



## INNOVATOR INSIGHT

# Strategic human raw material selection for cell therapy manufacturing

Daniel Benítez Ribas

The use of human-derived raw materials plays a critical role in the success of cellular therapies, such as CAR-T cell manufacturing. In this article, we focus specifically on human serum albumin and male AB serum, exploring their evaluation and integration into production processes. Drawing on eight years of clinical-grade ARI-0001 manufacturing experience, we examine regulatory requirements, quality considerations, and practical implementation strategies.

*Cell & Gene Therapy Insights* 2025; 11(10), 1249–1256 · DOI: 10.18609/cgti.2025.144

## OVERVIEW OF CELL & GENE THERAPIES

CGT manufacturing relies heavily on strategically selecting raw materials to ensure product quality, safety, and regulatory compliance. While presenting unique regulatory challenges, human-derived components remain essential for achieving optimal cell viability and expansion in many therapeutic applications. The complex regulatory landscape surrounding these materials requires careful consideration of their classification, intended use, and documentation requirements.

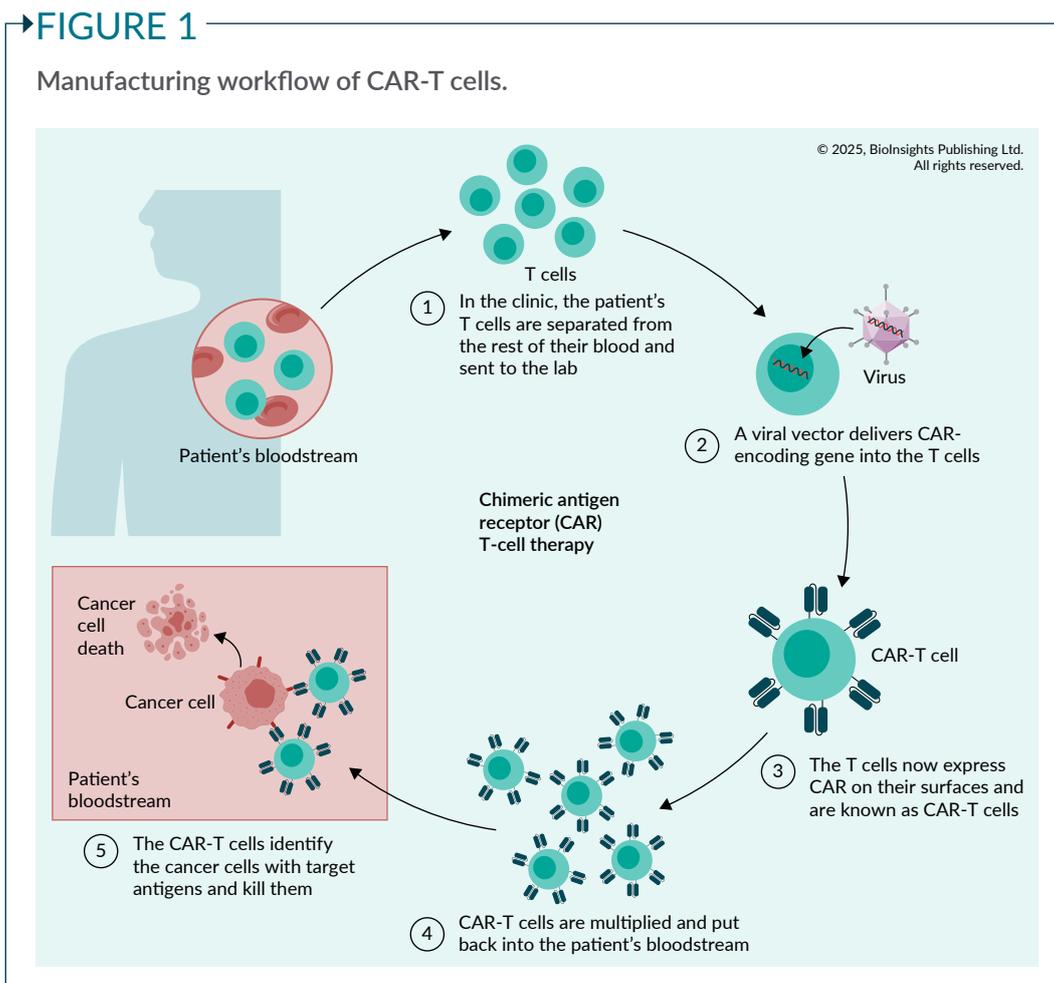
ATMPs encompass cell therapies, gene therapies, and tissue engineering products that contain substantially manipulated cells or tissues. These living medicines must be produced under GMP conditions, in our case following European (EU) GMP

Annex 4 guidelines. The incorporation of human-derived ancillary materials introduces additional considerations into the manufacturing process, requiring a balance between therapeutic necessity, regulatory compliance, and supply chain reliability.

