Raw Materials (RMs) in Cell & Gene Therapy: Navigating the Challenges

Authors: Luca Benedan, Nicolò Sacchetti, Stefano Baila

Other resources

1 Introduction

Advanced therapy medicinal products (ATMPs) are a subset of biological products widely recognized as revolutionary in medicine, offering personalized solutions for patients. Most ATMPs rely on cells (either genetically modified or non-genetically modified) and, among these, autologous therapies, are developed using a patient's own cells while allogeneic therapies provide off-the-shelf solutions, where cells from a healthy donor are used to treat multiple patients, expanding the range of treatment options.

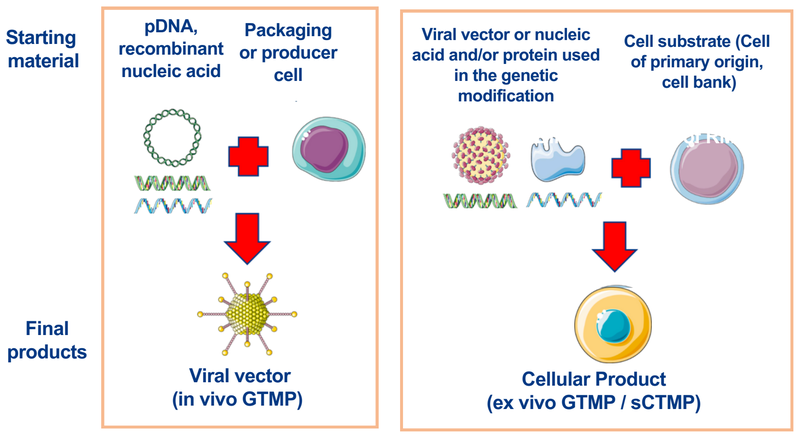
Although different products have been released on the market and manufacturing platforms are now available for some of them, many challenges still remain. One of these is the presence of novel and unregulated raw materials (RM)/ancillary materials (AM), employed during manufacturing processes. Of note, the different possible sources and origins of these materials add further complexity to the discussion, considering that they may be produced either by chemical synthesis, microbial fermentation or they may have biological origin (human/animal). As many labelling and naming conventions are used by the supplier of these materials, there is lack of clarity about standards and requirements that each type of material needs to achieve. Several guidelines aim to address this problem and help navigating this intricate landscape. Nevertheless, the broad variety of material categories, the different technologies and the dynamic nature of the Cell & Gene field, are common hurdles when defining the appropriate qualification and testing approach, which should also consider final product and process characteristics.

The aim of this poster is to illustrate the challenges associated with raw materials/ancillary materials employed in the manufacturing of ATMPs while suggesting possible strategies for their proper evaluation, taking into account current regulatory landscape, type and origin of the material and its intended use in the manufacturing process.

2 RMs definitions and regulation

Guideline	Term	Definition
EU Directive 2001/83/EC – Annex I (EU Directive 2003/63/EC)	Raw material (RM)	Any other substances used for manufacturing or extracting the active substance(s) but from which this active substance is not directly derived, such as reagents, culture media, fetal calf serum, additives, and buffers involved in chromatography, etc. are known as raw materials
EMA/CAT/22473/2025 – Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials	Raw material (RM)	Reagents that are used during the manufacturing process but that are not part of the finished product.
FDA Guidance for Industry - Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)	Regents/Ancillary materials (AM)	Reagents (or ancillary materials) are those materials used for manufacturing (e.g., cell growth, differentiation, selection, purification, or other critical manufacturing steps) that are not intended to be part of the final product.
ISO 20399:2022 – Biotechnology – Ancillary materials present during the production of cellular therapeutic products and gene therapy products	Ancillary material (AM)/Raw material (RM)	Material that comes into contact with the cellular therapeutic product during cell processing but is not intended to be part of the final product formulation, excluding scaffold, non-biological consumable and plasticware.
USP <1043> – Ancillary Materials for Cell, Gene, and Tissue-Engineered Products	Ancillary material (AM)	Materials that come into contact with the cellular starting material, CGT product intermediates, or final CGT product during manufacturing, but are not intended to be present in the final CGT product.
Ph. Eur. 5.2.12 – Raw materials of biological origin for the production of cell-based and gene therapy medicinal products	Raw material (RM)	The raw materials used in the manufacture of active substances are not intended to form part of the active substance

Starting Materials



Although they are sometimes named as critical raw materials, starting materials cannot be considered as raw materials as they are the materials from which the active substance is manufactured (EMA/CAT/22473/2025).

