SAFC®
Pharma & Biopharma Raw Material Solutions

Whitepaper

Risk Mitigation Strategies for Raw and Starting Materials used in Gene Therapies

Despite being described as one of the most complicated treatments ever devised, gene therapy is projected to become a $5 billion per year industry, worldwide, by 2026. The US Food and Drug Administration (FDA) has predicted they will be approving between ten and twenty gene and gene-modified cell therapies per year by 2025.

Recently approved cell and gene therapies are delivering impressive results for patients who otherwise have exhausted all treatment options or have had no options available to them. The combination of these results, along with a deeper understanding of the underlying biology, is fueling this explosive growth. With nearly 800 of these therapies currently in development , the FDA's prediction appears to be on target.

While these innovative modalities are generating significant excitement and anticipation among patients and caregivers, manufacturers are faced with many challenges in the journey from development to commercialization including:

- **Lack of a standardized pathway:** Unlike most monoclonal antibodies which follow a relatively templated process in discovery and clinical development, gene and cell therapies often have highly complex discovery paths and mechanisms of action.
- **Accelerated development timelines:** Because gene therapies tend to focus on rare diseases with a high unmet need, they often have accelerated regulatory review pathways. Traditional phases are often consolidated and phase-related activities performed in parallel to accelerate progress.
- **Newly established and evolving regulatory guidance:** The FDA finalized guidance for several aspects of development of gene therapies in 2020. The novelty of the guidance, however, contributes to the complexity and risk of advancing these novel therapeutics.
- **Risks related to process development and manufacturing:** Success in this complex and highly competitive field requires managing uncertainties and risks throughout process development and manufacturing. This can be especially challenging when operating with compressed regulatory timelines and a sense of urgency to address significant unmet patient needs.

Within this challenging environment, a number of risk mitigation strategies related to the materials used to produce viral vectors can be employed. In addition to mitigating risk, these strategies can help accelerate progress towards commercialization of these remarkable therapeutics.

Sourcing Raw Materials

Animal or human origin materials not manufactured under a quality management system and used at a stage in the vector manufacturing process where there is no opportunity for clearance can pose a risk to patient safety. Fortunately, several steps can help ensure critical raw materials are not contaminated by adventitious agents:

- Avoid use of animal-derived components, if possible
- Source from well-known, safe geographies and use screened donors
- Test for species-relevant contaminants

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- Inactivate by validated methods using heat, irradiation and filtration
- Use at least two orthogonal mitigation methods for high risk material

Raw materials and cell culture media, historically used for research purposes, can be manufactured under good manufacturing processes (GMP) to reduce variability, ensure traceabilty and ensure supply robustness. Use of GMP under a quality management system (e.g., ISO 9001) ensures high lot-to-lot consistency and the documentation to help users with their risk assessments and align with regulatory guidelines. Suppliers should also have standard operating procedures and a corrective and preventative action (CAPA) methodology in place to rapidly and effectively address any quality issues.

To further protect processes and patients, a supply agreement between the user and suppler should be created to establish:

- Technical specifications
- Quality specifications
- Change management details

Accessing Comprehensive Documentation

The complexity of gene therapies, combined with compressed timelines, evolving guidelines and lack of extensive historical process information, makes producing and gathering data for regulators time- and resource-intensive. Companies able to rapidly and efficiently collect such information for regulatory submissions can increase the chance of getting a therapy approved in a timely manner. In contrast, delays in accessing critical supporting documentation from suppliers can cause uncertainty across the supply and manufacturing chain and delay progress of a novel gene therapy.

Our Emprove® program reduces this burden for gene therapy manufacturers. The program is designed to provide comprehensive and thorough documentation of raw and starting materials for both risk assessment and regulatory submission. The program reflects the latest regulatory requirements and anticipates industry expectations not yet covered by regulations, a critical aspect given the rapid evolution of the gene therapy industry. Emprove® raw materials also have rigid criteria related to change modifications, which ensures the user is proactively informed of changes.

Three types of dossiers are available for hundreds of raw and starting materials in the Emprove® program and are used to facilitate raw material qualification, risk assessment and process optimization efforts (Table 1):

- The Material Qualification Dossier supports raw material qualification and speeds up drug filing preparation. It includes content on manufacturing processes, product characterizations, regulatory certificates, stability summary, and more.
- The Quality Management Dossier supports quality risk assessment according to ICH Q9 and EU 2015/C95/02 by offering extended information on the supply chain, Quality Management System as well as stability data.
- The Operational Excellence Dossier supports process optimization and safety risk assessment activities around Elemental Impurities (ICH Q3D), Product Quality Reports, and analytical procedures and Technically Unavoidable Particle Profiles (if applicable)

Table 1: Emprove® program dossiers provide comprehensive documentation for qualification, risk assessment and process optimization

Raw and Starting Materials		
Material Qualification Dossier Information to start a material qualification	**Quality Management Doossier** Answers questions during quality risk assessment	**Operational Excellence Dossier** Supports process optimization and safety risk assessment
- General Information - Manufacturing Flow Chart - Characterization - Control of drug substance - Reference standard - Materials - Container closure systems - Stability	- Quality self-assessment - Audit report summary - Supply chain information - Stability data*	- Product quality report - Elemental impurity information - Analytical procedure - Technically Unavoidable Particle Profiles (if applicable)

Ensuring High Quality Endonuclease

In viral vector purification, impurity clearance is critical and directly impacts patient safety. A critical step in the purification process is reduction in the size and quantity of extracellular nucleic acids by endonuclease enzymes. While use of this reagent predates the gene therapy industry by decades, it remains a vital component in the manufacture of viral vectors, digesting DNA in the extracellular space. Endonucleases are available from many sources and selection of the appropriate quality for viral vector manufacturing is essential.

Benzonase® endonuclease is a genetically engineered nuclease from *Serratia marcescens*, able to attack and degrade all forms of DNA and RNA. Because of its critical role in viral vector manufacturing, it is manufactured according to ICH Q7 GMP guidelines and has a Drug Master File in place with the FDA which can be cited in regulatory filings. In addition to the stringent quality control and extensive documentation packages for Benzonase® endonuclease that are available via the Emprove® program, the Safety Plus version offers enhanced quality and elevated risk mitigation.

Benzonase® endonuclease Safety Plus Emprove® Expert is manufactured using a non-animal origin, chemically defined fermentation medium. Release testing confirms the absence of mycoplasma and adventitious viruses for enhanced product safety. Tailgate samples for the large pack size are provided to avoid opening the large pack during incoming goods control, adding a further layer of safety.

Conclusion

In the development and manufacture of gene therapies, biopharmaceutical companies must effectively balance the need for accelerated timelines with risk mitigation. Among the strategies which can be employed to support these objectives are those focused on raw and starting materials. These materials must be of the highest quality, be supported by a robust and transparent supply chain and come with the documentation needed to meet regulatory requirements. Attention to these details will help ensure that progress toward the commercialization of breakthrough gene therapies continues at rapid pace.

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1) The STAT Guide to Viral Vectors, the Linchpin of Gene Therapy (2020)

2) "Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies," Food and Drug Administration, press release, January 15, 2019, fda.gov.

3) Alliance for Regenerative Medicine 2019 annal report **https://alliancerm.org/sector-data/2019-annual-report/**

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