International Conference, 19-21 September 2022

Collaboration, Innovation and Scientific Excellence: the European Pharmacopoeia 11th Edition

Session 6: Cell and gene therapies

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

edqm
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

The Regulation of ATMPs in Europe

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Collaboration, Innovation and Scientific Excellence: the European Pharmacopoeia 11th Edition
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Introduction

ATMPs = Advanced Therapy Medicinal Products

- **Medicinal products**
- **Regulated under the pharmaceutical and ATMP frameworks :**
  - Directive 2001/83/EC
  - **Regulation (EC) 1394/2007**
- Authorised in the EU via the **centralised procedure**
- **Committee for Advanced Therapies** (CAT): specific Committee dedicated to ATMPs

Definition

Definition

Directive 2001/83/EC, Directive 2009/120/EC & Regulation (EC) 1394/2007

ATMPs are **biological medicinal products** administered to **human beings**

ATMPs		Characteristics/effects
Gene therapy medicinal product	**recombinant** nucleic acid	**Direct effect** To regulate, repair, replace, add or delete a genetic sequence **Vaccines against infectious diseases are excluded**
Somatic cell therapy medicinal product	cells or tissues	**Substantial manipulation** or/and **Non homologous use** To treat, prevent or diagnose a disease through **pharmacological, immunological or metabolic** action
Tissue engineered product	cells or tissues	**Substantial manipulation** **or/and** **Non homologous use** To **regenerate**, **repair** or **replace** a **human tissue**

Combined ATMP = ATMP combined with a medical device

Reflection paper on classification of advanced therapy medicinal products 2015 (EMA/CAT/600280/2010 rev.1)

Substantial manipulation / non homologous use

➢ **Substantial manipulation:**

- The cells or tissue(s) have been **manipulated** during the **manufacturing process** so that their **biological characteristics, physiological functions or structural properties have been modified** to be relevant for their intended function.
- depends on the level of manipulation during manufacturing process

➢ **Non-homologous use of the cells**

- The cells **are not used** for the **same essential function** in **donor and recipient**.
- depends on the therapeutic indication

ATMP classification depends not only on **the product,** but also on **the therapeutic application.**

The Committee for Advanced Therapies (CAT) is in charge to classify the ATMPs (*Regulation 1394/2007*)

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What is a substantial manipulation during the manufacturing process?

Non substantial manipulations are listed in Annex I of Reg 1394/2007

cutting
grinding
shaping
centrifugation
soaking in antibiotic or antimicrobial solutions
sterilization
irradiation
cell separation, concentration or purification
filtering
lyophilization
freezing
cryopreservation
vitrification

Substantial manipulations

cell expansion (culture)
genetic modification of cells
differentiation/activation with growth factors,
enzymatic digestion (to destroy cell to cell interactions)
etc.

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Example of substantial manipulation

Skin / keratinocytes

Homologous use: yes (skin substitute)

Substantial modification ?

= modification of the **biological characteristics, physiological functions or structural properties**

no → **Skin graft** *(used such as)* → **= non ATMP**

yes → **Suspension of keratinocytes** *(keratinocytes isolated from skin biopsy by enzymatic digestion with the destruction of the tissues architecture and functional interactions of the cells* → **= ATMP**

≠ **human pancreatic Langerhans' islets**
- incomplete enzymatic digestion
→ intact structure and function of tissue unit
- homologous use
= non ATMP

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Example of non homologous use

Haematopoietic stem cells
Collected from bone marrow, cord blood, apheresis

Substantial manipulation: No

Homologous use ?

The essential function of the HSC is the « **hematopoietic or immune reconstitution**"

yes → **HSC transplantation** → **= non ATMP**

no → **Orthopedic use, regeneration of cartilage and bone** → **= ATMP**

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ATMP regulation

How ATMPs are regulated?

2007

Regulation (EC) 1394/2007 modifies pharmaceutical **Directive 2001/83/EC** and **Regulation 726/2004**

→ specific to ATMPs

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 13 November 2007
on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

2009

- **Regulation 668/2009/EC**
  → Evaluation and **Certification** of Non-clinical & Quality data of ATMPs for micro-small and medium-sized enterprises (SME)

- **Directive 2009/120** amending Directive 2001/83/EC
  → specific requirements for quality, non clinical & clinical data for ATMPs
  → **Risk Based Approach**

Key points of Regulation 1394/2007 EC

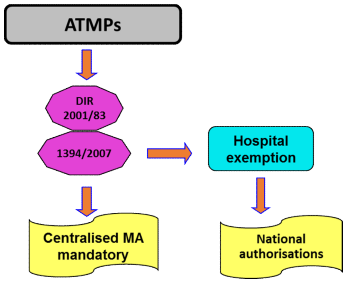
In addition to **pharmaceutical framework**, **specific rules** concerning the authorisation supervision and pharmacovigilance of ATMPs

- Definition of a **new therapeutic class: the ATMPs**
- Creation of the **Committee for Advanced Therapies (CAT) =** the dedicated committee at the European Medicines Agency is responsible for assessing the quality, the safety and efficacy of ATMPs and following scientific developments in the field
- **Centralised** procedure **mandatory**
- Demonstration of quality, safety & efficacy of ATMPs
- **Post authorisation measures**: Risk management Plan and follow-up of safety and efficacy
- Cell and tissue **donation** procurement and testing in compliance with **Directive 2004/23 or Directive 2002/98**

Hospital Exemption

- ***art 28 Reg. 1394/2007***
- **Exemption to the centralized procedure**

- ***ATMPs***
- *which are prepared on **a non-routine basis** according to specific quality standards,*
- *used **within the same Member State** in a hospital*
- *under the exclusive professional responsibility of a medical practitioner,*
- *in order to comply with an individual medical prescription*
- *for a custom-made product*
- *for an **individual patient***



- **Under the remit of each state member**

GMO regulation applied to ATMPs

Products:

- Genetically modified cell products
- Adeno-associated virus based products
- Recombinant virus

GMO framework:

- Directive **2001/18/EC** on the **deliberate release** into the environment of genetically modified organisms
- Directive **2009/41/EC** on the **contained use** of genetically modified micro-organisms

Clinical trials :

- Under national remit (GMO competent authority)
- Depending on each country, either contained use directive or deliberate release directive or both apply
- GMO authorization needed to start the clinical trial

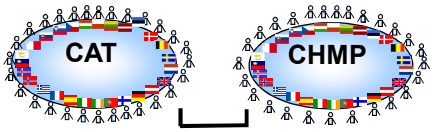
Marketing authorization

- Directive on deliberate release
- Specific environmental risk assessment (module 1.6.2)
- European consultation of national GMO authorities
- Negligible GMO environmental risk

*See the EC site: https://health.ec.europa.eu/medicinal-prod**ucts/advanced-therapies_en***

The CAT

CAT: Committee for Advanced Therapies



5 joint members

CHMP: Committee of Human Medicinal Products

Composition

- **27 national members** and 27 alternates including 5 joint members from the CHMP + **Norway and Iceland**
- **2 patients organization** members and 2 alternates
- **2 clinician** members and 2 alternates

Multidisciplinary scientific committee

CAT expertise covers the scientific areas relevant to advanced therapies, including:

- medical devices,
- tissue engineering,
- gene therapy,
- cell therapy
- biotechnology,
- surgery,
- pharmacovigilance & risk management
- ethics.

