THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

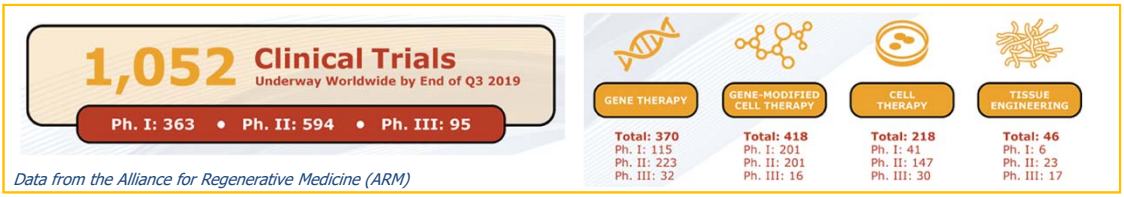
COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

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

Name / Company	ATMP	Approval	Description / Indication
ChondroCelect	TEP	2009 - 2016	Autologous cartilage cells / Repair of cartilage defects of the knee
Glybera	GTMP	2012-2017	Alipogene tiparvovec (AAV-1 – Lipoproteine lipase gene) / Familial lipoprotein lipase deficiency (LPLD)
MACI	TEP	2013-2014	Autologous chondrocytes / Repair of cartilage defects of the knee
Provenge	CTMP	2013-2015	sipuleucel-T (autologous PBMC activated with PAP-GMSF colony-stimulating factor) / Prostate Cancer
Holoclar	TEP	2015	Autologous human corneal epithelial cells Moderate to severe limbal stem-cell deficiency caused by burns
Imlygic	GTMP	2015	Talimogene laherparepvec (HSV-1-derived virus GM-CSF) Melanoma
Strimvelis	GTMP	2016	Autologous CD34+ cells transduced with retroviral vector encoding the human adenosine deaminase (ADA) cDNA sequence ADA-SCID deficiency
Spherox	TEP	2017	Spheroids of human autologous matrix-associated chondrocytes
Alofisel (darvadstrocel)	CTMP	2018	Expanded allogenic adipose-derived mesenchymal stem cells Treatment of perianal fistulas in patients with Crohn's disease
Kymriah (Tisagenlecleucel)	GTMP	2018	CD19-directed genetically modified autologous T-cell immunotherapy Treatment of B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse, relapsed or refractory (r/r) large B-cell lymphoma
Yescarta (Axicabtagene ciloleucel)	GTMP	2018	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
Luxturna (Voretigene neparvovec)	GTMP	2018	AAV vector-based gene therapy Treatment of biallelic RPE65 mutation-associated retinal dystrophy
Zynteglo/LentiGlobin	GTMP	June 2019 Conditional MA	Autologous CD34+ cells transduced with a lentiviral vector encoding the human βAT87Q-globin gene Treatment of transfusion-dependent β-thalassemia (TDT) in patients with non-β0/β0 genotypes



Data from the Alliance for Regenerative Medicine (ARM)

Place of the Ph. Eur. in the regulatory framework

Celine Pugieux-Amarantos, PhD,
Scientific officer, European Pharmacopoeia Department,
EDQM, Council of Europe

Directive 2001/83/EC on medicinal products for human use

Directive 2001/83/EC on medicinal products for human use and amendments

❖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)

Directive 2001/83/EC on medicinal products for human use

Directive 2001/83/EC on medicinal products for human use and amendments

❖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.

❖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)

!! Monographs on Insulins (0838, 1637, 1638), G-CSF (2206), GM-CSF (1641), Erythropoietin (1316), Interferon gamma (1440), Trypsin (0694) define requirements for substances used as APIs and might not be adapted for use as raw materials

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
5.1.6 Alternative methods for control of microbiological quality
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

Ph. Eur. Commission established **Raw Materials for the Production of Cellular and Gene Transfer Products Working Party**

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

Public consultation	Final version preparation	Publication Ph. Eur. 9th Edition
Pharmeuropa (Issue 26.4: Q4 2014 – Q1 2015)	Comments received during public consultation were evaluated	Publication July 2016 Implementation date: 1 January 2017

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

Introduction

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 (incl. Blood and other cellular components, platelet lysates, conditioned media)

4.1 *Definition / 4.2 Production / 4.3 Identification / 4.4 Tests / 4.5 Assay*

5. Proteins produced by recombinant DNA technology (incl. Growth actors, cytokines, hormones, enzymes and mAbs)

5.1 *Definition / 5.2 Production / 5.3 Identification / 5.4 Tests / 5.5 Assay*

6. Proteins extracted from biological material incl. enzymes (e.g. trypsin), polyclonal Abs, other proteins (e.g. albumin), peptides

6.1 *Definition / 6.2 Production / 6.3 Identification / 6.4 Tests / 6.5 Assay*

7. Vectors

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 <u>are not intended</u> to form part of the active substance

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

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

1. Scope
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

2. RISK ASSESSMENT

Evaluation of the impact of the raw material on the quality, safety and efficacy of cell-based/gene therapy medicinal products must be performed by the user of the raw material. No single measure or combination of measures can guarantee the quality, functionality and safety of a raw material for its intended use. Therefore, a risk assessment must consider the biological origin and traceability of the raw material, the production steps applied to it and the ability of the drug product manufacturing process to control or remove the raw material from the final medicinal product.

