Specific European Pharmacopoeia Texts & Use of RS for Biologicals

Advanced therapy medicinal products (ATMPs): the regulatory framework, raw materials for the production of ATMPs, microbiological quality, gene therapy products
## ATMPs – A market in evolution

<table>
<thead>
<tr>
<th>Name / Company</th>
<th>ATMP</th>
<th>Approval</th>
<th>Description / Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChondroCelect</td>
<td>TEP</td>
<td>2009-2016</td>
<td>Autologous cartilage cells / Repair of cartilage defects of the knee</td>
</tr>
<tr>
<td>Glybera</td>
<td>GTMP</td>
<td>2012-2017</td>
<td>Alipogene tiparvovec (AAV-1 – Lipoprotein lipase gene) / Familial lipoprotein lipase deficiency (FLLD)</td>
</tr>
<tr>
<td>Provenge</td>
<td>CTMP</td>
<td>2013-2015</td>
<td>Autologous mature peripheral blood mononuclear cells activated with PAP-GM-CSF colony-stimulating factor / Prostate Cancer</td>
</tr>
<tr>
<td>Maci</td>
<td>TEP</td>
<td>2013-2014</td>
<td>Autologous human chondrocytes / Repair of cartilage defects of the knee</td>
</tr>
<tr>
<td>Steroidics</td>
<td>CTMP</td>
<td>2013-2015</td>
<td>Autologous human peripheral blood mononuclear cells / Treatment of severe biallelic x-linked adrenoleukodystrophy</td>
</tr>
<tr>
<td>Imlygic</td>
<td>GTMP</td>
<td>2015</td>
<td>Talmogene selarigene (HSV-1-derived virus GM-CSF) / Melanoma</td>
</tr>
<tr>
<td>Moricizine</td>
<td>GTMP</td>
<td>2016</td>
<td>Autologous CD34+ cells transduced with retroviral vector encoding the human adenovirus deaminase (AD.A) cDNA sequence / A-SCID deficiency</td>
</tr>
<tr>
<td>Motifer (darvadstrocel)</td>
<td>CTMP</td>
<td>2018</td>
<td>Spheroids of human autologous matrix-associated chondrocytes / Treatment of peritoneal fibrosis in patients with Crohn’s disease</td>
</tr>
<tr>
<td>MyriPrest (tisagenlecleucel)</td>
<td>GTMP</td>
<td>2016</td>
<td>CD19-directed genetically modified autologous T-cell immunotherapy / Treatment of refractory large B-cell lymphoma after two or more lines of systemic therapy</td>
</tr>
<tr>
<td>Nativata</td>
<td>GTMP</td>
<td>2018</td>
<td>Autologous hematopoietic stem cells transduced with lentiviral vector encoding the B2aVL32 cas9-puro gene / Treatment of x-linked retinitis pigmentosa (RP) and achromatopsia (A) in patients with non-βthalassemia (βTDF) gene mutations</td>
</tr>
<tr>
<td>Spherox</td>
<td>TEP</td>
<td>2017</td>
<td>Spheroids of human autologous matrix-associated chondrocytes / Treatment of peritoneal fibrosis in patients with Crohn’s disease</td>
</tr>
<tr>
<td>Alofisel (darvadstrocel)</td>
<td>CTMP</td>
<td>2018</td>
<td>Expanded autologous adipose-derived mesenchymal stem cells / Treatment of severe biallelic x-linked adrenoleukodystrophy</td>
</tr>
<tr>
<td>Kymriah (tisagenlecleucel)</td>
<td>GTMP</td>
<td>2016</td>
<td>Autologous CD34+ cells transduced with lentiviral vector encoding the human AAV-1 angelman gene / Treatment of relapsed or refractory acute lymphoblastic leukemia (ALL) or acute lymphoblastic leukemia (ALL) in children</td>
</tr>
<tr>
<td>Yescarta (axicabtagene ciloleucel)</td>
<td>GTMP</td>
<td>2016</td>
<td>CD19-directed genetically modified autologous T-cell immunotherapy / Treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy</td>
</tr>
<tr>
<td>Luxturna (voretigene neparvovec)</td>
<td>GTMP</td>
<td>2018</td>
<td>Autologous hematopoietic stem cells transduced with lentiviral vector encoding the B2aVL32 cas9-puro gene / Treatment of x-linked retinitis pigmentosa (RP) and achromatopsia (A) in patients with non-βthalassemia (βTDF) gene mutations</td>
</tr>
<tr>
<td>Zynteglo/LentiGlobin</td>
<td>GTMP</td>
<td>June 2019</td>
<td>Autologous CD34+ cells transduced with a lentiviral vector encoding the human AAV-1 angelman gene / Treatment of transfusion-dependent β-thalassemia (TDT) in patients with non-β-thalassemia (βTDF) gene mutations</td>
</tr>
</tbody>
</table>