Example of RMs

Raw materials may be employed at different stages of manufacturing process (upstream/downstream). Some examples are provided in the table below:

Ancillary materials	Type/Use
Culture media	MEM, DMEM
Serum	FBS, Human AB Serum
Proteolytic enzymes/Digestion enzymes	Trypsin, animal origin-free trypsin-like enzymes, collagenase, DNase
Antibiotics	Beta lactam antibiotics should not be used as AMs due to the risk of patient hypersensitivity
Recombinant growth factors, cytokines	Activation or differentiation agents
Sterile process buffers	Fluids used in cell processing, purification
Purified chemicals	Induction agents, buffer components
Tox entities	Methotrexate, toxins
Chromatography resins	Affinity chromatography resins, ion exchange chromatography resins
Immunomagnetic beads	Cell selection reagents
Monoclonal antibodies	Antibodies targeting cells for selection, activation, or removal

3 Key challenges of RMs in ATMPs manufacturing

RMs are associated with variablelevels of risk depending on their nature, origin, manufacturing process as wellastheirintended use.

Broad variety of materials

Limited compendial materials are available. Most of RM are non-compendial and/or novel materials

Different grades of RMs

Approved drugs/biologics/med dev as well as GMP-grade are not always available. Research Use Only (RUO) are often employed.

Animal/human derived RMs

Although their use is generally discouraged, due to the nature of the products and their processes, the use of RM of animal/human origin may not be avoided.

Qualification of RMs

RM qualification is the responsibility of the RM user, who should conduct both documentation and experimental activities to assess the source, identity, purity, safety, and overall suitability of a specific RM with respect to its intended use.

Compendial vs non-compendial

Compendial	Non-Compendial
Compendial materials refer to those materials that have a dedicated pharmacopoeial monograph and have been tested and release according to it. This means that testing meets the standard and specifications outlined in the Pharmacopoeia and it is manufactured following relevant GMPs.	Non-compendial materials are those that do not have a dedicated monograph or those that have different hydration than that described in the reference monographs. This category also includes materials which require modified testing procedures and specifications that differ from those outlined in the monograph.

Different grades of AMs

Approved biologics, or drugs	•High quality materials that have been approved/licensed as drugs or biological products. •Any changes to packaging, dosage form, formulation, or storage conditions is qualified and documented.
GMP-grade	• In the context of AM, it does not pertain to any specific standard or requirement and does not ensure inherent quality system attributes • A cGMP compliance claim does not guarantee that materials are of high purity or have low levels of impurities. • AM users should request appropriate documentation to satisfy their requirements.
RUO	• The label indicates that the product should not be used for clinical or diagnostic use but may be used for research and development purposes • User should qualify the material with respect to its intended use prior to using • Sometimes, alternative terms are used to describe this category (Laboratory Use Only, Research Grade, Laboratory Grade)

Animal/human derived RMs

Include materials of biological origin that can be extracted from various biological sources or produced by recombinant DNA technology.

The main risk is the presence of adventitious agents or other biological impurities as well as the exposure of a patient to residual RM with potential harmful effects (e.g. immunogenicity).

Examples are serum (e.g FBS, HPL), proteins (e.g. mAb, hormons and enzymes extracted by biological sources or produced by rDNA technology) and vectors (e.g. helper virus/plasmid).

A risk-based approach is required for the selection and qualification of materials, and mitigation strategies should be implemented. USP <1043> and Ph. Eur. 5.2.12 can be used as guidance.

Notes FBS: Fetal Bovine Serum; mAb: monoclonal antibody; rDNA: recombinant DNA; HPL: Human platelet lysate

Qualification of RMs

- The qualification of RMs is the process of acquiring and evaluating data to establish the source, identity, purity, safety, and overall suitability of a specific RM used in the manufacturing process.
- The qualification of RMs with regard to their intended use is the responsibility of the user and includes both documentary and analytical activities.