Any risk factor must be evaluated in relation to the clinical benefit/risk of the cell-based or gene therapy medicinal product. When evaluating the risk posed by the raw material to the final medicinal product, the exposure of a patient to residual amounts of raw material with potential harmful effects (e.g. adverse immune reactions) should be considered in relation to the clinical benefit/risk of the cell-based or gene therapy medicinal product.

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

> The origin of the raw material and if relevant any biological substances used for the production of the raw material must be known. Special attention must be paid to risks related to the sourcing (including pooling) of the substances used for the production of the raw material. Depending on the source of the raw material and the substances used in its production, raw materials can be divided into 3 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

> 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.

- Traceability required

Donation <-> final product

> 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.

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

- Pre-defined quality set by specifications
- Testing with qualified methods

3-3. *GENERAL QUALITY REQUIREMENTS*

Raw materials must meet pre-defined 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 immunochemical 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. Liquid or reconstituted freeze-dried raw materials comply with the limits defined for the particular raw material with regard to degree of opalescence (*2.2.1*) and degree of coloration (*2.2.2*).

Solubility. Freeze-dried raw materials dissolve completely in the prescribed volume of reconstituting liquid within a specified time, at a specified temperature, as defined for the particular raw material.

Osmolality (*2.2.35*): within the limits defined for the particular raw material.

pH (*2.2.3*): within the limits defined for the particular raw material.

Elemental impurities: within the limits defined for the particular raw material.

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 (*2.6.1*) 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.

Mycoplasmas (*2.6.7*). Raw materials are free from mycoplasmas.

Stabiliser. 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

> 3-3-3. **ASSAY**
>
> **Content**. The content (e.g. protein content)/composition of the raw material is determined by an appropriate qualified method.
>
> **Biological activity**. Where relevant, the biological activity is determined by a suitable assay. Where relevant (e.g. for enzymes), the biological activity is expressed per milligram of total protein (specific 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*

- 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

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*

- 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

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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*

2.6.27. MICROBIOLOGICAL EXAMINATION OF CELL-BASED PREPARATIONS

This chapter does not concern the examination of human blood or blood components, which is covered by Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 and Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC.

1. INTRODUCTION

The approaches to microbiological examination of cell-based preparations outlined in this general chapter take into account the characteristics and limitations of these preparations, in particular their shelf-life, which may not always allow for completion of conventional microbiological examination tests before administration to the patient, as well as the amounts available for testing and sampling-related issues. These approaches may be applied when the test for sterility, described in general chapter *2.6.1. Sterility*, is required but cannot be performed for technical reasons or due to the characteristics of the specific cell-based preparation.

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)

First version

2.6.27. MICROBIOLOGICAL CONTROL OF CELLULAR PRODUCTS

GENERAL PRECAUTIONS

GROWTH PROMOTION TEST

METHOD VALIDATION

TESTING OF THE PREPARATION TO BE EXAMINED

OBSERVATION AND INTERPRETATION OF RESULTS

New version

2.6.27. MICROBIOLOGICAL EXAMINATION OF CELL-BASED PREPARATIONS

1. INTRODUCTION
1-1. *SHELF-LIFE*
1-2. *SAMPLE COMPOSITION*
1-3. *SAMPLE SIZE*
1-4. *RATIONALE FOR METHOD SELECTION*
2. GENERAL CONSIDERATIONS
2-1. *GENERAL PRECAUTIONS*
2-2. *HANDLING CONSTRAINTS*
2-2-1. **Shelf-life**
2-2-2. **Sampling**
3. METHODS FOR MICROBIOLOGICAL EXAMINATION OF CELL-BASED PREPARATIONS
3-1. *AUTOMATED GROWTH-BASED METHOD*
3-1-1. **Growth promotion test**
3-1-2. **Method suitability**
3-1-3. **Testing of the preparation to be examined**
3-1-4. **Observation and interpretation of results**
3-2. *ALTERNATIVE METHODS*
3-2-1. **Combination of preculturing and detection by alternative methods**
3-2-2. **Direct detection by alternative methods** (*5.1.6*)
3-2-3. **Method validation**