**1,052 Clinical Trials Underway Worldwide by End of Q3 2019**

**Place of the Ph. Eur. in the regulatory framework**

Celine Pugieux-Amarantos, PhD,
Scientific officer, European Pharmacopoeia Department,
EDQM, Council of Europe
A **biological medicinal product** is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physicochemical-biological testing, together with the production process and its control.

**Immunological medicinal products (e.g. vaccines, serums, allergens)**

**Medicinal products derived from human blood and human plasma (e.g. albumin, coagulation factors, human immunoglobulins)**

**Biotechnology products:** e.g. Recombinant human proteins (e.g. insulin, growth hormone),

- Recombinant monoclonal Antibodies
- Advanced therapy medicinal products (ATMPs)

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, foetal calf serum, additives, and buffers involved in chromatography, etc. are known as **raw materials**.

=> Essential and overarching directive, but not sufficient to address all types of biologics
ATMP regulatory framework

Regulation 1394/2007 (overarching legislation for ATMPs)
- Creation of the Committee for Advanced Therapies (CAT) within the EMA
- European centralised procedure for MA, to benefit from the pooling of expertise from EU member states
- Hospital exemption under strict rules

+ Amendments of Directive 2001/83/EC (e.g. Commission Directive 2009/120/EC)
  (include specific rules concerning the authorization, traceability and pharmacovigilance of ATMPs)

+ Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products (22/11/2017)

+ Additional legislation and guidelines on GLP, GMP, clinical trials, Pharmacovigilance, Medical devices

+ EMA Guideline on human cell-based medicinal products

+ European Pharmacopoeia texts

Ph. Eur. texts applicable to gene and cell therapies

General overarching texts
5.14 Gene transfer medicinal products for human use
5.2.12 Raw materials of biological origin for the production of cell-based and gene therapy medicinal products

Monographs
Bovine serum (2262)
Human haematopoietic stem cells (2323)

Methods: numeration & viability
2.7.23 Numeration of CD34+/CD45+ cells in haematopoietic products
2.7.24 Flow cytometry
2.7.28 Colony-forming cell assay for human haematopoietic progenitor cells
2.7.29 Nucleated cell count and viability
2.6.35 Quantification and characterisation of residual host-cell DNA

Microbiology aspects & viral safety
2.6.1 Sterility
2.6.14 Bacterial endotoxins
2.6.30 Monocyte-activation test
2.6.7 Mycoplasmas
2.6.27 Microbiological examination of cell-based preparations
5.1.7 Viral safety
5.2.8 (TSE)
General chapter

5.2.12 Raw materials of biological origin for the production of cell-based and gene therapy medicinal products

Establishment of the RCG Working Party

Cooperation between EDQM and EMA

RCG WP
2012 June
14 experts from MS + 1 EMA representative + 1 observer

Survey to National Pharmacopoeia Authorities 2012 December

EDQM / EMA Symposium
2013 April
International Symposium With manufacturers, regulators and other users

✓ User’s needs identified
✓ Classes of raw materials defined
✓ Current variable practices to be harmonised
Overarching general chapter

