade starting materials can be introduced to a process the better, even with the increased cost. This allows for a more accurate picture when characterizing raw materials and more time to evaluate vendor's manufacturing capabilities and quality systems.

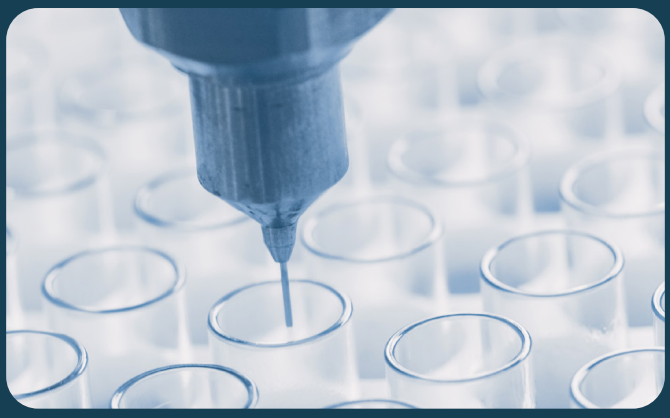
Cell culture remains a core component of gene therapy manufacturing. Serum-free media or other animalfree media sources should be evaluated or at least considered when designing a new cell culture process. This will help to eliminate any issues surrounding animal origin, specifically bovine sources, to make for smoother regulatory submissions and global supply planning. It also helps to limit the introduction of adventitious agents to a therapeutic.

Aseptic Processing, Contamination Control, Single Use Systems, and Analytical Sampling

Aseptic qualification and Aseptic Process Simulation (APS) runs are an integral (and required) part of many biologic manufacturing processes. APS runs are designed to replicate the manufacturing process using a medium that supports the growth of a wide variety of microorganisms to test the capability of aseptically manufacturing with proposed procedures, materials, equipment, and personnel. The number, type, and re-qualification of the APS should be based on risk assessments. Risk assessments are used to determine the severity and the likelihood of a worst-case manufacturing scenario. APS runs are designed based on the risk assessment to include the maximum amount of allowable processing time, interventions, personnel and parameter tolerance to ensure the process remains contamination-free.

Although bioburden, endotoxin and sterility testing are core tests for product safety, removing manual and open processing steps and the early introduction of single use or closed systems is extremely important for managing contamination risk in a process.

Special care should be given to evaluate QC and analytical sampling over the course of the manufacturing process. This is to ensure the correct volumes are collected to complete all designated testing, as well as handled in a timely manner and labeled appropriately. It is a common mistake to overlook the importance of well managed sampling plans and methods when designing and evaluating a manufacturing process.



Timeline Management

Project management is another cornerstone of ensuring project success. Choosing a project manager with particular experience planning manufacturing timelines is an invaluable asset to any team. Especially when using a CDMO model, the availability to book suites and general lead times for biologics manufacturing have become challenging in recent months and years due to both COVID-19 therapies and vaccine production, as well as general boom across the biotech industry. Early communication and planning with external or internal partners are crucial to the timely completion of any project.

Process Scale-Up

Many manufacturing processes will need to be scaled up either due to demand or to support different phases of a particular project. The transition between adherent and suspension methods for cell culture is a complex and fairly common issue with gene therapy processes. The adherent cell culture method allows for cheaper and more flexible process design early in manufacturing development, however many companies will need to transition from adherent to suspension methods to produce at scale for clinical and commercial product. If this is a consideration for a process, it is important to recognize the time and resource differences between adherent and suspension cultures to ensure enough time is planned to transition between the two. Comparability between past and proposed processes is an analytical and a regulatory requirement when completing any process changes or scale-up projects.

