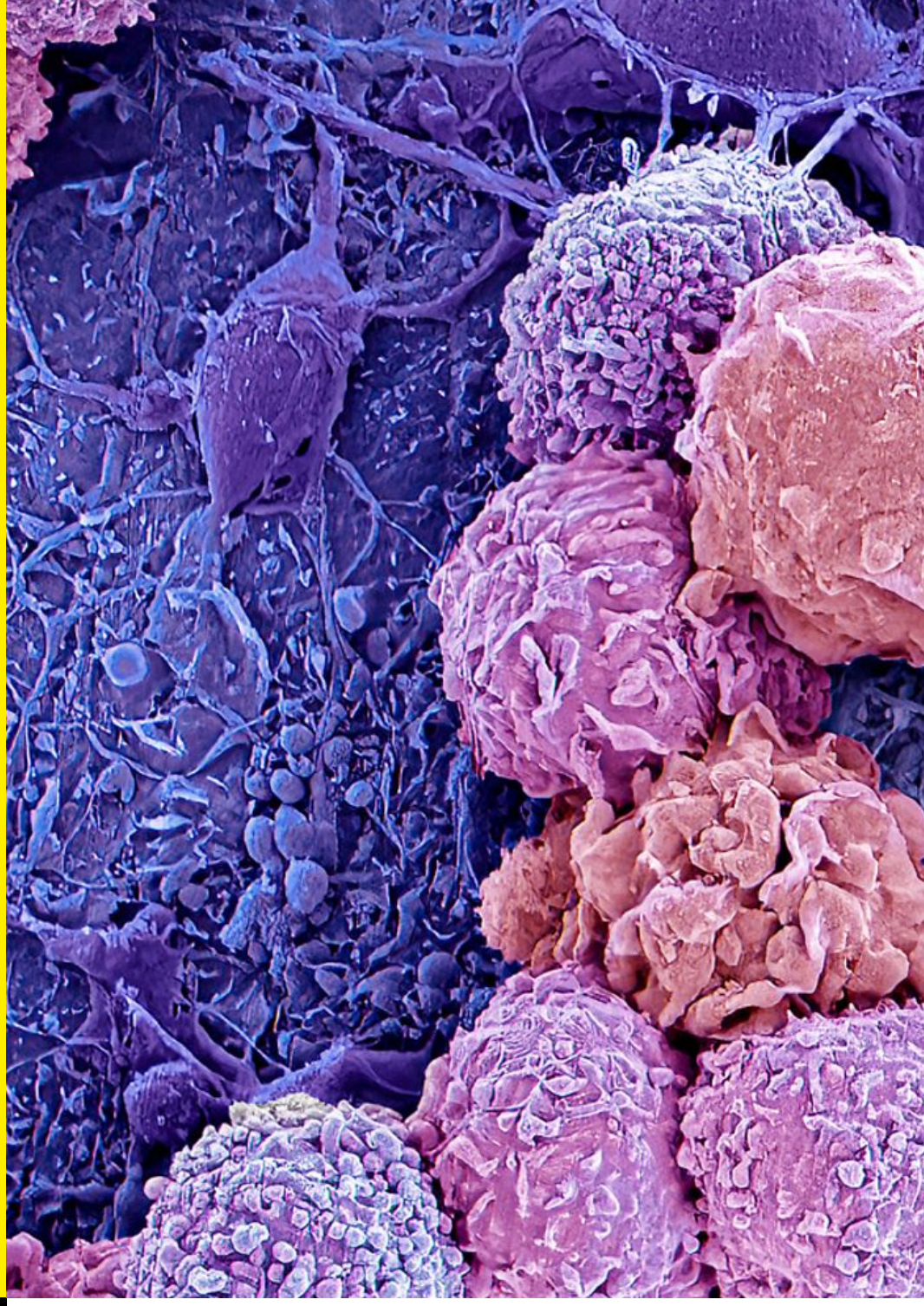
SARTORIUS



Raw Materials in Focus: Enabling Platform-Based Development in Advanced Therapies

Editorial

Challenges in Traditional Drug Development

Traditional drug development has focused on targeting specific pathological mechanisms to treat diseases. However, as our understanding of underlying molecular networks continue to evolve, it is now recognized that most disease states can arise from multiple, intricate and complex biological processes. For instance, while central to the development of melanoma, the activating V600E BRAF mutation is only found in about 50% of clinical cases that lack chronic sun exposure.[1] Additionally, it is now recognized that frontotemporal dementia (FTD) shares clinical features with amyotrophic lateral sclerosis (ALS), linked by 17 common genes in familial forms of both conditions.[2] The complex and unclear causes of these severe conditions indicate that an ideal pathological marker for therapeutic targeting often doesn't exist for any given patient population. Consequently, the effectiveness of a specific therapeutic agent is limited by the prevalence of the targeted disease marker within the patient population.