First meeting in January **2009** / Monthly meeting

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Tasks of the CAT

- **Marketing Authorisation Application:** **responsible for the evaluation of marketing authorisation of ATMPs** and to formulate the **draft opinion** on each ATMP application submitted to EMA for final opinion by the CHMP
- **Classification**: to provide **advice on whether a product falls within the definition of an ATMP** (free of charge)
- **Certification**: to assess quality and non-clinical data for Micro, Small and Medium Enterprises
- **Scientific Advice:** to advise on the quality, safety and efficacy and other aspects of an ATMP
- **PRIME (priority medicines):** to contribute to the draft opinion for ATMPs for approval by the CHMP (via SAWP)
- **Support to other committees**
- **Guidelines for ATMPs**
- **Involvement in working groups organized by the European Commission**
  - GMP for ATMPs
  - GCP for ATMPs
  - GMO regulation

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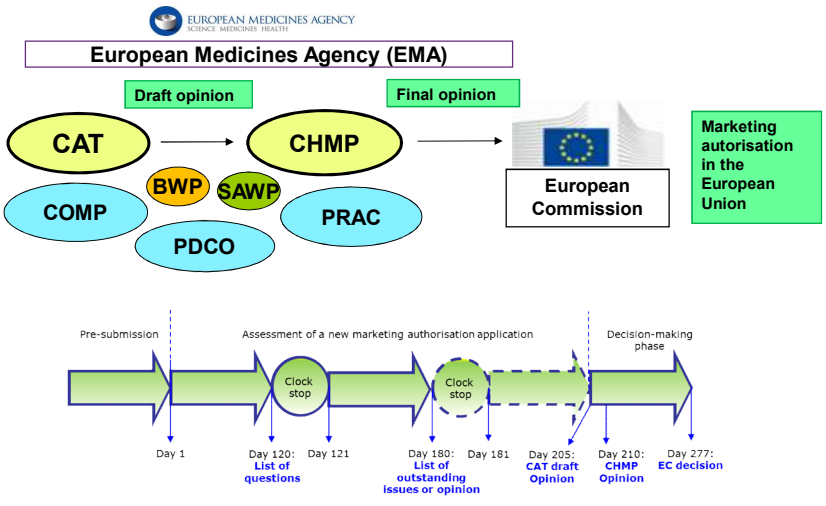
ATMP Marketing Authorisation Application

CAT = main committee responsible for the evaluation of the benefit risk for ATMPs

Full responsibility for the dossier

- quality, non-clinical and clinical parts
- benefit/risk assessment
- therapeutic indication
- post-authorisation measures to monitor safety and efficacy
  - depending on the specificities of the ATMP and the data available at the time of marketing authorization
  - long term efficacy and safety follow up (registries, observational studies)
- Decision on a case-by-case basis

ATMP Centralized procedure



Scientific evaluation ot the quality efficacy and safety => Benefit/risk ratio

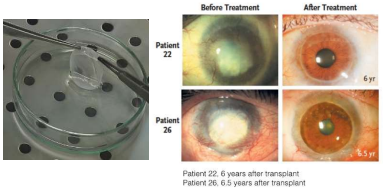
Overview (2009-2022)

Classification	Scientific Advice	Marketing Authorisation Application	Authorised products
570 **classifica-tions**	535 scientific advices	**36 submitted MAA**	**22 authorised ATMPs**
	48 Prime	**4** negative opinions	6 withdrawals post MA
	14 certifica-tions	**9** withdrawals	**16 active authorised ATMPs**

Somatic cell therapy medicinal products & Tissue engineered products

Name	MA	Product	Indication
MACI®	*2013*	*Autologous chondrocytes*	*cartilage defects of the knee*
Provenge®	*2013*	*Autologous PBMC-GMSF*	*prostate cancer*
Zalmoxis®	*2016*	*Allogenic T cells modified with a suicide gene*	*adjunctive treatment in haploidentical HSCT*
Holoclar®	**2015**	**Autologous human corneal epithelial cells**	**limbal stem cell deficiency due to ocular burns.**
Spherox®	**2017**	**Autologous chondrocytes**	**cartilage defects of femoral condyle and patella of the knee**
Alofisel®	**2018**	**Allogeneic mesenchymal adult stem cells**	**complex perianal fistulas in Crohn's disease**

HOLOCLAR



Tissue engineered products ***Somatic cell therapies*** ***Gene therapies*** ***in italic: withdrawn***

Gene therapy medicinal products : genetically modified cells

***Ex-vivo* gene therapy**

CD34+ cells

Name	MA	Product	Indication
Strimvelis	2016	Autologous CD34+ cells –ADA gene	ADA-SCID
Zyngleto®	*2019*	*Autologous CD34+ cells - βA-T87Q-globin gene*	*transfusion-dependent β-thalassaemia non β0 /β0*
Libmeldy	2020	Autologous CD34+ cells - ARSA gene	metachromatic leukodystrophy ARSA-/-
Skysona®	*2021*	*Autologous CD34+ cells - ALD gene*	*early cerebral adrenoleukodystrophy*

CAR-T cells

Name	MA	Product	Indication
Yescarta®	2018	Autologous CAR-T cells anti CD19	DLBCL and PMBCL 3rd line + FL 4th line
Kymriah®	2018	Autologous CAR-T cells anti CD19	r/r B ALL + DLBCL 3rd line + FL 3rd line
Tecartus®	2020	Autologous CAR-T cells anti CD19	mantle cell lymphoma (MCL) 3rd line + r/rALL-B ≥26 yo
Abecma	2021	Autologous CAR-T cells anti BCMA	Multiple myeloma 4th line
Breyanzi	2022	Autologous CD4/CD8 CAR-T cells anti CD19	DLBC, PMBCL, FL3B, 3rd line
Carvykti	2022	Autologous CAR-T cells anti BCMA	Multiple myeloma 4th line

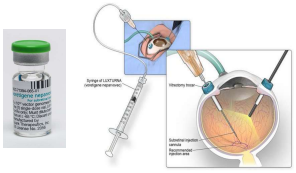
Tissue engineered products *Somatic cell therapies* *Gene therapies* *in italic: withdrawn*

Gene therapy medicinal products: recombinant viral vectors

***in-vivo* gene therapy**

Name	MA	Product	Indication
Glybera®	*2012*	*AAV-1 – LPL*	*familial lipoprotein lipase deficiency*
Imlygic®	2015	Oncolytic HSV-1-derived virus GM-CSF	unresectable metastatic melanoma (Stage IIIB, IIIC and IVM1a)
Luxturna®	2019	AAV2-huRPE65	inherited retinal dystrophy RPE65-/-
Zolgensma®	2020	AAV9-huSMN	spinal muscular atrophy (SMA1)
Upstaza	2022	AAV2-huAADC	aromatic L-amino acid decarboxylase (AADC) deficiency
Roctavian	2022	AAV5-hFVIII	Severe Hemophilia A

Luxturna



Zolgensma

Tissue engineered products *Somatic cell therapies* *Gene therapies* *in italic: withdrawn*

Conclusion

- ATMPS are **complex medicinal products**
  - Autologous products
  - Unique administration with the possibility of curing a disease
  - Broad spectrum of indications
  - Rare diseases, life threatening with unmet medical need
- **Dedicated European Committee (CAT)** to ensure that ATMPs placed on the market are of high quality with a demonstrated benefit risk for the patients
- Increase in the number of ATMPs placed on the market

  → **European Pharmacopeia update**

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Thank you for your attention

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WHAT'S NEW?

Update on the activities of the Ph. Eur. in the cell and gene therapies field

Conference 11th Edition European Pharmacopoeia

Dr Solène Le Maux & Dr Olga Kolaj-Robin – EDQM, Council of Europe

Activities of the EDQM in the cell and gene therapies field

OMCL Gene Therapy Working Group (GTWG)

Guide to the quality and safety of tissues and cells for human application

Ph. Eur. Groups of Experts and Working Parties

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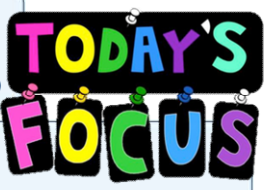
Cell Therapy Products Working Party (CTP WP)

Gene Therapy Products Working Party (GTP WP)

Raw materials for the production of cellular and gene transfer therapy products (RCG WP)



Elaboration and revision of Ph. Eur. texts

2.6.39 Microbiological examination of human tissues
2.7.28 Colony-forming cell assay for human haematopoeitic progenitor cells
2.7.29 Nucleated cell count and viability
2.6.27 Microbiological examination of cell-based preparations
2.7.24 Flow cytometry
2.7.23 Numeration of CD34/CD45 cells in haematopoietic products
5.32 Cell-based preparations
2323 Human haematopoietic stem cells

5.14 Gene transfer medicinal products for human use
3186 Gene therapy medicinal products for human use
5.34 Additional information on gene therapy medicinal products for human use

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

Activities of the EDQM in the cell and gene therapies field

OMCL Gene Therapy Working Group (GTWG)

Guide to the quality and safety of tissues and cells for human application

Ph. Eur. Groups of Experts and Working Parties

Prepares OMCLs for quality control of GTPs

Activities:

- Define common work program (vectors & methods)
- Share information, know-how, resources, materials, transfer/establish common methods & reference materials
- Perform collaborative studies

Examples of current studies:

1) Physical particles determination - **ELISA** (AAV2, AAV8)
2) Viral & infectious genomes titre - **qPCR** (AAV2)
3) Residual host cell DNA – **qPCR**

Potential future studies:

1) Retro/lentivirus vectors
2) Poxvirus vectors
3) Non-replicative adenovirus vectors
4) HSV1-based vectors

Based on best available scientific evidence to provide professionals with a useful overview of the most recent developments

Contribute to the **harmonisation** among European countries

INCREASED QUALITY AND SAFETY OF ORGANS, TISSUES AND CELLS

IMPROVED CLINICAL OUTCOMES

MINISTERS' DEPUTIES Recommendations

Recommendation CM/Rec(2020)5[1]
of the Committee of Ministers to member States
on the quality and safety of tissues and cells for human application
(Adopted by the Committee of Ministers on 7 October 2020 at the 1385th meeting of the Ministers' Deputies)

https://rm.coe.int/09000016809fdcde

Continuous update (3-year cycle) **5th edition due in 2022**

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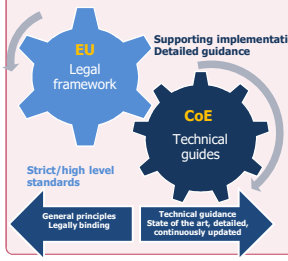


BTC legislative proposal in the EU (cascade model):

NEW!

