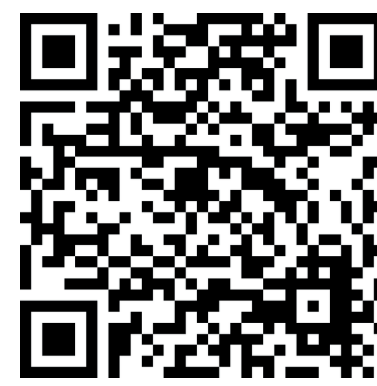




Raw Materials (RMs) in Cell & Gene Therapy: Navigating the Challenges

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Other resources

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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

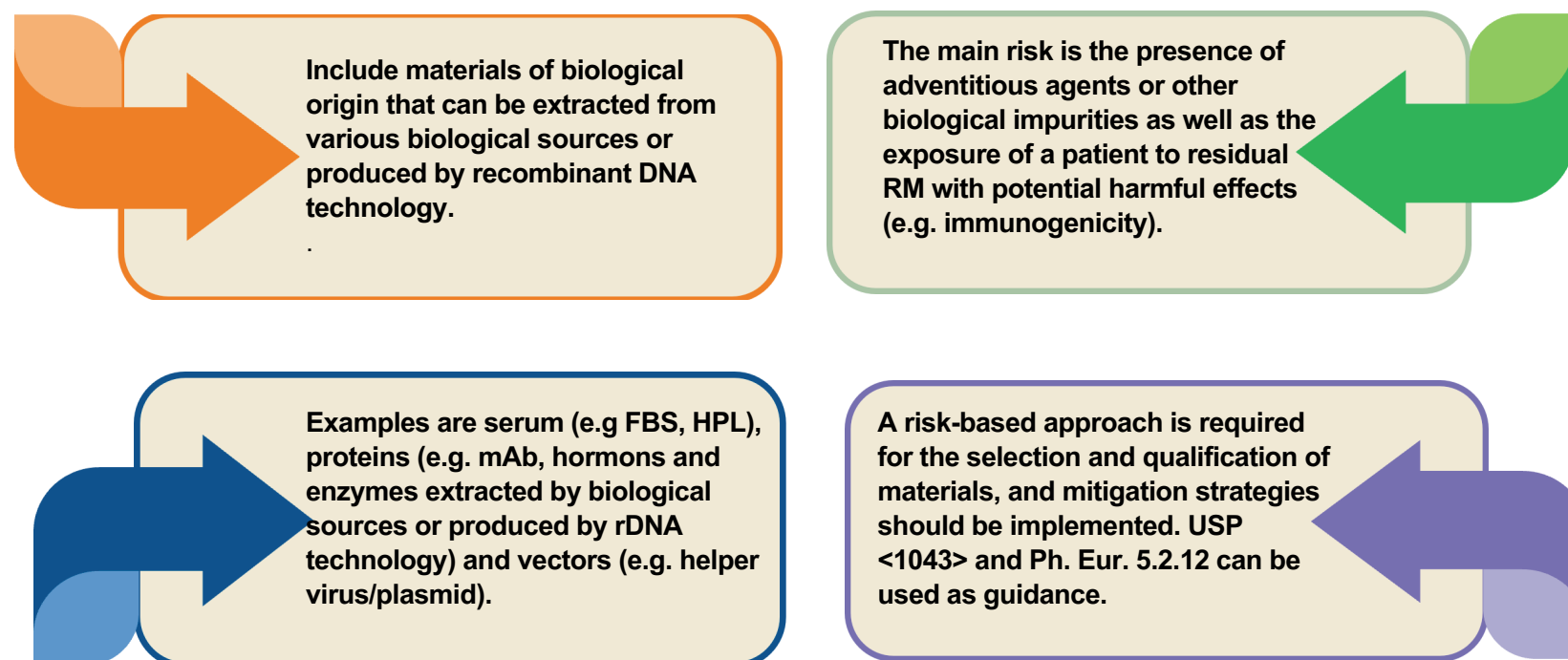
Guideline	Term	Definition
EU Directive 2001/83/EC – Annex I (EU Directive 2003/63/EC)	Raw material (RM)	Any other substances used for manufacturing or extracting the active substance(s) but from which this active substance is not directly derived, such as reagents, culture media, fetal calf serum, additives, 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)	Reagents/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

3 Key challenges of RMs in ATMPs manufacturing

RMs are associated with variable levels of risk depending on their nature, origin, manufacturing process as well as their intended use.

Broad variety of materials	Different grades of RMs
Limited compendial materials are available. Most of RM are non-compendial and/or novel materials	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	Qualification of 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.	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.