## CAR-T CELL MANUFACTURING WORKFLOW & RAW MATERIAL INTEGRATION: ARI-0001

CAR-T cell production follows a well-established manufacturing sequence beginning with patient leukapheresis and progressing through T-cell isolation, lentiviral transduction, expansion, quality control testing, and final product release, as seen in **Figure 1**. Each manufacturing step requires specific raw materials to maintain cell viability, support expansion, and ensure product stability.





CAR-T cells function by specifically targeting tumor-associated antigens expressed on malignant cells. **Figure 2** shows an example of a target that is the CD19 molecule, a tumor-associated antigen expressed on B cells. CD19 is present not only on malignant B cells in leukemia and lymphoma but also on healthy B lymphocytes. Following genetic modification, the CAR construct is expressed on the T-cell membrane, and the extracellular domain of the CAR contains an antibody-derived recognition region capable of binding CD19.

Upon encountering a cell expressing CD19, CAR-T cells initiate intracellular signaling cascades that first induce target-cell lysis and subsequently promote T-cell proliferation and cytokine secretion to support cell survival. As living cellular therapies, CAR-T cells are capable of integrating

multiple, complex signals to generate coordinated immune responses.

The ARI-0001 CAR-T cell product was initially developed at the Hospital Clínic de Barcelona. This second-generation CAR construct incorporates the extracellular domain of the monoclonal antibody A3B1, which functions as the antigen-recognition domain. The construct also contains a CD8 transmembrane domain, a 4-1BB costimulatory domain, and a CD3 $\zeta$  T-cell receptor (TCR) signaling domain. The CAR transgene is introduced into T cells using a third-generation lentiviral vector, and the modified cells are expanded in the closed, automated bioreactor system CliniMACS<sup>®</sup> Prodigy (Miltenyi Biotec) to generate the final product for clinical administration.

The manufacturing workflow for ARI-0001 CAR-T cells is organized into defined steps, including timelines, specific

reagents, and materials required for production. Notably, human serum albumin and human AB serum are used as critical reagents throughout various stages of the process. These reagents are applied at specific manufacturing steps to ensure optimal cell viability, proliferation, and functionality of the final CAR-T cell product.

This approach reflects the dual nature of human-derived raw materials: their essential role in supporting cellular processes, and their regulatory complexity as human-sourced components that require additional documentation and safety validation.

### HUMAN SERUM ALBUMIN: REGULATORY CLASSIFICATION & APPLICATIONS

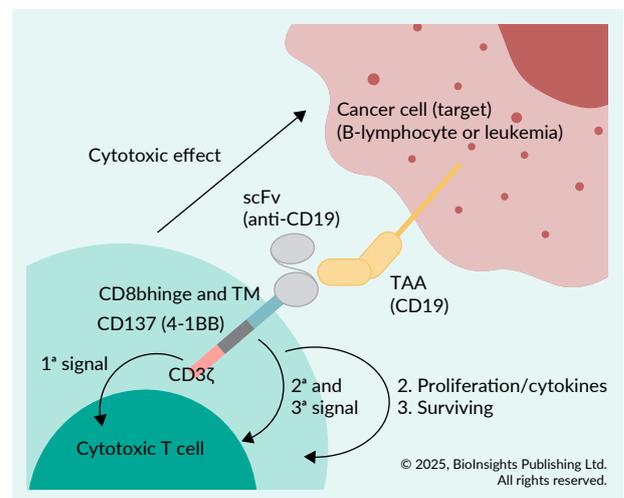
Human serum albumin functions in two distinct capacities within CAR-T cell manufacturing, each carrying different regulatory implications. As an ancillary material, albumin supports intermediate processing steps, including cell isolation, expansion, cryopreservation, and washing processes. The first application of albumin in ARI-0001 CAR-T cells is typically washed-out during processing and does not constitute an active ingredient in the final product; however, it is still present.