Where there are technical requirements in the **EU legislation** they must be followed

Where there are no technical rules in EU legislation – the safety and quality standards defined by **reference expert bodies** (EDQM) must be followed

Where there is no EU level rule or referenced body guidance, the **establishments** must set their **own rule** taking into account any relevant recognised international standards and scientific evidence, and assess risk/benefit. Process must be **reviewed and approved by CA**

Cell and gene therapy – relevant Ph. Eur. texts

TODAY'S FOCUS

General overarching texts

- 5.14 Gene transfer medicinal products for human use
- 3186 Gene therapy medicinal products for human use*
- 5.34 Additional information on gene therapy medicinal products for human use*
- 5.2.12 Raw materials of biological origin for the production of cell-based and gene therapy medicinal products*
- 5.32 Cell-based preparations

General 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^{p}
- 2.7.29 Nucleated cell count and viability^{p}
- 2.6.35 Quantification and characterisation of host-cell DNA

General chapters: Microbiology aspects & viral safety

- 2.6.1 Sterility
- 5.1.6 Alternative methods for control of microbiological quality
- 2.6.27 Microbiological examination of cell-based preparations**
- 2.6.39 Microbiological examination of human tissues
- 2.6.14 Bacterial endotoxins - 2.6.30 MAT^{p} - 2.6.32 rFC
- 2.6.7 Mycoplasmas
- 5.1.7 Viral safety
- 5.2.8 TSE

Monographs

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

under elaboration
under revision
first publication in Ph. Eur. 11th Edition
^{p}public consultation finished
**published in Pharmeuropa 34.3*
***to be published in Pharmeuropa 34.4*

Non exhaustive list

Microbiological examination of human tissues (2.6.39)

Recommendations on the selection of analytical methods
for the assessment of the microbiological quality of human tissue

Selection of analytical procedures based on a risk assessment

Critical issues for microbiological examination of tissues	Analytical procedure	Example of a microbiological testing strategy
Procurement of tissue *Tissue processing* *Sampling* *Storage conditions*	*Reference to Ph. Eur. Chapters* *2.6.1, 2.6.27, 2.6.12, 2.6.13, 5.1.6* *2.6.7, 2.6.2, 2.6.14, 2.6.30, 2.6.32*	*Cornea example to support the main principles:* • *Specificities of the cornea* • *Approach for a testing strategy* • *Method selection*

Stand alone chapter - not mandatory *per se*

Colony-forming cell assay for human haematopoietic progenitor cells (2.7.28)

- Introduction includes a clarification on the definition of CFC and their functional capacity
- Inclusion of automated technologies
- Improvement of standardisation of the analytical procedures
- Address the possibility to use serum-free medium and recombinant growth factors
- Recommendations on analytical validation

"**Equipment** which can evaluate the number of colonies and determine their type after image digitisation is also commercially available. The enumeration of colonies may be **fully automated or semi-automated** since the digitised image can be reviewed by the operator."

- **Replicate dishes seeded** for the examination of a suspension of single cells
- Standardisation using the **number of plated cells** and the **numbers of CD34/CD45+ cells seeded by plate**
- **Commercially available media** encouraged
- Recommendation of **serum-free medium** and **recombinant growth factors**

Pharmeuropa 34.1
Public consultation finished

Nucleated cell count and viability (2.7.29)

REVISION

1. ***General considerations***
2. ***Technical considerations***
   - 2.1. Sample preparation and test conditions
   - 2.2. Dye-exclusion methods
3. ***Manual cell counting and viability***
   - 3.1. Cell count
   - 3.2. Viability analysis
4. ***Automated cell counting and viability***
   - 4.1. Cell count
   - 4.2. Viability analysis
   - 4.3. Methods
     - Flow cytometry
     - Image cytometry
5. ***Procedure validation***
   - Prerequisites
   - Suitability of sample material
   - Recommended experimental design
   - Recommendation on validation parameters

modified

- Improvement of the standardisation
- Table summarising information on commonly used dyes
- Addition of image cytometry
- Table summarising main characteristics of flow cytometry and image cytometry
- Recommendations on analytical validation

Pharmeuropa 34.1
Public consultation finished

Microbiological examination of cell-based preparations (2.6.27)

Growth promotion test outlines the conditions for confirming the suitability of the culture media used for microbiological examination

REVISION

- Harmonisation of the incubation time with general chapter *2.6.1. Sterility*

Micro-organisms used for growth promotion test
Staphylococcus aureus
Bacillus subtilis
Pseudomonas aeruginosa
Candida albicans
Aspergillus brasiliensis
Clostridium sporogenes
Bacteroides fragilis

Strains listed in the growth promotion test of general chapter 2.6.1 with an incubation of not more than 3 days in the case of bacteria and not more than 5 days in the case of fungi.

ALIGNED

Collaborative studies and data from the literature indicate that *B. fragilis* grows within 3 days

WORK IN PROGRESS

NOW

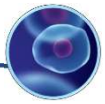
Incubation time
for a maximum of 7 days

Pharmeuropa 34.4
Public deadline: 31Dec2022

PROPOSAL

Revised incubation time
for not more than 3 days in the case of bacteria and not more than 5 days in the case of fungi

Cell Therapy Products WP, drafts on-going



Ongoing Projects

REVISION

Flow cytometry (2.7.24)

- Principles of the method
- Technical considerations
- Sample preparation
- Data acquisition and analysis
- Examples of Application
- System qualification
- Assay validation

NEW

General update of the chapter to reflect the techniques currently in use

Need for a general text covering quality of cell-based preparations

Cell-based preparations (5.32)

General requirements

- Production
  - → Source cells
  - → Preparation and processing of cells
  - → Substances used in production
  - → In-process controls
- Final lot
  - → Identification
  - → Tests
  - → Assays

NEW

Specific sections

- Mesenchymal stem cells
- Haematopoietic stem cells
- Limbal stem cells
- Chondrocytes

Chapter ought to be general enough to encompass both:
- products that are already on the market
- new products to come

Ph. Eur. Gene Therapy Products texts - evolution

Gene transfer medicinal products for human use (5.14)

General chapter

- Definition, Production
  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 for human use

- Adeno-associated-virus vectors for human use
- Retroviridae-derived vectors for human use

Adopt
Ph. E
(Jan

Adopted 2008
Ph. Eur. 6.6
(Jan 2010)

Gene therapy medicinal products for human use (3186)

- G
- A
- C

General chapter

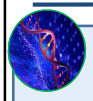
Raw materials of biological origin for the production of cell-based and gene therapy medicinal products (5.2.12)

- Scope
- Risk assessment
- General requirements
- Sera and serum replacements
- Proteins produced by rDNA technology
- Proteins extracted from biological material
- Vectors

Adopted 2015
Ph. Eur. 9.0
(Jan 2017)

Revised from 5.14
New sections

Ph. Eur. Gene Therapy Products texts - evolution



Gene transfer medicinal products for human use (5.14)

General chapter

- Definition, Production
  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 for human use

- Adeno-associated-virus vectors for human use
- Retroviridae-derived vectors for human use

Pharmeuropa 34.3
Deadline: 30/09/22

Gene therapy medicinal products for human use (3186)