Animal/human derived RMs



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

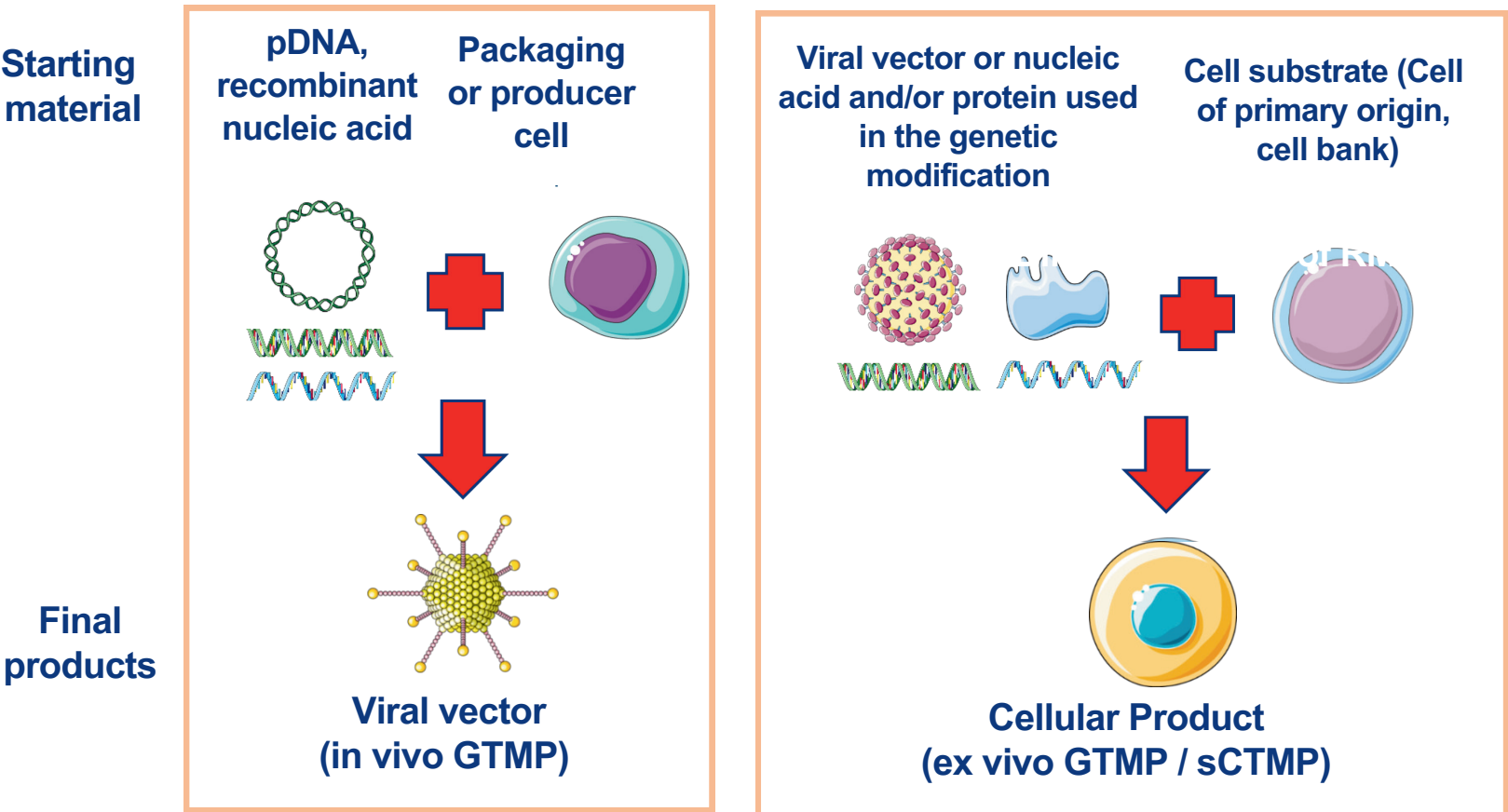
Qualification of RMs

- 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.

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

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)

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

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Example of testing strategy for RM

RM	Grade	Proposed Strategy	Notes
Recombinant protein	GMP	<ul style="list-style-type: none">IDBSE/TSE evaluationAminoacid profile (optional)Osmolality (optional)Bioburden/Sterility (depending on the labelling)EndotoxinpH (optional)Subvisible particles (optional, in liquid form)Adventitious agents (mycoplasma, virus depending on material origin)Shelf-life testing	<ul style="list-style-type: none">Optional tests should be carried out if they are necessary to control a critical material attribute.Test results from the CoA may be used, unless they pertain to critical material attributes. In such cases, confirmatory testing should be performed.Provided that GMP-grade is highly-recommended, lower grade requires a more extensive control strategy.
Serum	GMP	<ul style="list-style-type: none">IDAminoacid profileBSE/TSE evaluationTotal proteinOsmolalitySterilityEndotoxinpHAdventitious agents (mycoplasma, viruses)Subvisible particles (optional)Shelf-life testing	<ul style="list-style-type: none">Ph. Eur. Monographs, when available (e.g. Bovine Serum), should be followed.Optional tests should be carried out if they are necessary to control a critical material attribute.Test results from the CoA may be used, unless they pertain to critical material attributes. In such cases, confirmatory testing should be performed.
Cell culture media	GMP	<ul style="list-style-type: none">IDBSE/TSE evaluationAminoacid profile (optional)OsmolalitypHEndotoxinMycoplasmaSubvisible particles (optional)Adventitious virus testing (if contains animal-derived components)Shelf-life testing	<ul style="list-style-type: none">Optional tests should be carried out if they are necessary to control a critical material attribute.Test results from the CoA may be used, unless they pertain to critical material attributes. In such cases, confirmatory testing should be performed.Provided that GMP-grade is highly-recommended, lower grade requires a more extensive control strategy.

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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.



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