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

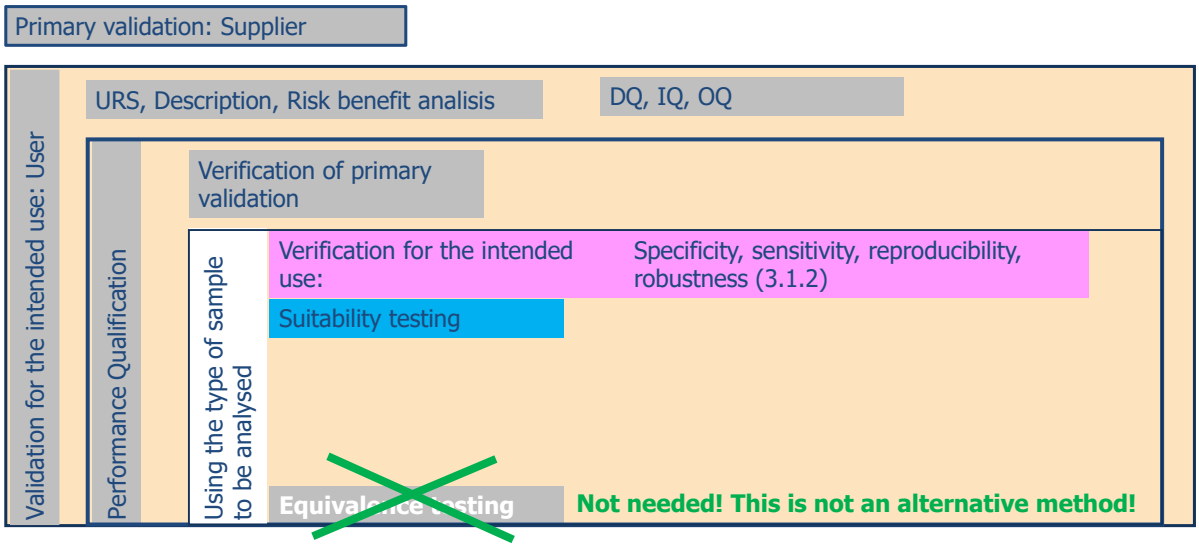
- New: Supplement 10.3

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



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

Quiz

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

Quiz

Gene transfer medicinal products for human use (5.14)

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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

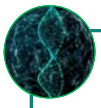
Addition to WP | Adoption | Revision #1 | GTP WP reinstatement | Revision #2

2000 | 2005 | 2008 | 2018 | 2019

GTMPs in Europe

Glybera | IMLYGIC | Strimvelis | YESCARTA | KYMRIAH | LUXTURNA | zynteglo

Gene transfer medicinal product for human use (5.14)



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5.14. GENE TRANSFER MEDICINAL PRODUCTS FOR HUMAN USE

- 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

04/2019:51400

5.14. GENE TRANSFER MEDICINAL PRODUCTS FOR HUMAN USE

(...)

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)

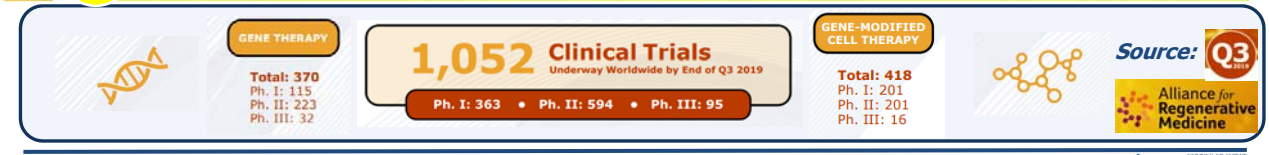
- Expansion of *Genetically modified cells* → *Autologous genetically modified human cells*
- Revision of *Adeno-associated virus vectors*
- Elaboration of *Oncolytic herpes simplex virus*

- 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

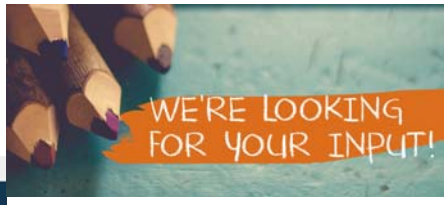
Revision #2

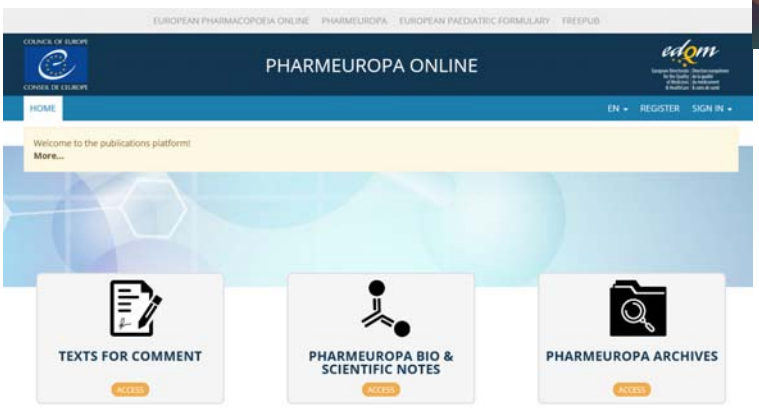
2019



Gene transfer medicinal product for human use (5.14)

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





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