General monograph

- Definition
- General requirements on:
  - the Production of GTMPs
  - Recombinant vectors
  - Genetically modified cells
- Genetically modified autologous human cells
- Adeno-associated-virus vectors for human use
- Oncolytic herpes simplex virus for human use

Additional information on gene therapy medicinal products for human use (5.34)

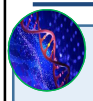
General chapter

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

new general monograph (3186) and general chapter (5.34) are envisaged to replace the current chapter 5.14

Revised from 5.14 *Reproduced directly from 5.14*
New sections *Reproduced from 5.14 with limited changes*

Ph. Eur. Gene Therapy Products texts - evolution



Gene transfer medicinal products for human use (5.14)

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

General chapter

Pharmeuropa 34.3
Deadline: 30/09/22

Cross-referencing of the chapter 5.2.12 and general monograph 3186

Pharmeuropa 34.3
Deadline: 30/09/22

Additional information on gene therapy medicinal products for human use (5.34)

General chapter

- Plasmid vectors for human use
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- Retroviridae-derived vectors for human use

Explanatory document available under Technical information in Pharmeuropa online

PHARMEUROPA ONLINE
TECHNICAL INFORMATION

Revised from 5.14 *Reproduced directly from 5.14*
New sections *Reproduced from 5.14 with limited changes*

Gene therapy medicinal products for human use (3186)

2 General requirements

2.1 General provisions for GTMP production

- Substances used in production (qualification of materials, reference to 5.2.12 for raw materials, avoidance of antibiotics; use of β-lactam antibiotics and streptomycin forbidden)
- Viral safety (5.1.7)
- Transmissible spongiform encephalopathies (5.2.8; performance of risk assessment and its minimisation)
- Containers (reference to Materials used for the manufacture of containers (3.1 & subsections) and Containers (3.2 and subsections)
- Labelling (requirements of European Union or other applicable regulations)

2.2 Recombinant vectors for human use

(viral vectors, oncolytic viruses, nucleic acid vectors, genetically modified micro-organisms)

- General provisions on recombinant vector production
- Characterisation of the vector
- Vector harvest
- Purified harvest
- Final lot

2.3 Genetically modified cells for human use

(Genetically modified autologous, allogeneic or xenogenic cells)

- Vectors used for genetic modification of cells
- Source cells used for production of genetically modified cells
- Production of genetically modified cells
- Final lot

4. Adeno-associated virus vectors for human use
5. Recombinant oncolytic herpes simplex viruses for human use

3. Genetically modified human autologous cells

Ph. Eur. Gene Therapy Products texts – cross-references

EXAMPLES

General monograph

Gene therapy medicinal products for human use (3186)

- Definition
- General requirements on:
  - the Production of GTMPs
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Raw materials of biological origin for the production of cell-based and gene therapy medicinal products (5.2.12)

"Supplementary recommendations are available in general chapter *5.34. Additional information on gene therapy medicinal products for human use* to assist users."

INFO

Informative cross-reference

Ph. Eur. Gene Therapy Products texts – cross-references

EXAMPLES

General monograph

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

(5.2.2) Chicken flocks free from specified pathogens for the production and quality control of vaccines
(5.2.3) Cell substrates for the production of vaccines for human use

"Unless otherwise justified and authorised, the substrates used in the manufacture of recombinant vectors comply with the relevant requirements of general chapters *5.2.2.* and *5.2.3.*, or with the requirements of the section entitled *Bacterial cells used for the manufacture of plasmid vectors for human use* of general chapter *5.34.*"

Ph. Eur. Gene Therapy Products texts – cross-references

EXAMPLES

General monograph

Gene therapy medicinal products for human use (3186)

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  - Recombinant vectors
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- Retroviridae-derived vectors for human use

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

critical starting material

- **Requirement to comply with the relevant section of chapter 5.34 with the exception of Final lot (6.5)**
- **Some relevant test listed in Final lot (6.5) might be also applicable**

Ph. Eur. Gene Therapy Products texts – cross-references

EXAMPLES

General monograph

Gene therapy medicinal products for human use (3186)

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- Retroviridae-derived vectors for human use

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

7. Vectors

"In cases where vectors are not considered as starting materials, such as vectors used as helper plasmids or helper viruses, the principles of this general chapter and the principles of production and quality control as outlined in general monograph *Gene therapy medicinal products for human use (3186)* are to be followed."

Ph. Eur. Gene Therapy Products texts – cross-references

EXAMPLES

General monograph

Gene therapy medicinal products for human use (3186)

- Definition
- General requirements on:
  - the Production of GTMPs
  - Recombinant vectors
  - Genetically modified cells
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- Retroviridae-derived vectors for human use

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

7. Vectors

"The raw materials of biological origin comply with the requirements of general chapter *5.2.12. Raw materials of biological origin for the production of cell-based and gene therapy medicinal products,* unless otherwise justified and authorised."

Ph. Eur. Gene Therapy Products texts: built-in flexibility

oHSV AAV **Residual reagents. Based on risk analysis,** tests for residues of reagents used during production and posing safety concerns are carried out on the purified harvest. **Where relevant,** the residual bovine serum albumin is determined by a **suitable** immunochemical **method** (*2.7.1*). If authorised for use in production, residual antibiotic concentration **is determined by liquid chromatography** or by **other suitable methods**.

EXAMPLES

Assay. The number of transduced cells **is determined by a suitable method, such as** flow cytometry (*2.7.24*). The number of transduced cells **is within the limits approved for the particular product**. (...) GM cells

Biological activity. Biological activity **is determined by a suitable test** [...]. The biological activity **is within the limits approved for the particular product**. AAV

✓ **Flexible wording**
✓ **Reference to suitable methods**

Gene therapy medicinal products for human use (3186)

✓ **No numerical acceptance criteria**

AAV **Capsid titre** (empty and full particles). The capsid titre **is determined by a suitable method such as** ELISA (*2.7.1*), size-exclusion chromatography (*2.2.30*) or analytical ultracentrifugation.

GM cells Genetically modified autologous human cells comply with the requirements given below under Identification, Tests and Assay. The following **tests are performed at appropriate stages depending on the manufacturing process.**

oHSV AAV **Virus/Vector aggregates.** Virus/vector aggregates **are determined by a suitable method such as** light scattering, size-exclusion chromatography (*2.2.30*), analytical ultracentrifugation or electron microscopy.

Ph. Eur. Gene Therapy Products texts: built-in flexibility

oHSV **Residual reagents. Based on risk analysis,** tests for residues of reagents used during production and posing

GM cells **Identification.** Cell identity and transgene identity are verified **by suitable methods,** su cytometry (2.7.24) and nucleic acid an techniques (NAT) (2.6.21).

antibiotic concent **chromatograph**

oHSV determined **method such** immunochemi

EXAMPLES

Assay. The number of transduced cells **is determined by a suitable method, such as** flow cytometry (*2.7.24*). The number of transduced cells **is within the limits approved for the particular product**. (...) GM cells

AAV **The vector genome titre** (full particles) is determined **with a suitable method such as** NAT (*2.6.21*) or size-exclusion chromatography (*2.2.30*). The vector genome titre is **within the limits approved for the particular product.**

AAV **The genomic integrity** of the plas or bacmids is **verified by suit methods such as** NAT (*2.6.21* restriction-enzyme analysis of the region corresponding to *rep*, *cap*, the genetic insert and the helper functions, **where applicable**.

Expression of the genetic insert is determined **complies with the pre-defined acceptance criteria for the particular product.**

Biological activity. Biological activity **is determined by a suitable test** [...]. The biological activity **is within the limits approved for the particular product**. AAV

✓ **Flexible wording**
✓ **Reference to suitable methods**

Gene therapy medicinal products for human use (3186)

✓ **No numerical acceptance criteria**

AAV AAV **The ratio of viral genomes to infectious particle titre is within the limits approved**

Percentage of full and empty particles is calculated using the ratio between the capsid titre and ve **determined by a** percentage of full **within the limit particular product**

oHSV **Virus identity** is verified by a **suitable method such as** immunochemical methods (*2.7.1*) targeting viral proteins. **The genetic insert and the modified viral sequences** are

oHSV **The physical particle titre** is determined by a **suitable technique such as** liquid chromatography (*2.2.29*), NAT (*2.6.21*) or immunochemical methods (*2.7.1*). The physical particle titre **is within the limits approved for the particular product.**

GM cells **The differentiation potential** (for products containing stem or progenitor cells) is determined by a suitable method. The differentiation potential **complies with the pre-defined acceptance criteria for the particular product.**

AAV **such as** qPCR (*2.6.21*).