- Overarching general chapter with the aim to:
  - Identify the critical quality attributes of raw materials of biological origin
  - Harmonize variable practices and make the regulatory expectations more predictable
  - Encourage raw materials manufacturers to
    - Provide consistent, predefined quality
  - Record and share information on the origin and quality of the raw material
  - Help users managing batch-to-batch variations and changes in raw materials

5.2.12 - Overview

- Applies to raw materials of biological origin
- Raw materials are used for manufacturing or extracting the active substance(s) but are not intended to form part of the active substance
- Raw materials can be extracted from various biological sources or produced by recombinant DNA technology.
- Principles of this general chapter may also be applied to other classes of biological raw materials where appropriate
- Not in the scope of the chapter: chemically synthesised raw materials: e.g.
  Basal media (purely composed of chemicals), synthetic peptides or polynucleotides, medical devices and plastics
### 5.2.12 - Overview

<table>
<thead>
<tr>
<th>Section</th>
<th>Subsections</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Scope</td>
<td>1.1 Scope</td>
</tr>
<tr>
<td>2. Risk Assessment</td>
<td>2.1 Risk Assessment</td>
</tr>
<tr>
<td>3. General requirements</td>
<td>3.1 General requirements</td>
</tr>
<tr>
<td>Origin, Production, General quality requirements (ID/Tests/Assay/Ref. Mat-batch), Storage, Labelling</td>
<td>4.1 Definition</td>
</tr>
<tr>
<td>4. Sera and serum replacements (incl. Blood and other cellular components, platelet lysates, conditioned media)</td>
<td>4.3 Identification</td>
</tr>
<tr>
<td>5. Proteins produced by recombinant DNA technology (incl. Growth actors, cytokines, hormones, enzymes and mAbs)</td>
<td>5.5 Assay</td>
</tr>
<tr>
<td>6. Proteins extracted from biological material (incl. enzymes (e.g. trypsin), polyclonal Abs, other proteins (e.g. albumin), peptides)</td>
<td>6.1 Definition</td>
</tr>
<tr>
<td>7. Vectors</td>
<td>6.3 Identification</td>
</tr>
<tr>
<td></td>
<td>6.5 Assay</td>
</tr>
</tbody>
</table>

### 5.2.12 - Introduction

- Published for information: not legally binding but reflects the consensus of Ph. Eur. member states
- Biological nature triggers the need for specific quality requirements
- Clarify the responsibility
- Address the quality of raw materials at early stage of development to avoid extra work
- Risk-based evaluation of the impact of the raw material on the medicinal product
5.2.12 Raw materials of biological origin for the production of cell-based and gene therapy medicinal products

1. Scope

- Raw materials are used for manufacturing or extracting the active substance(s) but are not intended to form part of the active substance.

<table>
<thead>
<tr>
<th>Applies to:</th>
<th>Not in the scope:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- sera and serum replacement;</td>
<td>- chemically synthesised raw materials: e.g. basal media (purely composed of chemicals);</td>
</tr>
<tr>
<td>- proteins produced by recombinant DNA technology;</td>
<td>- synthetic peptides or polynucleotides;</td>
</tr>
<tr>
<td>- proteins extracted from biological materials;</td>
<td>- medical devices and plastics.</td>
</tr>
<tr>
<td>- vectors.</td>
<td></td>
</tr>
</tbody>
</table>

2. Risk Assessment

- Evaluation of the impact must be performed by the user
- Origin and traceability
- Risk factor must be evaluated in relation to the clinical benefit/risk
5.2.12 Raw materials of biological origin for the production of cell-based and gene therapy medicinal products

1. Scope
2. Risk Assessment
3. General requirements

*Origin, Production, General quality requirements (ID/Tests/Assay/Ref. Mat_batch), Storage, Labelling*

- **Origin must be known**

- **Three source categories**

  1. raw materials of human or animal origin
  2. raw materials produced using substances of human or animal origin
  3. raw materials free from substances of human or animal origin

---

5.2.12 Raw materials of biological origin for the production of cell-based and gene therapy medicinal products

1. Scope
2. Risk Assessment
3. General requirements

*Origin, Production, General quality requirements (ID/Tests/Assay/Ref. Mat_batch), Storage, Labelling*

- **Risks to be minimized**

- **Traceability required**

  Donation <-> final product

  Due to the inherent risk of transmitting adventitious agents, it is recommended to minimise, wherever possible, the use of raw materials of human or animal origin. If such raw materials are required for the production of cell-based/gene therapy medicinal products, appropriate measures are taken to minimise the risks of transmitting adventitious agents such as viruses, prions, bacteria and protozoa.