The second application positions albumin as an excipient in the final cryopreserved product, which remains present during patient administration. This dual functionality requires careful regulatory documentation to address both ancillary material and excipient requirements under relevant regulatory standards and guidelines.

Therapeutic-grade human albumin, meeting >96% purity specifications, qualifies as a licensed biological product under pharmacopoeia standards. This classification provides several regulatory advantages, including established safety profiles, reduced comparability requirements versus novel excipients, and clear documentation

FIGURE 2

Mechanism of action of CAR-T cells.



pathways. The material functions as a low-risk ancillary material while remaining eligible for final formulation use.

Process advantages of European Pharmacopoeia/US Pharmacopoeia (EP/USP) albumin include enhanced cell viability and stability during processing steps and reduced shear stress in bioreactors. Regulatory benefits encompass pre-qualified safety profiles, established pharmacopoeial standards, and reduced comparability requirements versus novel excipients.

### MALE AB SERUM: QUALITY CONSIDERATIONS & SUPPLIER EVALUATION

Male AB serum presents certain regulatory considerations due to the absence of therapeutically approved and registered products for this application. However, its continued use highlights its practical value and relevance in established cell therapy workflows. Unlike albumin, AB serum is completely washed-out during processing and does not appear in the final product.

Source and traceability requirements mandate that serum must originate from healthy donors screened according to

blood donation standards. Donors undergo testing for infectious diseases, including HIV-1/2, hepatitis B and C, and syphilis. Serum sourcing must occur through licensed blood establishments that maintain complete donor records and traceability documentation.

Quality control specifications require comprehensive Certificates of Analysis (CoA), including identity testing, sterility confirmation, mycoplasma testing, endotoxin levels typically <0.5 EU/mL, and viral marker testing using nucleic acid testing and serology. When applicable, documentation must include irradiation or virus inactivation status, ensuring these treatments do not compromise functional components such as complement or growth factors.

The preference for male serum derives from several practical considerations. Male donors typically exhibit less variability and provide better cell culture consistency due to hormonal stability. Additionally, male serum carries a lower risk of anti-HLA antibodies that may be present in female donors, particularly those with previous pregnancies. This reduced variability contributes to more uniform donor serum profiles and enhanced manufacturing reproducibility.

### MALE AB SERUM: REGULATORY STRATEGY & RISK MITIGATION APPROACHES

Regulatory agencies express a preference for xeno-free and serum-free culture systems when feasible. When human serum AB is employed, manufacturers must provide scientific justification demonstrating the necessity for cell viability, activation, or expansion. This justification should include process comparability data supporting transitions between serum lots or potential conversion to serum-free conditions.

Batch qualification strategies become essential for mitigating inherent variability in human-derived materials. Effective

approaches include pre-screening individual lots against defined performance criteria and strategically pooling qualified lots to reduce batch-to-batch variation. These strategies require robust analytical methods and clear acceptance criteria aligned with product specifications.

Viral safety risk assessment remains mandatory despite human origin. Nucleic acid testing for viruses and validated viral inactivation steps are strongly recommended when feasible without compromising functional integrity. Storage and handling procedures must follow GMP-compatible standard operating procedures, typically requiring controlled temperatures at -20 °C or -80 °C with validated thawing, aliquoting, and use procedures.