This therapeutic disconnect between unmet medical need, prevalence of a druggable target, and the required resources for drug development is even more widespread in the context of rare disease. Typically, the size of the entire patient population is not sufficient to justify a favourable business case of a drug development campaign. As such, drug developers are often limited to the selection of molecular targets in disease states that are present in sufficient numbers to justify the staggering costs of the therapeutic development process.

However, like our understanding of the underlying cause of disease, the therapeutics being developed to treat them are also progressing. In the past decade, incremental technology progression has given way to an avalanche of advanced therapies that, for the first time, have the potential to correct the underlying genetic causes of complex disease syndromes. These advanced therapies (ATs), including cell, gene and RNA therapies, challenge the very foundation of the traditional "one drug, one disease" model by enabling rapid modifications to target patient-specific disease drivers.

Platforming for Facilitated Regulatory Approval and Rapid Drug Development

The flood of novel therapeutic technologies with curative potential is bringing additional scrutiny to the traditional drug development process from a regulatory perspective as well. The former head of the Center for Biologics Evaluation and Research (CBER), Dr. Peter Marks, is aware of the shortcomings of the current regulatory process in the face of this impending wave of new applications for novel technologies. He has stressed the need to transform the regulatory environment to support the development of these treatments through accelerated endpoints, flexibility from the regulators, and standardized manufacturing of ATs.[3]

The concept of platformed technologies, originally developed by the FDA's Oncology Center of Excellence (OCE) and described in the Omnibus Appropriations Act of 2023, has emerged as a potential catalyst in this AT-focused renaissance. Emphasizing the use of standardized manufacturing, platformed technologies can support regulatory approval of multiple but related biological products.[4] At the core of the proposal, Marks emphasizes the ability of manufacturers to use data from one regulatory application to support additional applications that are related and produced by the same technology.[5]

Ultimately, an AT manufacturer securing a platform designation could, in theory, significantly accelerate clinical development while reducing costs, which is vital for patients with rare diseases and the advancement of personalized medicine.

This concept of standardized manufacturing of related biologics, such as CRISPR-Cas9 and antisense oligonucleotides, is actively being explored in both basic research and clinical settings. These therapeutic modalities offer significant potential for modification of the targeting moiety, the gene target, while maintaining constant manufacturing, formulation, delivery, and safety testing methods of the therapeutic asset. Notable examples include:

- **Precision genome editing for cancer immunotherapy:** CRISPR-Cas9 was used to knock out endogenous T cell receptor (TCR) genes and insert a patient-specific tumor neoantigen-specific TCR, creating personalized TCR-modified T cells.[6]
- **Correction of mutant alleles in Huntington's disease:** CRISPR-Cas9 has been used to correct multiple mutant alleles associated with the late-onset neurodegenerative disorder Huntington's disease.[7]
- **Tailored therapy for a rare neurodegenerative disorder:** In an N-of-1 trial involving a child with neuronal ceroid lipofuscinosis 7 (CLN7), researchers developed a patient-specific splice-modulating antisense oligonucleotide drug to correct missplicing and restore gene function, thereby improving symptoms.[8]

The Anatomy of a Platform Technology

Dr. Marks makes his vision clear as to how platforming technology can facilitate drug development for cell and gene therapy by eliminating the need for constant reinvention of manufacturing processes, characterization methods, and toxicology studies:

> *"Let us think about a gene therapy paradigm where there are different tracks—a secreted protein track, an intracellular enzyme track, a cell surface track, a structural protein track—where you could start to think about what we need for the vector information, what you would need for the clinical information to get an accelerated approval, and what you would need to get to a full approval for each of those tracks."*[9]

Once a product using a designated platform is approved, follow-on products would be explicitly permitted to reference data from the previous application, and manufacturing changes to the platform can be done in a single supplemental application for all drugs on such platform.[10]