Ph. Eur. GTP texts: zoom on replication-competent vectors/viruses

Adeno-associated virus vectors for human use

- Requirement for minimisation of DNA sequence homology in the starting materials/design of manufacturing strategy to reduce/minimise the risk of generation rcAAV.
- Requirement to test replication-incompetent helper viruses used for production of AAV for replication-competent helper viruses. No replication-competent viruses are detected.

Baculoviruses not defined as helper viruses

- Requirement to test purified harvest for rcAAV. The limit is approved by the competent authority.

Test based on multiple rounds of amplification; Purified harvest – more adequate stage for testing

- Requirement to test purified harvest for residual viruses used for production. No residual virus is detected.

Easily detectable by biological methods

Retroviridae-derived vectors for human use

Both cells used for production and the produced vector must be tested for rc viruses.

- Requirement to test Producer cells in all production systems outlined (stable, full transient and partial transient) for rc viruses using suitable methods (examples given).

No rc viruses are detected.

- Requirement to test single harvest for rc viruses using suitable methods (examples given).

No rc viruses are detected.

- Requirement to test purified harvest or final lot if no dilution step or pooling is performed after purified harvest for rc viruses using suitable methods (examples given).

No rc viruses are detected.

Absence of rc vector required for GM autologous cells

Ph. Eur. GTP texts: ongoing and envisaged revisions

General chapter
Gene transfer medicinal products for human use (5.14)

General monograph
Gene therapy medicinal products for human use (3186)

General chapter
Additional information on gene therapy medicinal products for human use (5.34)

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

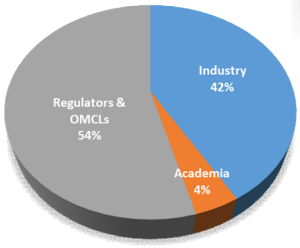
Pharmeuropa 34.3
Public deadline: 30 Sep 2022
NPA deadline: 30 Nov 2022

Revision of sections of 5.34 reproduced directly or with limited changes from 5.14 ongoing:

- 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

Gene and Cell Therapy Working Parties

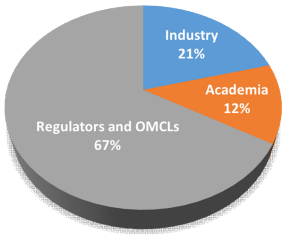
GTP WP
Members: 24



Meetings

GTP WP	CTP WP
Since 2018	Since 2020
25	8
	+ 18 subgroup TCs

CTP WP
Members: 24



Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: **https://go.edqm.eu/Newsletter**
LinkedIn: **https://www.linkedin.com/company/edqm/**
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Facebook: **@EDQMCouncilofEurope**
FAQ & HelpDesk: **https://www.edqm.eu/en/faq-helpdesk-ph-eur**

Additional information

on EDQM activities in the cell and gene therapies field others than the Ph. Eur.

Activities of the EDQM in the cell and gene therapies field

OMCL Gene Therapy Working Group (GTWG)

Guide to the quality and safety of tissues and cells for human application

Ph. Eur. Groups of Experts and Working Parties

- OMCL GTWG is part of the GEON*
- Established in 2008, meets once per year
- Includes 11 OMCLs
- Prepares OMCLs for quality control of GTPs

Activities:

- Define common work program (vectors & methods) based on feedback from experience and EU market tendencies/expectations
- Share information, know-how, resources, materials, transfer/establish common methods & reference materials
- Perform collaborative studies

Examples of current studies:

1) Physical particles determination - **ELISA** (AAV2, AAV8)
2) Viral & infectious genomes titre - **qPCR** (AAV2)
3) Residual host cell DNA - **qPCR**

Potential future studies:

1) Retro-/lentivirus vectors
2) Poxvirus vectors
3) Non-replicative adenovirus vectors
4) HSV1-based vectors

* General European OMCL Network

Activities of the EDQM in the cell and gene therapies field

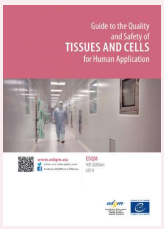
OMCL Gene Therapy Working Group (GTWG)

Guide to the quality and safety of tissues and cells for human application

Ph. Eur. Groups of Experts and Working Parties

Since 2013

5th edition due in 2022



MINISTERS' DEPUTIES — Recommendations

Recommendation CM/Rec(2020)5[1]
of the Committee of Ministers to member States
on the quality and safety of tissues and cells for human application

(Adopted by the Committee of Ministers on 7 October 2020 at the 1380th meeting of the Ministers' Deputies)

https://rm.coe.int/0900001680 9fdcde

- Comprehensive guidelines **based on best available scientific evidence** to provide professionals with a useful overview of the most recent developments in the field
- Ensure high level of **quality and safety standards**
- Contribute to the **harmonisation** of these activities among European countries, facilitating uniform standards and practices
- **Continuous update** and maintenance
- **Consensus document** elaborated by ad hoc working group (under the aegis of the CD-P-TO) composed of experts nominated by Member States and professional associations
- Addressed to the **46 CoE member states**

INCREASED QUALITY AND SAFETY OF ORGANS, TISSUES AND CELLS

IMPROVED CLINICAL OUTCOMES

Activities of the EDQM in the cell and gene therapies field

OMCL Gene Therapy Working Group (GTWG)

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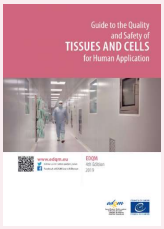
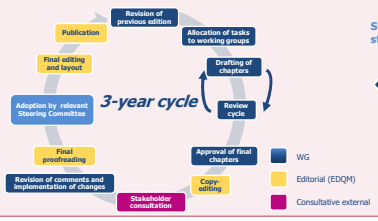
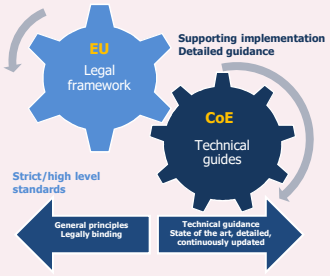






BTC legislative proposal in the EU (cascade model):

NEW

Where there are technical requirements in the **EU legislation** they must be followed

Where there are no technical rules in EU legislation – the safety and quality standards defined by **reference expert bodies** (EDQM) must be followed

Where there is no EU level rule or referenced body guidance, the **establishments** must set their **own rule** taking into account any relevant recognised international standards and scientific evidence, and assess risk/benefit. Process must be **reviewed and approved by CA**

Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

www.pei.de

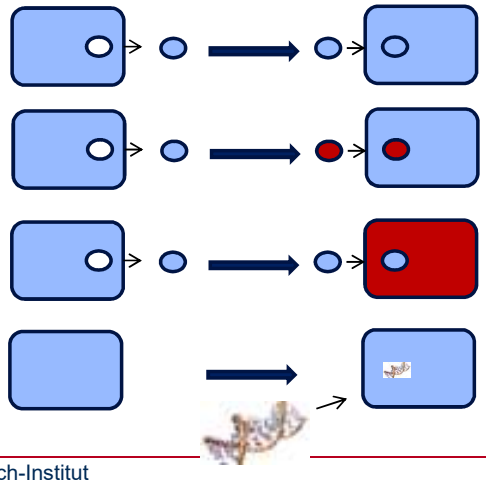
NCA Point of View on ATMPs

Jürgen Scherer
Head of Section
ATMP; Tissue Preparations

Das Paul-Ehrlich-Institut ist ein Bundesinstitut im Geschäftsbereich des Bundesministeriums für Gesundheit.
The Paul-Ehrlich-Institut is an Agency of the German Federal Ministry of Health.