  For human blood and tissue-derived materials, only carefully evaluated donors who have been adequately tested for infectious transmissible agents may be used. These materials comply with appropriate EU and/or national legislation applicable to transplantation and transfusion. Traceability measures enable each donation to be followed from the donation to the raw material and to the final product, and vice-versa.
5.2.12 Raw materials of biological origin for the production of cell-based and gene therapy medicinal products

1. Scope
2. Risk Assessment
3. General requirements

Origin, Production, General quality requirements (ID/Tests/Assay/Ref. Mat_batch), Storage, Labelling

- Suitable quality management system
- Suitable in-process controls
- Sterility or known microbial contamination
- Additives

The production process is optimised to consistently minimise and/or remove adventitious agents and harmful impurities, whilst retaining the quality of the raw material. This can be achieved using one or a combination of the following measures:

- using validated inactivation/removal procedures such as gamma sterilisation or low pH during chromatography, where possible;
- demonstrating the ability of a production process to minimise, remove or inactivate adventitious agents or harmful impurities;
- testing for adventitious agents or harmful impurities.

A raw material is sterile and produced under aseptic conditions and/or subject to terminal sterilisation, unless otherwise justified. If the raw material is not sterile, the level of microbial contamination must be known.

Additives, such as stabilisers, may be added to the raw material. In cases where antibiotics and stabilisers of biological origin are used in the production of the raw material, their presence is justified and careful consideration is given to their selection, use, quality and concentration in the raw material, as well as their impact on the actual raw material itself.

---

3.3. GENERAL QUALITY REQUIREMENTS

Raw materials must meet predefined quality requirements for identity, purity and biological activity. In order to ensure the function of the raw material, it is subject to testing using appropriately qualified methods. The identity test must reflect the uniqueness of the raw material and distinguish it from other related or similar substances. Impurities include both process-related substances (e.g. in the case of recombinant proteins: host-cell-derived proteins (HCP), host-cell-derived DNA and vector-derived DNA (residual DNA), other biological or chemical substances) and product-related substances (e.g. aggregates and degradation products). The content of a raw material may be expressed either in absolute or relative terms. The assay for determination of biological activity may be used to establish the content.
5.2.12 Raw materials of biological origin for the production of cell-based and gene therapy medicinal products

1. Scope
2. Risk Assessment
3. General requirements

   Origin, Production, General quality requirements (ID/Tests/Assay/Ref. Mat_batch), Storage, Labelling

3.3-1. IDENTIFICATION
The identity tests are specific for the particular raw material and address the molecular structure/composition or other relevant physico-chemical, biological or immunological properties. Methods used in the determination of biological activity and purity may also serve to identify the raw material. Identification may be carried out by comparison with a defined reference material or a representative batch of the raw material.

3.3-4. REFERENCE MATERIAL OR REFERENCE BATCH
An appropriate reference material or a representative batch of the raw material is used to perform the above-mentioned identification, tests and assay. Where available, the use of established reference standards, such as European Pharmacopoeia reference standards or WHO International Standards, is recommended.