From this profound, industry changing vision, a draft guidance for drug developers to obtain platform designation was put forth for industry comments in May of 2024.[4] In essence, to qualify for a platform designation, therapeutics must employ technology that is well understood and consistently reproducible.[11] Although not yet finalized, advanced therapy modalities anticipated to be eligible for platform designation include lipid nanoparticle (LNP)s for mRNA vaccines or gene therapy products, chemically defined targeting moieties in conjugation with well-characterized synthetic siRNAs, and LNPs encapsulating various short, single stranded or double stranded oligonucleotides.[4,12]

Though not specifically mentioned, cell therapy and viral vector products could also qualify based on the specified requirements set forth in draft guidance.[4,12] Cell therapy, particularly autologous cell therapy, presents challenges due to the genetic diversity of the raw cellular substrate used in the manufacturing process. However, recent manufacturing trends aimed at improving patient accessibility and reducing costs for autologous cell therapies have led to enhanced targeting moiety designs, significantly streamlined manufacturing processes, and nonviral editing mechanisms. These advancements have resulted in cell products with equivalent or enhanced potency compared to standard processes.[13-15] Further, recent mechanistic studies are shedding light on cellular phenotypes crucial for patient engraftment and long term tumour surveillance.[16] Therefore, by developing robust and simplified manufacturing processes, supported by thorough process characterization and identification of critical quality attributes, autologous cell therapies can be positioned as platform-ready therapeutics.

The Importance of Raw Materials in Developing a Platform

Given the critical importance of standardizing manufacturing methods to facilitate regulatory review and prevent repeated reinvention, it is essential to maintain control and a comprehensive definition of the manufacturing process. Regulators expect consistency in characteristics that should remain unchanged, allowing them to focus on intentional modifications to the asset. This requires reliable process controls to ensure a robust and well-managed manufacturing process capable of delivering the expected product. According to Directive 2001/83/EC, raw materials (referred to as 'ancillary materials' in the US under USP<1043> and ISO 20399) used in these processes must be thoroughly characterized and defined, as the quality of these materials can affect the potency of the therapeutic.[17-19] A study found that switching the base medium from RPMI1640 to IMDM, while using the same lot of serum, resulted in significant changes in T cell phenotype.[20] Thus, inherent variability present in raw material composition or quality can bring inconsistencies that can wreak havoc on biomanufacturing processes of ATs, complicating efforts to achieve a platform designation.

Human serum albumin (HSA) is a commonly used raw material and excipient in various unit operations across the AT manufacturing spectrum, due to its benefits in enhancing the function and stability of LNPs, viral vectors, and cell therapies.[21-24] Mechanistically, the unique structure of the protein has evolved over millions of years to provide several supportive functions, such as binding and facilitating the delivery of diverse ligands, providing conformational flexibility for surface coating, and acting as a potent antioxidant.[22] However, HSA, often mistakenly assumed to be a single purified protein, is actually a complex mixture of post translationally modified, ligand-bound, enzymatically cleaved, or otherwise modified albumin species, along with serum-contaminating byproducts from the organic extraction process. [25,26] Studies have shown that these heterogeneous preparations can lead to significant variations in the functional capacity of the albumin.[27] The differential functional capacity of HSA can impact the overall function of the therapeutic asset. The exact effects depend on the type and extent of HSA modifications, as well as the sensitivity of the manufacturing process to specific HSA deviations.

Thus, the incorporation of a high-quality, consistent, and chemically defined recombinant version of HSA in various AT manufacturing unit operations would be advantageous. The use of recombinant albumin has become increasingly common across therapeutic modalities and unit operations, ranging from cell culture media applications to final formulation. This trend is consistent with the FDA's recent draft guidance on using human- and animal-derived materials, which emphasizes the importance of ensuring the safety, quality, and consistency of raw materials to mitigate risks and maintain product integrity.[28] However, the emergence of the platforming technology draft guidance from the regulators, along with its potential benefits, now mandates the use of consistent raw materials to ensure expected manufacturing outcomes are in line with the foundational platform principles.