Advanced Therapy Medicinal Products – ATMP vs. "Transplants"

Legally defined in 1394/2007/EC and 2009/120/EC (Ax I to 2001/83/EC)



No substantial manipulation Homologous use	No ATMP
Substantial manipulation	ATMP
Non-Homologous use	ATMP
Genetic modification	ATMP

Specific Features of ATMP

Wide spectrum of products with high therapeutic potential

- Simple/Complex manufacturing – Quality Issues
- Complex mode of action – Non-clinical issues
- Challenging clinical development
  (often addressing UMN, controls, orphan, long term)
- Personalised approaches

European legal framework established by Regulation 1394/2007

Regulation (EC) No 1394/2007 – the race was on

there were quite some failures

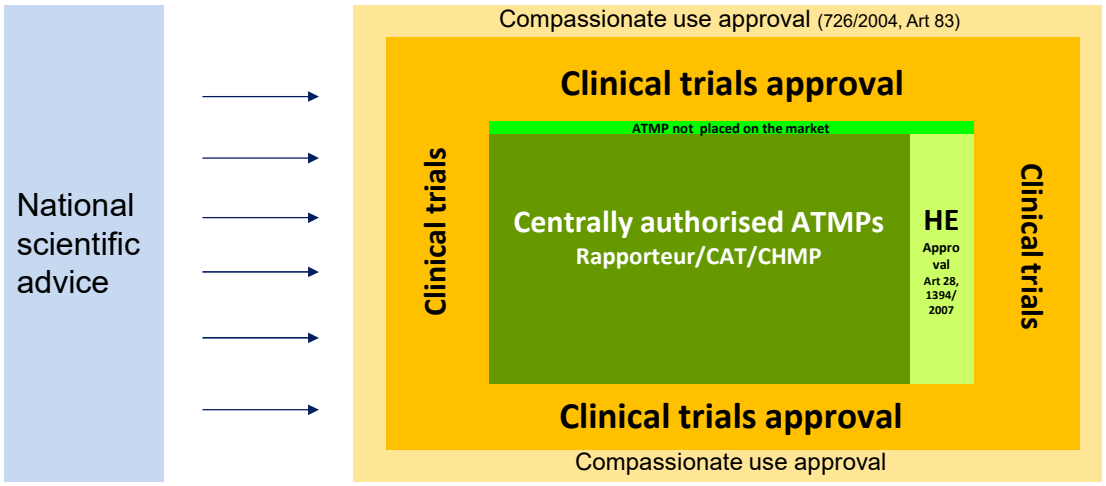
GTMP
CBMP/TEP

ATMP field now is dynamic and succeeding

Oncology
Regenerative
Gene defects

Trade name, active substance	Therapeutic area	Zulassung
Roctavian (valoctocogen roxaparvovec)	treatment of severe haemophilia A	2022
Upstaza (eladocagene exuparvovec)	AADC deficiency with a severe phenotype	2022
Carvykti (ciltacabtagene autoleucel)	Multiple myeloma	2022
Breyanzi (lisocabtagene maraleucel)	B-cell-lymphom a(DLBCL, PMBCL, FL3B)	2022
Abecma (idecabtagene vicleucel)	Multiple myeloma	2021
Skysona (Elivaldogen autotemcel)	cerebral adrenoleukodystrophy	2020
Tecartus (Brexucabtagene autoleucel)	Mantle cell lymphoma	2020
Libmeldy (atidarsagene autotemcel	metachromatic leukodystrophy in children	2020
Zolgensma Onasemnogen abeparvovec	spinal muscular atrophy	2020
Zynteglo (Betibeglogen autotemcel	Transfusion-dependent β-thalassemia	2019
Luxturna Voretigen neparvovec	RPE65 dependet retinal dystrophy	2018
Kymriah (Tisagenlecleucel)	Lymphatis leukemia (ALL) B-cell-lymphoma (DLBCL)	2018
Yescarta (Axicabtagen ciloleucel)	B-cell-lymphoma (DLBCL and PMBCL)	2018
Alofisel (darvadstrocel)	rectal fistula	2018
Spherox ((spheroids of human autologous matrix-associated chondrocytes)	Repair of cartilage defects	2017
(Zalmoxis) (allogeneic T cells genetically modified)	GvHD after HSCT	2016
Strimvelis (autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence)	severe combined immunodeficiency (ADA-SCID)	2016
Imlygic (talimogene laherparepvec)	unresectable melanoma	2015
Holoclar (ex vivo expanded autologous human corneal epithelial cells containing stem cells)	Severe limbal stem cell deficiency due to ocular burns	2015
(MACI) (matrix-applied characterised autologous cultured chondrocytes)	Repair of cartilage defects	2013
(Provenge) (sipuleucel-T)	metastatic (non-visceral) castrate resistant prostate cancer	2013
(Glybera) (alipogene tiparvovec)	lipoprotein lipase deficiency	2012
(ChondroCelect) (characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins)	Repair of cartilage defects	2009

Role of NCAs for making ATMP available



Hospital Exemption for ATMPs 1394/2007 Art 28

prepared on a non-routine basis according to specific quality standards,
and used within the same Member State in a hospital
under the exclusive professional responsibility of a medical practitioner,
individual medical prescription for a custom-made product for an individual patient

§ 4b Provisions of the German Drug Law (II)

- Placing on the market needs to be approved by PEI
- Based on positive benefit risk evaluation by Competent Authority
- Temporary authorisation
- Periodic reports on manufacturing and further experience
- Provisions to withdraw or revoke authorisation
- Competent Authority entitled to impose conditions

HE approved ATMP in Germany

BioSeed-C, Autologes 3D-Chondrozytentransplantat, 28,8 Mio. Zellen pro Einheit	Chondrocytes for TE
co.don chondrosphere, 10-70 Sphäroide/cm2, matrixassoziierte Zellen zur Implantation	Chondrocytes for TE
NOVOCART 3D	Chondrocytes for TE
NOVOCART Inject	Chondrocytes for TE
Obnitix	MSC to treat GvHD after HSCT
AMESANAR, allogene ABCB5-positive mesenchymale Stromazellen	MSC to treat CVU associated with CVI, after SOC
Zytokin-aktivierte Killerzellen (CIK-Zellen), allogen, ≤ $1x10^8$ CD3+CD56-T-Zellen/kg Körpergewicht in ≤ 100 ml Infusionsdispersion	Relapse of leucemia after HSCT

Hospital Exemption for ATMPs

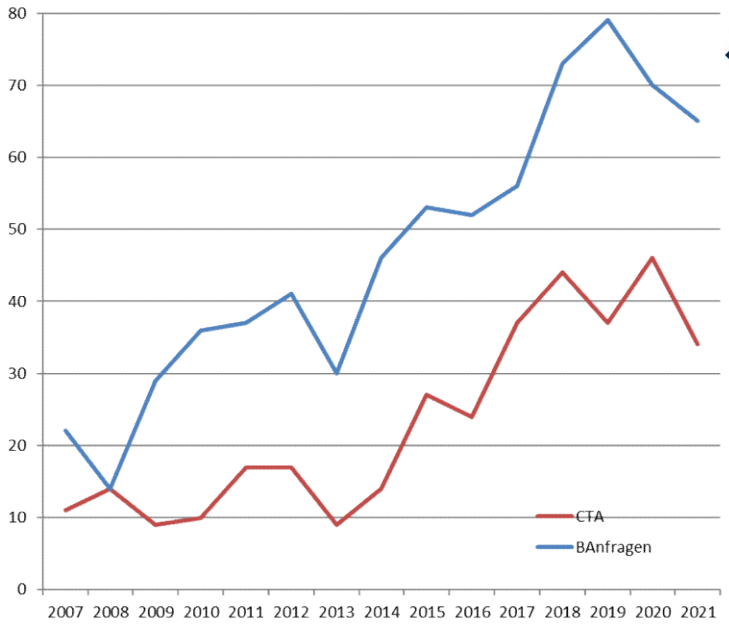
Should the number of patients treated under HE be limited to a defined number?