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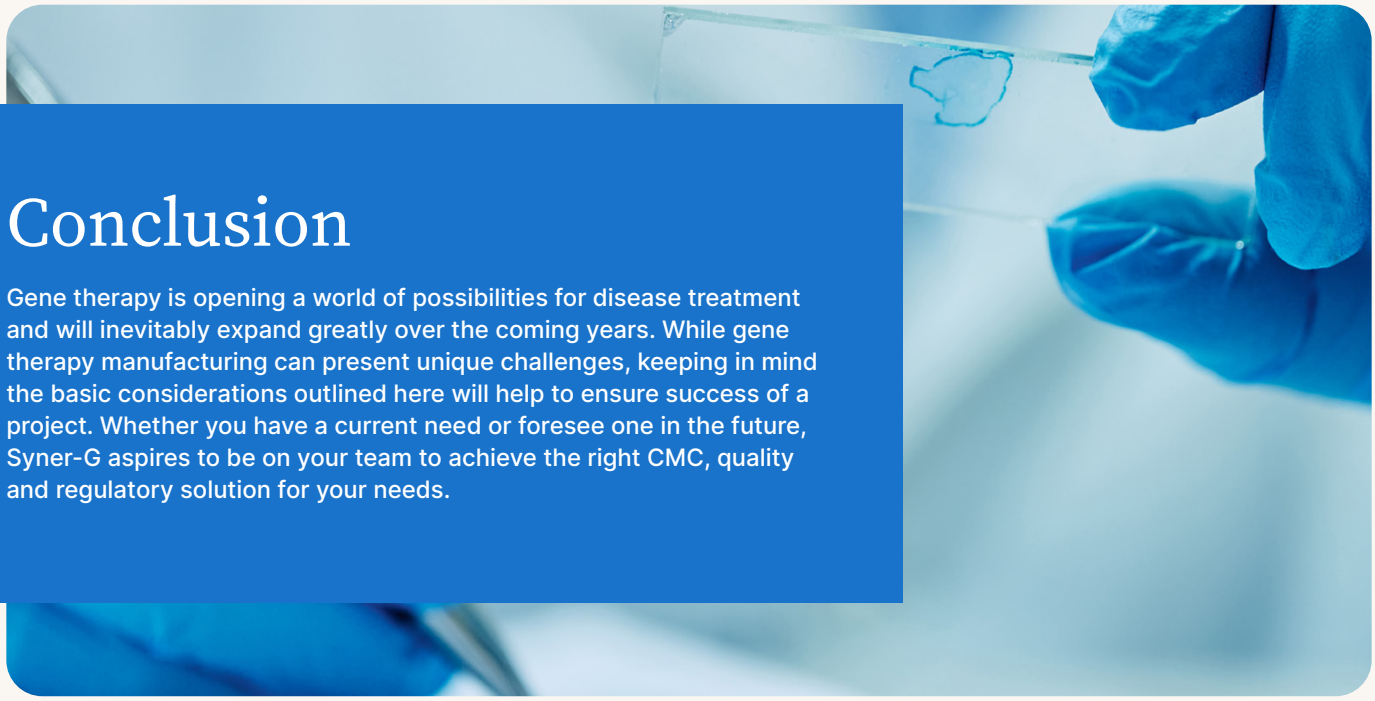
Regulatory Considerations

In the US, gene therapy products are regulated by the FDA's Center for Biologics Evaluation and Research. In the EU, gene therapy products are categorized under advanced therapies and these products are designated as Advanced Therapy Medicinal Products.

Given the novelty of these treatment modalities, the lack of significant pharmaceutical development precedence and the potential for increased risk to patients, the regulatory framework for the clinical development and commercialization has been minimal and conservative. Recent emergence of increased interest has resulted in issuance of several guidance documents from the FDA and EMA to facilitate the expedited development of safe and efficacious life saving gene therapies.



Conclusion

Gene therapy is opening a world of possibilities for disease treatment and will inevitably expand greatly over the coming years. While gene therapy manufacturing can present unique challenges, keeping in mind the basic considerations outlined here will help to ensure success of a project. Whether you have a current need or foresee one in the future, Syner-G aspires to be on your team to achieve the right CMC, quality and regulatory solution for your needs.

ABOUT

Syner-G

Syner-G is the premier solution provider of Chemistry, Manufacturing, and Controls (CMC) services for the life sciences industry. The company's approach is based on CMC 360™, a fully integrated suite of CMC solutions that encompasses pharmaceutical development, regulatory affairs, and quality/cGxP compliance. The entire Syner-G organization is built around the premise of guiding small molecule, biologics, cell and gene therapy, and medical device innovators through the CMC process.

Since its founding in 2007, Syner-G has enabled clients in their quest to bring life-saving and life-enhancing products to patients. Today, the company has grown to more than 100 employees globally, been recognized as one of the "Top 10 Drug Development and Consulting Services Companies" by Pharma Tech Outlook, and served as an integral part of more than 500 various types of successful regulatory filings. For customers looking for offshore resources, Syner-G also offers CMC services based in India. Syner-G's operations in India follow the same CMC 360™ model used in the U.S., further differentiating the company from typical CMC consultants.

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