Leveraging Recombumin® for Platform-Driven Advanced Therapies

The use of consistent, high-quality reagents is essential to ensure reproducibility in the platform's therapeutic components that are intended to remain unchanged. Due to the incompatibility of HSA with the core requirements outlined in the draft guidance for platformed technologies, developers should consider recombinant sources of human albumin. Sartorius's Recombumin® portfolio offers a high-quality, cGMP-grade, animal- and human-origin-free recombinant human albumin, enabling the development of platform-driven advanced therapies by:

- Providing the functional benefits of HSA without protein modifications that can introduce functional variability, thereby boosting the performance of the manufacturing process.
- Offering extensive analytical and functional characterization, making it the most consistent recombinant albumin available on the market.
- Supplying complete regulatory support packages available with multiple commercial and clinical phase use cases.
- Recombumin®, as a fully recombinant, chemically defined, and ultra-pure solution, can be tailored to optimize ligand and additive profiles for specific applications.

Recombumin® Consistency in Action

A leading biotechnology company has partnered with a major pharmaceutical firm to advance iPSC-derived cardiomyocyte cell therapy for heart disease treatment. A critical aspect of their success has been the transition from HSA to Recombumin® in their manufacturing process. This strategic shift significantly enhanced the consistency and control of their therapeutic product. Unlike HSA, which presented challenges in maintaining uniformity, Recombumin® enabled the company to adhere to stringent specifications, ensuring a high-quality and reliable manufacturing output. This improvement in process control serves as a prime example of the importance of selecting optimal raw materials.

Incorporating Recombumin® into all aspects of cell therapy manufacturing can ensure the consistency of the final cell product in the short term and facilitate the designation of cell therapy assets as platform-compliant in the eyes of regulators.

Paving the Way for Future Success in Advanced Therapies

The rapid advancement of ATs is poised to transform the landscape of clinical science over the next decade. These innovative treatments can target complex pathogenic networks that were once considered untreatable, offering the potential for durable clinical benefits. Furthermore, the core components of many ATs are highly adaptable, making them suitable for deployment in rare diseases, where traditional commercial routes are not viable due to small population sizes. Recognizing this swift evolution in the AT field, regulators are implementing transformational changes, such as modality platforming, to reduce overall investment and development time.

Although the current draft guidance does not explicitly mention cell therapies or viral vectors as eligible for platform designation, industry trends in both therapeutic modalities are rapidly advancing these biologically based manufacturing methods towards being considered platform-compliant technologies. In viral vector manufacturing, significant progress in the understanding of vector critical quality attributes has enabled higher product quality and lower process and product impurities.[29] In autologous engineered cell therapy, significant emphasis has been placed on novel targeting moiety constructs that allow for a highly streamlined manufacturing process by eliminating the cell expansion step. This approach reduces extensive *ex vivo* manipulation of cell products, and when combined with comprehensive manufacturing process analytics, it can mitigate the genetic variability of the starting cellular material.

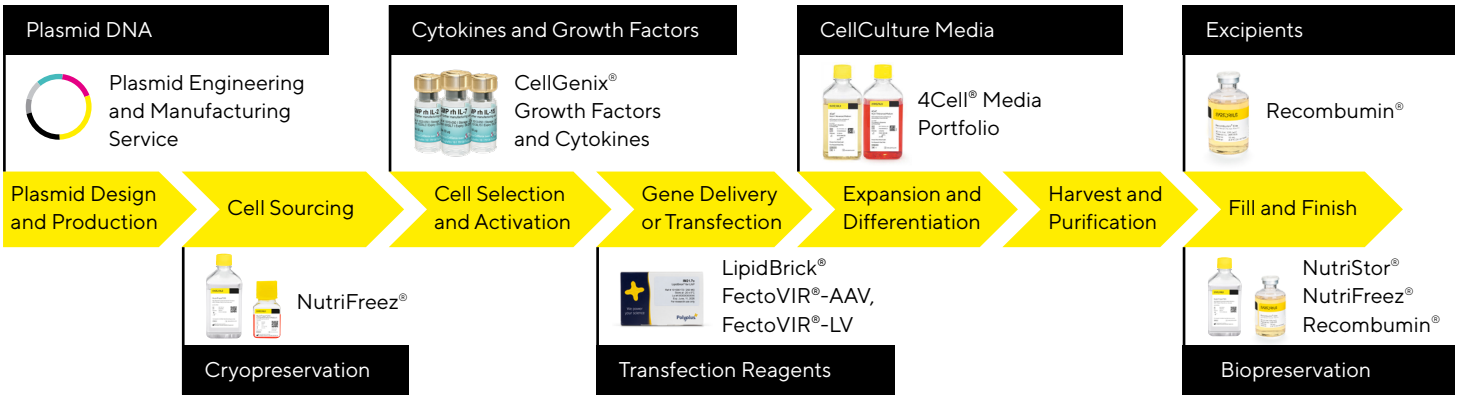


Figure 1: *High level advanced therapy workflow for demonstrative purposes.*

Sartorius is driving a monumental shift in the traditional drug development by supplying platform-ready high-quality raw materials for AT manufacturing. In addition to Recombumin®, Sartorius Advanced Therapies Solutions also provides:

- Plasmid engineering and manufacturing services support tailor-made plasmids for advanced therapy applications and are available in research grade, high quality grade and GMP grades. All grades are manufactured in an animal origin free facility.
- Preclinical and GMP-grade cytokines that are animal-derived component free ensure a seamless transition from preclinical development to the clinical stage.
- Chemically defined and ACF cell culture media portfolios for HEK cells and immune cells, respectively, that enable reproducible, regulatory-friendly, and platform-compatible cell culture.
- LipidBrick®, a cationic lipid library, enables the formation of cationic lipid nanoparticles (cLNPs) that ensures safe nucleic acid delivery to extrahepatic areas vital for leveraging disease targets beyond the liver.[30]
- Comprehensive portfolio of chemically defined delivery reagents suitable for ATs (viral vector and non-viral vector-based therapies).
- As a multifunctional excipient, ancillary, and raw material, Recombumin®'s superior quality enhances performance and reliability and is free from animal and human origins.
- Animal component free biopreservation solutions enable high viability and stability for long-term cryopreservation and short-term cold storage in cell therapies.

With Sartorius, drug developers can utilize raw materials with dependable and repeatable performance crucial to achieve process standardization. By partnering with Sartorius, drug developers can realize these benefits and ultimately bring transformative ATs to the patients who need them most.

Explore how the Advanced Therapies Solutions portfolio can contribute to the robustness of your processes and help you stay ahead of the changing regulatory landscape.

Learn more about advanced therapy quality and regulatory considerations.

Ready to request your sample?
sartorius.com/en/pr/request-cell-gene-therapy-sample

Authors

Dr. Randall Alfano
Segment Technology Manager
Advanced Therapy Solutions
Sartorius

randall.alfano@sartorius.com

After earning his PhD in Systems Biology and Translational Medicine from the Texas A&M College of Medicine, Randall has held several positions in protein and cell therapy process development. As a Segment Technology Manager, Randall supports cell therapy customers by addressing process-specific pain points with the incorporation of critical raw materials from the Sartorius AT product portfolio.

Dr. Sam Hickman
Product Manager for Raw Materials
Advanced Therapy Solutions
Sartorius

sam.hickman@sartorius.com

After earning his PhD in Biochemistry and Biophysics, Sam conducted postdoctoral research at the University of Oxford. He then led process development as a Senior Scientist at a UK-based biotech start-up, focusing on designing and optimizing manufacturing processes for cell products. In 2023, Sam joined Sartorius, where he supported customers in advancing their programs toward commercialization with albumin-enabled solutions. Currently, he is a Product Manager for critical raw materials used in advanced therapies and beyond.