5.2.12 Raw materials of biological origin for the production of cell-based and gene therapy medicinal products

1. Scope
2. Risk Assessment
3. General requirements

   Origin, Production, General quality requirements (ID/Tests/Assay/Ref. Mat_batch), Storage, Labelling

3.3-2. TESTS
Tests that may be applicable to raw materials include the following (see also the sections below for specific raw materials):
- Appearance
- Solubility
- Osmolality
- pH
- Elemental impurities

Total protein: (2.5.33); within the limits defined for the particular raw material.
Related substances: The content of product related substances is within the limits defined for the particular raw material.
Microbiological control: Depending on the raw material concerned, it complies with the test for sterility (2.6.7) or the microbial contamination is determined (2.6.12).
Viral contaminants: Depending on the raw material concerned, relevant virus contamination is determined.
Bacterial endotoxins (2.6.14) less than the limit defined for the particular raw material.
Mycoplasma (2.6.7). Raw materials are free from mycoplasmas.
Stabilisers: Where applicable, it complies with the limits defined for the particular raw material.
Water (2.5.12). Freeze-dried raw materials comply with the limits defined for the particular raw material.
5.2.12 Raw materials of biological origin for the production of cell-based and gene therapy medicinal products

1. Scope
2. Risk Assessment
3. General requirements
   Origin, Production, General quality requirements (ID/Tests/Assay/Ref. Mat_batch), Storage, Labelling

4. Sera and serum replacements
   4.1 Definition / 4.2 Production / 4.3 Identification / 4.4 Tests / 4.5 Assay

   - e.g. bovine serum, human serum and platelet lysates, conditioned media
   - Focus on consistency (typically complex biological mixtures) and safety
   - More than 1 type of assay to show suitability may be necessary
5.2.12 Raw materials of biological origin for the production of cell-based and gene therapy medicinal products

1. Scope
2. Risk Assessment
3. General requirements
   - Origin, Production, General quality requirements (ID/Tests/Assay/Ref. Mat_batch), Storage, Labelling
4. Sera and serum replacements
   - 4.1 Definition / 4.2 Production / 4.3 Identification / 4.4 Tests / 4.5 Assay
5. Proteins produced by recombinant DNA technology
   - 5.1 Definition / 5.2 Production / 5.3 Identification / 5.4 Tests / 5.5 Assay
     - e.g. growth factors, cytokines, hormones, enzymes, monoclonal antibodies
     - Specific activity of the produced proteins
     - Supplementary tests for derived proteins, residual host-cell or vector DNA, related proteins

6. Proteins extracted from biological material
   - 6.1 Definition / 6.2 Production / 6.3 Identification / 6.4 Tests / 6.5 Assay
     - e.g. enzymes, polyclonal Abs, other proteins (e.g. albumin)
     - Supplementary tests for process-related impurities
     - Assay for protein content and biological activity
5.2.12 Raw materials of biological origin for the production of cell-based and gene therapy medicinal products

1. Scope
2. Risk Assessment
3. General requirements
   Origin, Production, General quality requirements (ID/Tests/Assay/Ref. Mat_batch), Storage, Labelling
4. Sera and serum replacements
   4.1 Definition / 4.2 Production / 4.3 Identification / 4.4 Tests / 4.5 Assay
5. Proteins produced by recombinant DNA technology
   5.1 Definition / 5.2 Production / 5.3 Identification / 5.4 Tests / 5.5 Assay
6. Proteins extracted from biological material
   6.1 Definition / 6.2 Production / 6.3 Identification / 6.4 Tests / 6.5 Assay
7. Vectors

Microbiological control

Dr Emmanuelle Charton,
Head of Division B, European Pharmacopoeia Department,
EDQM, Council of Europe
Specificity of cell therapy products:

• Fragile, precious
• Limited shelf life
• Often: cannot be cryopreserved
• Small size of the batch, limited sample volume
• Cannot be terminally sterilized by filtration or other physico-chemical means
• Microbial contaminants may be found out or inside the cells (microbiological /sterility testing cannot be limited to cell supernatant)

Chapter 2.6.27: Microbiological control of cellular products

• Automated growth based system
• Originally developed for use with the monograph on Human haematopoietic stem cells (2323) in place of the test for sterility (2.6.1) which is often not the method of choice for these products.
  ✓ better sensitivity
  ✓ broader range
  ✓ more rapid
• Referred to in chapter 5.14 Gene transfer medicinal products for human use and 2323 Human haematopoietic stem cells
Microbial examination of cell based preparations