Key areas of RM qualifications are:

- Identification and sourcing: identification of RMs, quantity used, manufacturing step and identification of alternative sources
- Selection and suitability for the intended use: definition of selection criteria based on purity (chemical/biological), identity, activity, material grade, traceability and manufacturing process.
- Characterisation: verification of identity, purity, functionality, and absence of contaminants. Level of testing is defined through an appropriate risk assessment and knowledge gained during manufacturing process development.
- Vendor qualification and audit: audit of vendor facility and GMP capabilities. Review of RM testing program and vendor's manufacturing process including relevant documentation.
- Quality control and quality assurance: constant monitoring by QAU department to ensure compliance with cGMP.

Identification and selection of RMs

Assess RMs criticality with respect to ATMP product and define CMAs (Critical Material Attributes)

Request and assess supplier documentation concerning RMs testing, manufacturing process and stability

Decide if any mitigation is needed (additional documentation, incoming testing, removal step in ATMP process)

Plan qualification program

4 USP <1043> risk-based approach

USP <1043> proposes a risk-based evaluation of AM used in the production of ATMPs to assess potential risks to product quality.

With patient safety as the primary focus, it is essential to investigate and understand the removal of potentially harmful impurities from AM in the manufacturing process and the impact of the AM on critical quality attributes (CQAs) of the product.

For this reason, a risk assessment should be conducted in line with the ICH Q9 guideline, along with a scientifically sound qualification program to evaluate each AM and select the appropriate risk reduction strategy.

Four potential risk categories are presented: Tier 1, Tier 2, Tier 3 and Tier 4.

Tier/Risk	Definition	Examples	Risk mitigation
Tier 1 (very low risk)	A licensed biologic, drug, or medical device. It is considered a highly qualified material that is well-suited for use in manufacturing of CGT product.	Recombinant insulin for injection, IV bags, syringes, needle, sterile fluids for injection	-DMF cross reference (when possible or practical) -Certificate of analysis -Assess lot-to-lot effect on process performance -Assess removal from final product -Assess AM stability as stored and used in CGT product manufacturing -Visual inspections -Assess particulates and extractable
Tier 2 (low risk)	A well-characterized material produced under an established quality system. It is suitable for ATMPs manufacturing, but the AM is not a licensed or approved medical product.	Recombinant growth factors and cytokines (produced from nonmammalian, recombinant sources), human AB serum, immunomagnetic beads, proteolytic enzymes, sterile process buffers.	All of the qualification and risk mitigation activities in Tier 1, plus the following: -Confirm certificate of analysis test results that are critical to CGT product identity, purity, or potency -Verify AMs containing animal- or human-derived materials have been purified, tested, and certified to be free of adventitious agents -Vendor audit
Tier 3 (medium risk)	AM which is either intended for research use, locally produced under laboratory conditions, or not intended for use in ATMPs manufacturing	Recombinant growth factors and cytokines, monoclonal antibodies (for diagnostic use), tissue culture media, purified chemicals (reagent grade),	All of the qualification and risk mitigation activities in Tier 2, plus the following: -Confirm certificate of analysis test results -Upgrade manufacturing process and/or testing for material to be suitable for therapeutic use
Tier 4 (high risk)	The AM is produced for industrial or research use and may contain harmful impurities, and/or may contain animal- or human-derived components harbouring adventitious agents.	Animal or human derived materials, Toxic entities (e.g., methotrexate, bacterial toxins), Animal or human cells used as feeder layers	All of the qualification and risk mitigation activities in Tier 3, plus the following: -Safety testing for residuals in CGT product -Recombination-competent retroviral testing for relevant gene therapy AM -Adventitious agent testing for animal source-relevant viruses

5 Conclusions

1. RM are materials that come into contact with cellular starting material, product intermediates, or final product during manufacturing, but are not intended to be present in the final ATMP product.
2. Challenges include presence of non-compendial materials, availability of different material grade, qualification strategy and the risk associated with the use of biological-derived materials.
3. Materials of human/animal-origin and those associated with presence of harmful impurities should be avoided. In case this is not possible, mitigation by testing and manufacturing process upgrade is needed.
4. RM qualification strategy should be justified considering material grade, RM attributes, user requirements and supply chain.
5. A risk-based approach is recommended to run a scientifically sound qualification program.

eurofins | Cell & Gene Therapy

Eurofins Biolab Srl
Via Bruno Buozzi, 2 Vimodrone | Italy

EurofinsBiolab@bpt.eurofinseu.com
https://www.eurofins.it/biopharma

consultancyitaly@bpt.eurofinseu.com
https://www.eurofins.it/consultancy-services

Associazione Farmaceutici Industria