### CLINICAL EXPERIENCE & MANUFACTURING CONSISTENCY

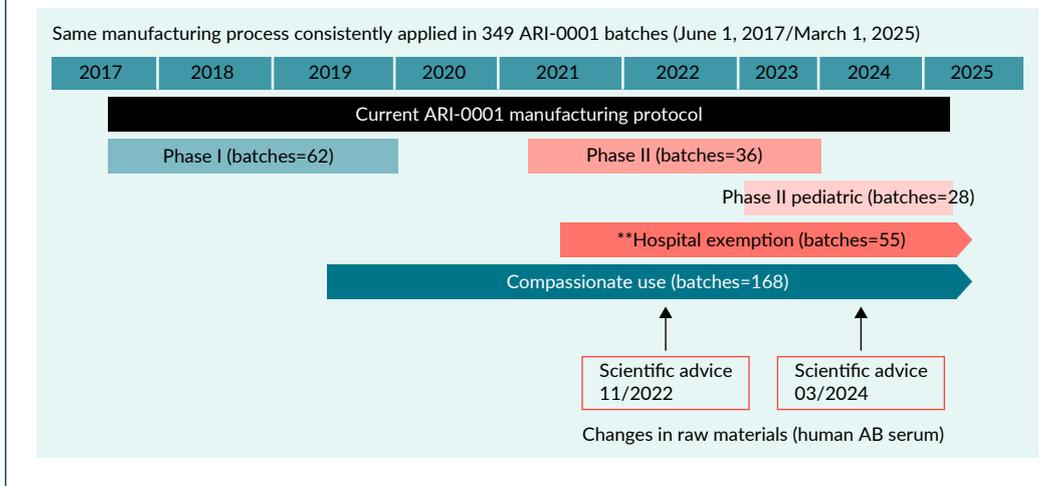
Eight years of ARI-0001 manufacturing experience from the Hospital Clínic de Barcelona team demonstrates the feasibility of maintaining consistent raw material strategies throughout clinical development, as seen in [Figure 3](#). Since January 2017, nearly 350 ARI-0001 products have been manufactured using the same processing approach, spanning Phase 1 and 2 clinical trials, pediatric studies, compassionate use applications, and hospital exemption production.

This manufacturing consistency provided the foundation for ARI-0001's hospital exemption authorization from the Spanish Agency of Medicines and Medical Devices in 2021. The authorization represented the first advanced therapy medicinal product approved through hospital exemption for cancer treatment in Europe, specifically for patients over 25 years with relapsed/refractory acute lymphoblastic leukemia.

Sustained manufacturing success validates the importance of early raw material strategy development and consistent

► **FIGURE 3**

Manufacturing process experience showing consistent application across 349 ARI-0001 batches from 2017–2025.



supplier relationships. Process robustness emerges from thorough material qualification, appropriate risk mitigation strategies, and comprehensive documentation supporting regulatory submissions throughout development phases.

### STRATEGIC CONSIDERATIONS FOR RAW MATERIAL SELECTION

Organizations evaluating raw material suppliers should prioritize regulatory compliance and quality systems that support progression from early clinical trials through commercial manufacturing. Material consistency and comprehensive safety testing provide the foundation for reliable supply chains while ensuring patient safety throughout clinical development.

The selection process must balance multiple factors, including biological compatibility advantages of human-derived materials, regulatory acceptance pathways, and practical considerations such as supply security and cost management. Materials derived from human sources provide enhanced biological compatibility for cultivating human cells, especially in patients whose cellular function has been compromised by multiple treatment regimens.

Early-phase development should emphasize flexibility and risk assessment while ensuring basic safety requirements. Late-phase development necessitates enhanced focus on GMP compliance, supply security, and smooth transition planning. Proactive planning and supplier collaboration facilitate successful transitions between development phases without compromising product quality or timeline adherence.

### FUTURE TRENDS & REGULATORY EVOLUTION

Cell therapy production continues evolving toward reduced reliance on human-derived materials, driven by regulatory preferences and supply chain considerations. However, human-derived raw materials remain widely utilized due to their demonstrated effectiveness in supporting cellular processes critical for therapeutic success.

Current regulatory frameworks continue to develop specific guidelines and standards for ancillary materials. Clear frameworks defining requirements and responsibilities for both users and suppliers will influence the pace of commercialization while ensuring patient safety and continued innovation in cell-based therapies.

When properly documented with comprehensive Certificates of Analysis, Origin, and Compliance, human-derived materials maintain acceptance for therapeutic applications. The key lies in thorough characterization, appropriate risk assessment, and robust quality systems supporting consistent material performance throughout product lifecycles.

### SUMMARY

Strategic raw material selection requires balancing regulatory compliance, material performance, and supply chain reliability throughout cell therapy development. When appropriately qualified and

documented, human serum albumin and male AB serum provide essential support for CAR-T cell manufacturing while maintaining regulatory acceptability.

The ARI-0001 workflow demonstrates that consistent raw material strategies can support progression from early clinical development through regulatory approval. Success depends on thorough supplier evaluation, comprehensive documentation, appropriate risk mitigation, and proactive planning for development phase transitions. As regulatory frameworks evolve, organizations must maintain flexibility while ensuring patient safety and product quality remain paramount in raw material selection decisions.

## Q&A



Daniel Benítez Ribas

**Q** What are the main considerations when evaluating a raw material supplier, and which criteria should organizations prioritize to meet their specific needs?