2.6.1. Compendial sterility test
- PDG Harmonised chapter
- Visual detection of micro-organisms
- Incubation for at least 14 days

2.6.27. Not mandatory
- Not part of International Harmonisation
- Recognition of the limitation of conventional microbiological methods
- Automated growth-based methods: Incubation for at least 7 days
### 2.6.27 Microbiological examination of cell-based preparations

**SUPPLEMENT 9.2 Revision (July 2017)**

- Greater flexibility for the incubation temperature(s) and examples of temperature settings where the test volume allows 2 incubation conditions.
- List of micro-organisms used for method validation better reflects common contaminants of cell-based preparations.
- Information about the sensitivity to be achieved during validation has also been included.
- The possibility to use alternative methods is given throughout the chapter (Chapter 5.1.6 Alternative methods for control of microbiological quality)

---

<table>
<thead>
<tr>
<th>First version</th>
<th>New version</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2.6.27. MICROBIOLOGICAL CONTROL OF CELLULAR PRODUCTS</strong></td>
<td><strong>2.6.27. MICROBIOLOGICAL EXAMINATION OF CELL-BASED PREPARATIONS</strong></td>
</tr>
<tr>
<td>GENERAL PRECAUTIONS</td>
<td><strong>1. INTRODUCTION</strong></td>
</tr>
<tr>
<td>GROWTH PROMOTION TEST</td>
<td><strong>1.2. SAMPLE COMPOSITION</strong></td>
</tr>
<tr>
<td>METHOD VALIDATION</td>
<td><strong>1.3. SAMPLE SIZE</strong></td>
</tr>
<tr>
<td>TESTING OF THE PREPARATION TO BE EXAMINED</td>
<td><strong>1.4. RATIONALE FOR METHOD SELECTION</strong></td>
</tr>
<tr>
<td>OBSERVATION AND INTERPRETATION OF RESULTS</td>
<td><strong>2. GENERAL CONSIDERATIONS</strong></td>
</tr>
<tr>
<td><strong>2.1. GENERAL PRECAUTIONS</strong></td>
<td><strong>2.2. METHODS FOR MICROBIOLOGICAL EXAMINATION OF CELL-BASED PREPARATIONS</strong></td>
</tr>
<tr>
<td>2.2.1. Shelf-life</td>
<td><strong>3.1. AUTOMATED GROWTH-BASED METHOD</strong></td>
</tr>
<tr>
<td>2.2.2. Sampling</td>
<td><strong>3.1.1. Growth promotion test</strong></td>
</tr>
<tr>
<td><strong>3. METHODS FOR MICROBIOLOGICAL EXAMINATION OF CELL-BASED PREPARATIONS</strong></td>
<td><strong>3.1.2. Method suitability</strong></td>
</tr>
<tr>
<td>3.1. EXAMINATION OF CELL-BASED PREPARATIONS</td>
<td><strong>3.1.3. Testing of the preparation to be examined</strong></td>
</tr>
<tr>
<td>3.2. DIRECT DETECTION BY ALTERNATIVE METHODS</td>
<td><strong>3.1.4. Observation and interpretation of results</strong></td>
</tr>
<tr>
<td><strong>3.2.1. Combination of preliminary and detection by alternative methods</strong></td>
<td><strong>3.2.2. Direct detection by alternative methods (5.1.6)</strong></td>
</tr>
<tr>
<td><strong>3.2.3. Method validation</strong></td>
<td><strong>3.2.3. Method validation</strong></td>
</tr>
</tbody>
</table>

©2020 EDQM, Council of Europe. All rights reserved.
3-1-2. Method suitability

• Due to the heterogeneity of the cell based preparation sourcing, content and manufacturing procedure the suitability of the method is to be confirmed in the presence of the specific sample composition.

3-1-2. Method suitability

• New: Supplement 10.3

A clarification has been carried out in section 3-1-2. Method suitability. This section has been modified to avoid confusion between ‘validation’ and ‘confirmation of the suitability of the method’ for the automated growth-based method. The critical parameters described are to be verified as part of confirmation of method suitability.