- Limited by the constraints given for ATMP under HE
- No legal provisions for a specific number
- Approach taken by many MS to minimise risks
- Limitation not needed and not justified for DE implementation of HE as benefit risk evaluation is done

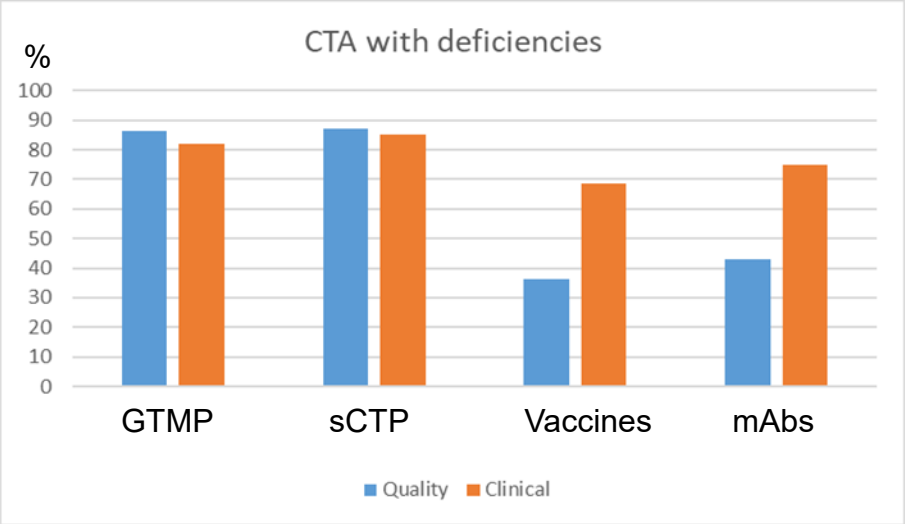
Conclusion:

Hospital Exemption is an important complement to the centralized MA approach as it represents a valuable option for specific situations (local use, individual prescription, custom-made, developmental phase)

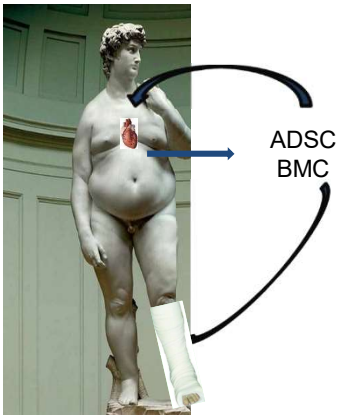
CTA and SciAdvice Procedures for ATMP at PEI



Quality of ATMP is a major issue



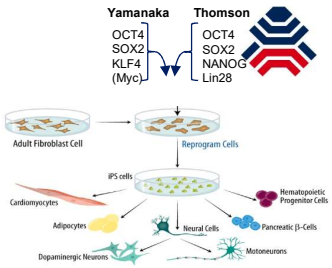
Support and guidance is needed as well as flexibility



ADSC
BMC

Somatic
cell therapy

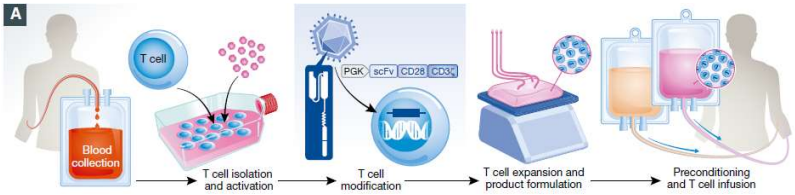
Genetic modification/editing



iPS cells

Heterogeneity of ATMP

Genetically modified cells /CAR-T



Tissue
Engineering

Some Challenging Quality Issues

- Starting Materials
  - biopsy quality, age, sex, disease, genotype
  - Qualiyt and availability of plasmids/vectors
- Autologous Products – consistency
- Different cell types populations
- Impurities (RCV, transduction efficiency,..)
- Manual vs. Automated

- QC methods & relevant parameters, Potency assay
- Small scale, Shelf life

- Changes during development - comparability

Regulatory framework

Need of requirements/guidance, being instructive, providing necessary flexibility but being not too prescriptive

- EU legal framework (1394/2007; 2001/83 Ax I incl. risk-based approach)
- CHMP/CAT/ICH guidelines
- GMP for ATMP
- Ph. Eur. texts (quality oriented, practical, methodological)
- National provisions (e.g. request state of the art quality in DE)

Ph. Eur. Approach

Ph Eur texts are regarded and accepted as state of the art and provide flexibility as general chapter. General chapters become mandatory when referred to in a monograph.

However, Ph. Eur. approach still provides options:

From Ph.Eur. General notices (1.1. General Statements):

„An article is of Ph.Eur. quality if it complies with all of the requirements stated in the monograph. This does not imply that a manufacturer must perform all of the test decribed in a monograph when assessing compliance with the Ph.Eur before release. The manufacturer may obtain assurance that an article is of Ph.Eur. quality on the basis of its design, together with its control strategy and data derived for example from validation studies of the manufacturing process.“

„With the agreement of the competent authority, alternative analytical procedures may be used for control purposes, provided that they enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official procedures were used.“

How to resolve Difficulties

- Know and respect legal and regulatory framework
- Use available guidance
- Consider flexibilities given in the regulatory system

- Do not ignore!
- Workaround based on a scientific rationale
- Be stringent and impartial with your own data

- Exchange with regulatory authorities

Batch testing

ATMPs are not subjected to Offical Control Authority Batch Release

CAP testing of ATMP has not been done up to now but may be an option in the future and will be challenging (new/complex methods, reference material)

Collaborative approach and harmonised tests are needed for testing by OMCLs

EDQM crucial for coordination and alignment of OMCLs

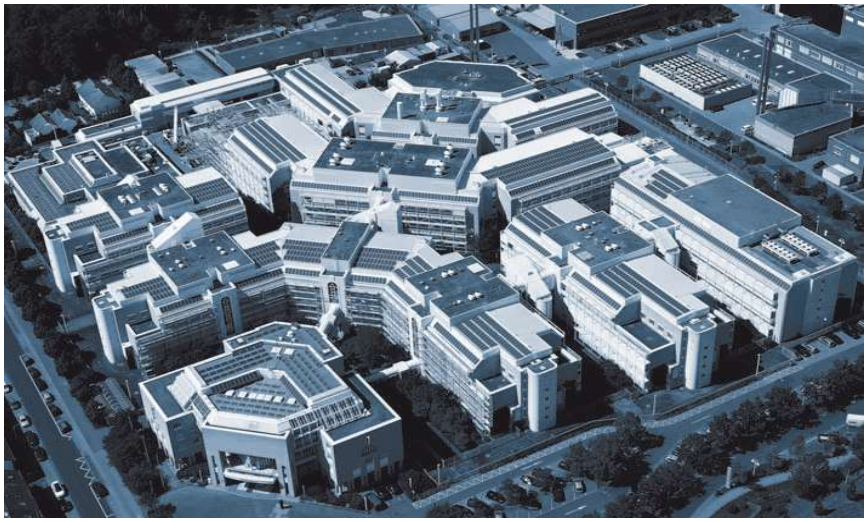
Conclusions

ATMPs have huge potential to improve therapeutic options and to address UMN but are challenging in view of manufacturing, QC, clinical development

Guidance is available by plenty of documents.
Next to CHMP/CAT guidelines, Ph.Eur. contributes significantly.

Exchange between developers and regulators, on EU level as well as on national level, is needed. Procedures for advice are established.

Our Focus is on Health



Novartis, CGT, Les Ulis

Reduction of Kymriah throughput time by improvement of sterility test and implementation of rapid microbiology testing

Aline Le Tiec
QC Head
20-SEP-2022

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Agenda

1. Cell & Gene Therapy Platform and CELLforCURE
2. Kymriah
3. Objective
4. Optimization of sterility test
5. Optimization of environmental monitoring analysis

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Cell & Gene Therapy Platform and CELLforCURE

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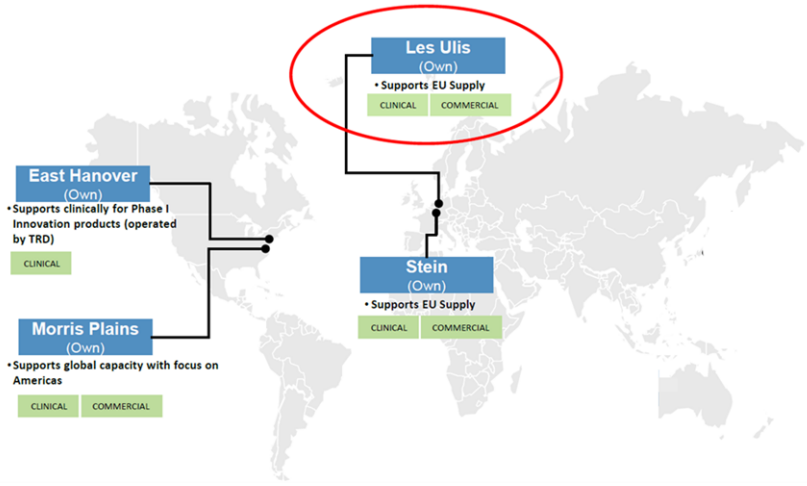
Cell & Gene Therapy Platform