References

1. Ascierto, P. A. et al. The role of BRAF V600 mutation in melanoma. Journal of Translational Medicine 10, (2012).
2. Gelon, P. A. et al. Synaptic dysfunction in ALS and FTD: anatomical and molecular changes provide insights into mechanisms of disease. Front Mol Neurosci 15, (2022).
3. Weschler, J. FDA Eyes New Strategies to Spur Gene Therapy Development. Applied Clinical Trials https://www.appliedclinicaltrialsonline.com/view/fda-eyes-new-strategies-to-spur-gene-therapy-development (2023).
4. U.S. Department of Health and Human Services. Platform Technology Designation Program for Drug Development Guidance for Industry DRAFT GUIDANCE. https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances (2024).
5. Marks, P. et al. On Your Marks: An Interview with Peter Marks. Gen Biotechnology https://www.liebertpub.com/doi/full/10.1089/genbio.2024.29128.pma (2024).
6. Foy, S. P. et al. Non-viral precision T cell receptor replacement for personalized cell therapy. Nature 615, 687–696 (2023).
7. Shin, J. W. et al. Permanent inactivation of Huntington's disease mutation by personalized allele-specific CRISPR/Cas9. Hum Mol Genet 25, 4566–4576 (2016).
8. Kim, J. et al. Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease. New England Journal of Medicine 381, 1644–1652 (2019).
9. Choy M. Peter Marks Discusses the Road Ahead for Cell and Gene Therapy. BCG https://www.bcg.com/publications/2021/peter-marks-discusses-cell-gene-therapy (2021).
10. American Society of Gene + Cell Therapy. Request for Information: National Biotechnology and Biomanufacturing Initiative. American Society of Gene + Cell Therapy https://asgct.org/advocacy/policy-statement-landing/2023/request-for-information-national-biotechnology-and (2023).
11. Eglovitch J. Pharma industry questions FDA on platform technology designation program. Regulatory News https://www.raps.org/news-and-articles/news-articles/2024/1/pharma-industry-questions-fda-on-platform-technolo (2024).
12. Benton, K. What Does FDA's Draft Platform Guidance Mean For CGT Companies? Cell&Gene (2024).
13. Li, Y. et al. Charting new paradigms for CAR-T cell therapy beyond current Achilles heels. Front Immunol 15, (2024).
14. Ng, B. et al. IL-18-secreting multiantigen targeting CAR T cells eliminate antigen-low myeloma in an immunocompetent mouse model. Blood 144, 171–186 (2024).
15. Moretti, A. et al. The Past, Present, and Future of Non-Viral CAR T Cells. Front Immunol 13, (2022).
16. Arcangeli, S. et al. Next-Generation Manufacturing Protocols Enriching TSCM CAR T Cells Can Overcome Disease-Specific T Cell Defects in Cancer Patients. Front Immunol 11, (2020).
17. ⟨1043⟩ Ancillary Materials for Cell, Gene, and Tissue-Engineered Products. United States Pharmacopeia (2024) doi:https://doi.org/10.31003/USPNF_M620_02_01.
18. ISO 20399:2022 Biotechnology — Ancillary materials present during the production of cellular therapeutic products and gene therapy products. International Standard (2022).
19. European Union. Directive 2001/83/EC of the European Parliament and of the council of 6 November 2001 on the Community code relating to medicinal products for human use. EUR-Lex https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-%3A02001L0083-20250101 (2001).
20. Xu, H. et al. Influence of various medium environment to in vitro human T cell culture. In Vitro Cell Dev Biol Anim 54, 559–566 (2018).
21. Olden B et al. Stabilizing DNA-PEI complexes improves scalability of suspension lentiviral viral vector and AAV processes. Cell & Gene Therapy Insights 8, 985–992 (2022).
22. Francis, G. L. Albumin and mammalian cell culture: Implications for biotechnology applications. Cytotechnology 62, 1–16 (2010).
23. Miao, L. et al. Synergistic lipid compositions for albumin receptor mediated delivery of mRNA to the liver. Nat Commun 11, (2020).
24. Li, R. et al. Preservation of cell-based immunotherapies for clinical trials. Cytotherapy 21, 943–957 (2019).
25. Raoufinia, R. et al. Overview of albumin and its purification methods. Adv Pharm Bull 6, 495–507 (2016).
26. Denizli, A. et al. Plasma fractionation: conventional and chromatographic methods for albumin purification. & Chem 39, 315–341 (2011).
27. Miyamura, S. et al. Comparison of Posttranslational Modification and the Functional Impairment of Human Serum Albumin in Commercial Preparations. J Pharm Sci 105, 1043–1049 (2016).
28. FDA. Considerations for the Use of Human and Animal-Derived Materials in the Manufacture of Cellular and Gene Therapy and Tissue-Engineered Medical Products. https://www.fda.gov/media/178022/download (2024).
29. Bulcha, J. T. et al. Viral vector platforms within the gene therapy landscape. Signal Transduction and Targeted Therapy vol. 6 Preprint at https://doi.org/10.1038/s41392-021-00487-6 (2021).
30. Guéguen, C. et al. Evaluating how cationic lipid affects mRNA-LNP physical properties and biodistribution. European Journal of Pharmaceutics and Biopharmaceutics 195, (2024).

Germany
Sartorius Stedim Biotech GmbH
August-Spindler-Strasse 11
37079 Goettingen
Phone +49 551 308 0

USA
Sartorius Stedim North America Inc.
565 Johnsom Avenue
Bohemia, NY 11716
Toll-free +1 800 368 7178

For further information, visit
sartorius.com

Status: 04 | 2025