3-1-2. Method suitability

For a validated automated growth-based method only a confirmation of the suitability of the method for the given cell-based preparation must be performed. The test system is validated with respect to specificity (absence of false positive results), sensitivity, reproducibility and robustness. Regardless of the type of cell-based preparation, the
## Implementation of 2.6.27

<table>
<thead>
<tr>
<th>Primary validation: Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>URS, Description, Risk benefit analysis</td>
</tr>
<tr>
<td>Verification of primary validation</td>
</tr>
<tr>
<td>Verification for the intended use: Specificity, sensitivity, reproducibility, robustness (3.1.2)</td>
</tr>
<tr>
<td>Suitability testing</td>
</tr>
<tr>
<td>Using the type of sample to be analysed</td>
</tr>
<tr>
<td>Equivalence testing</td>
</tr>
</tbody>
</table>

---

### 2.6.27 Quiz

**Question** I want to use a rapid microbiological method for an ATMP sterility test. Am I obliged to use 2.6.27?

**Response**. No. There is no ATMP Ph. Eur. monograph which renders 2.6.27 obligatory
**2.6.27 Quiz**

**Question** I want to use 2.6.27 for my ATMP. Do I have to cross validate the method against 2.6.1?

**Response** No. 2.6.27 can be used in place of 2.6.1 without cross validation.

---

**Gene transfer medicinal products for human use (5.14)**

Dr Olga Kolaj-Robin
European Pharmacopoeia Department
EDQM, Council of Europe
Gene transfer medicinal product for human use (5.14)

- Recombinant vectors
  - Genetically modified cells
  - Plasmid vectors for human use
  - Bacterial cells used for the manufacture of plasmid vectors for human use
  - Adenovirus vectors for human use
  - Poxvirus vectors for human use

- Addition of:
  - Retroviridae-derived vectors for human use
  - Adeno-associated virus vectors for human use

- General revision to consider recent developments in the field

GTMPs in Europe

Addition to WP
Adoption
Revision #1
GTP WP reinstatement
Revision #2

2005
2006
2008
2018
2019

- Published for information
- Provides framework of requirements applicable to the production and control of the products
- Applicable for approved products
- Application to products used during clinical trials decided by the competent authority
- Alternative production and control methods acceptable to the competent authority not excluded
Gene transfer medicinal product for human use (5.14)

Subsection structure

ADENO-ASSOCIATED-VIRUS VECTORS FOR HUMAN USE

Definition
Production
  Vector construction
  Production and harvest
  Purified harvest
  Final bulk
  Final lot
Identification
Tests
Assay
Labelling

- No numerical limits
- List of requirements for each stage of production
- Examples of suitable techniques

Gene transfer medicinal product for human use (5.14)

- Expansion of Genetically modified cells ➔ Autologous genetically modified human cells
- Revision of Adeno-associated virus vectors
- Elaboration of Oncolytic herpes simplex virus
- Revision of Retroviridae-derived vectors
- Elaboration of Genetically modified bacterial cells
- Revision of Plasmid vectors for human use
- Revision of Bacterial cells used for the manufacture of plasmid vectors for human use
- Revision of Adenovirus vectors for human use
- Revision of Poxvirus vectors for human use
- Potential elaboration of additional sections e.g. on allogeneic genetically modified cells or gene editing tools

Revision #2

2019

1,052 Clinical Trials

Gene Therapy

Total: 370
  Ph. I: 111
  Ph. II: 223
  Ph. III: 32

Gene-Modified Cell Therapy

Total: 418
  Ph. I: 201
  Ph. II: 203
  Ph. III: 14

Source: Alliance for Regenerative Medicine

©2020 EDQM, Council of Europe. All rights reserved.
Gene transfer medicinal product for human use (5.14)

Do not miss the opportunity to comment on the revised chapter when published in Pharmeuropa!

Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: https://go.edqm.eu/Newsletter
LinkedIn: https://www.linkedin.com/company/edqm/
Twitter: @edqm_news
Facebook: @EDQMCouncilofEurope

©2020 EDQM, Council of Europe. All rights reserved.