**DBR** The primary consideration should be regulatory compliance and quality systems, as this foundation enables progression from early clinical trials through late-stage development. Material consistency and safety testing are critical for guaranteeing product safety in clinical applications. While less critical than the first two factors, supply chain reliability remains essential for ensuring adequate material availability throughout development and manufacturing phases.

**Q** How can proper selection, evaluation, and qualification of raw materials impact CGT products' quality, safety, and efficacy?

**DBR** Consistency and process performance must be considered to minimize batch-to-batch variability when considering proper raw material management, which directly impacts regulatory compliance and patient safety. Additionally, materials must demonstrate therapeutic efficacy within the specific

manufacturing system. A product that meets regulatory and safety requirements but fails to support cellular function will not be viable for the intended application.

**Q** What are the potential benefits and challenges of human-derived raw materials?

**DBR** The primary benefit is biological compatibility. Human-derived materials, such as serum or albumin, provide superior cell growth and function when producing human cells for therapeutic use. This is particularly important for patients with compromised cellular quality due to previous treatments, where enhanced biological compatibility can reduce mortality after processes such as lentiviral infection and support necessary expansion. Human-derived materials also benefit from regulatory acceptance and compliance pathways established with local and regional agencies.

**Q** What essential factors should organizations consider when choosing critical raw materials for early and late phase development, and how can this ensure a smooth transition during development?

**DBR** In early phases, organizations should focus on flexibility while conducting appropriate risk assessments to guarantee safety. The priority is determining whether the product will be effective before investing in more stringent requirements. As products advance to late-phase development, emphasis shifts to ensuring GMP compliance, material compatibility, and supply security. Smooth transitions require proactive planning, supplier collaboration, and appropriate testing of components to facilitate successful raw material transitions between development phases.

## BIOGRAPHY

**Daniel Benítez Ribas** is the Qualified Person of the Immunotherapy Section (Immunology Department), responsible for ensuring the quality of cell therapies, including CAR-T cells such as ARI-0001 (varnimcabtagene autoleucel) and ARI-0002h (cesnicabtagene autoleucel) both approved by the AEMPS and produced under GMP regulations. He obtained his Bachelor's degree in Biology from the University of Barcelona, Barcelona, Spain in 1995 and completed his PhD at the Immunology Service of HCB in 2003. He conducted his postdoctoral research at Radboud University, Nijmegen, Netherlands, where he developed dendritic cell vaccines for metastatic melanoma. In 2008, he joined CIBERehd as a Principal Investigator at Hospital Clínic de Barcelona, supervising dendritic cell-based therapies for autoimmune diseases, including the first Phase 1b clinical trial in humans for Crohn's disease. Since 2016, he has been part of the Immunology Department at Hospital Clínic de Barcelona and IDIBAPS, focusing on cell-based therapies for cancer and autoimmune diseases, and overseeing several clinical trials. He has published over 135 articles in renowned journals and holds two patents, participating in numerous antitumor immunotherapy projects.

Daniel Benítez Ribas PhD, Qualified Person, Immunotherapy Department, Hospital Clínic de Barcelona, Barcelona, Spain

## AUTHORSHIP & CONFLICT OF INTEREST

**Contributions:** The named author takes responsibility for the integrity of the work as a whole, and has given their approval for this version to be published.

**Acknowledgements:** None.

**Disclosure and potential conflicts of interest:** The author has no conflicts of interest.

**Funding declaration:** The author received no financial support for the research, authorship and/or publication of this article.

## ARTICLE & COPYRIGHT INFORMATION

**Copyright:** Published by *Cell & Gene Therapy Insights* under Creative Commons License Deed CC BY NC ND 4.0 which allows anyone to copy, distribute, and transmit the article provided it is properly attributed in the manner specified below. No commercial use without permission.

**Attribution:** Copyright © 2025 Daniel Benítez Ribas. Published by *Cell & Gene Therapy Insights* under Creative Commons License Deed CC BY NC ND 4.0.

**Article source:** This article is based on a webinar, which can be found [here](#).

**Webinar conducted:** Jul 16, 2025.

**Revised manuscript received:** Oct 22, 2025.

**Publication date:** Nov 12, 2025.

# GRIFOLS



If you enjoyed this article,  
you might also like our webinar on the same topic

[WATCH NOW](#)