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Kymriah

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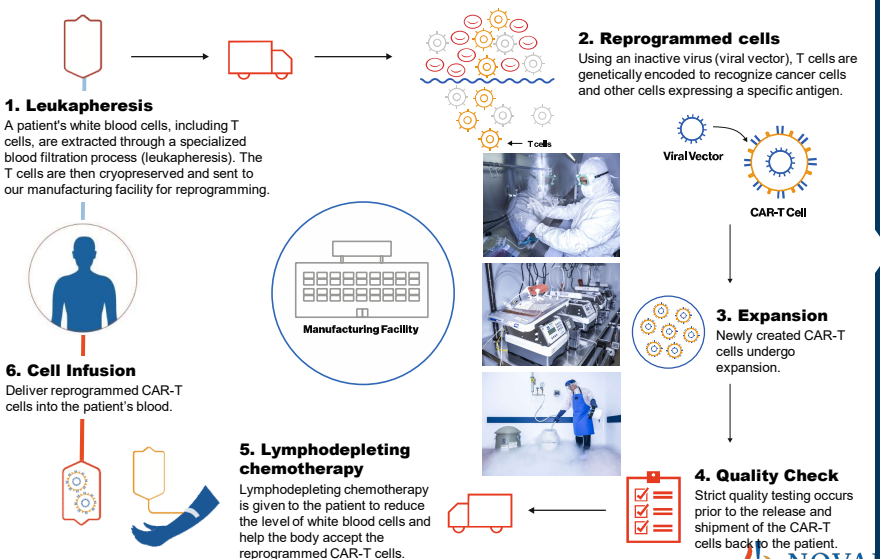
CAR-T Manufacturing



CAR-T is different from typical small molecule or biologic therapies because it is manufactured for each individual patient using their own cells

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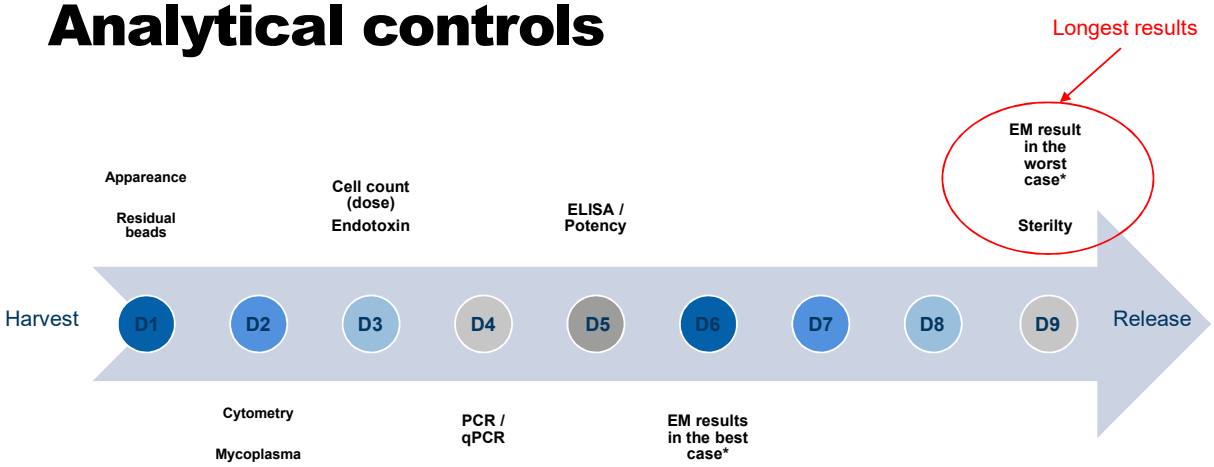
Analytical controls



**Environmental Monitoring (EM) analysis outsourced / No work on Sundays and national days off*

Objective

Optimization of

– **Sterility Assay**

– **Environmental Monitoring**

Optimization of sterility test

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Sterility test on Kymriah

- Production of viable cells which can not be filtered or sterilized
- Sterility test performed according to EP 2.6.27 “Microbiological examination of cell-based preparations”
  - 1% of total Final Product
  - Injection of 1mL in 3 different BacT/ALERT bottles directly by production operator during the harvest / final formulation

Total cell-based preparation volume (mL)	Total inoculum volume (divided between aerobic and anaerobic bottles)
$10 \leq V \leq 1000$	1 per cent of total volume of preparation to be tested
$1 \leq V < 10$	100 µL
$V < 1$	Not applicable

Extraction from EP 2.6.27

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BacT/ALERT

- BacT/ALERT, What is it ?
  - Sterility method described as alternative method in EP 5.1.6
  - Different modules: 28-37°C and 20-25°C
  - Use of different BacT bottles (aerobic and anaerobic)
- How are microorganisms detected ?

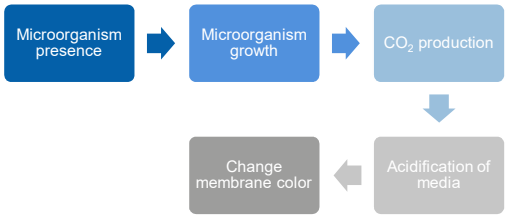

Table 2.6.27.-3. – *Possible temperature settings in automated culturing systems used alone or in combination with manual testing*

	Aerobic incubation	Anaerobic incubation
Option 1	20-25 °C (automated system), if necessary 30-35 °C (automated system)	30-35 °C (automated system)
Option 2	35-37 °C (automated system); where relevant, additional incubation at a lower temperature (manual method)*	35-37 °C (automated system)
Option 3	30-32 °C (automated system)	30-32 °C (automated system)
Option 4	30-32 °C (automated system)	35-37 °C (automated system)

Extraction from EP 2.6.27

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Sterility validation done in 2019

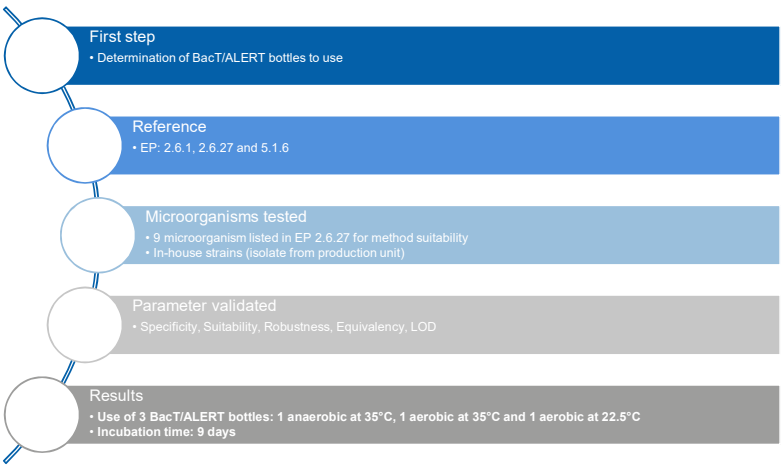

Table 2.6.27.-2. – *Micro-organisms used for method suitability*

Aerobic medium	
Aspergillus brasiliensis	for example, ATCC 16404, IP 1431.83, IMI 149007
Bacillus subtilis	for example, ATCC 6633, CIP 52.62, NCIMB 8054
Candida albicans	for example, ATCC 10231, IP 48.72, NCPF 3179
Pseudomonas aeruginosa	for example, ATCC 9027, NCIMB 8626, CIP 82.118
Staphylococcus aureus	for example, ATCC 6538, CIP 4.83, NCTC 10788, NCIMB 9518
Streptococcus pyogenes	for example, ATCC 19615, CIP 1042.26, NCIMB 13285
Micrococcus sp.	for example, ATCC 700405
Anaerobic medium	
Clostridium sporogenes	for example, ATCC 19404, CIP 79.3, NCTC 532 or ATCC 11437
Cutibacterium acnes	for example, ATCC 11827

Extraction from EP 2.6.27

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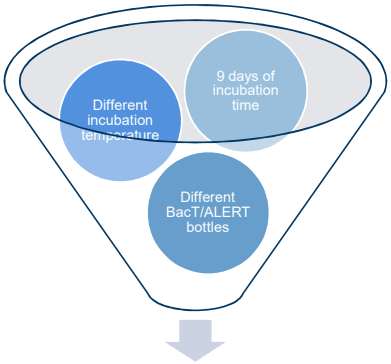
Sterility test on the CGT platform

- Validation of BacT/ALERT independently of the 3 sites



Reduction of incubation time and harmonization on CGT platform

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Optimization of BacT/ALERT

March 2021 - Optimization of BacT with the participation of 3 sites

May 2021 – Multisite validation

July 2021 – Validation at MP for the FDA approval

September 2021 – EMA approval

February 2022 – FDA approval

Incubation time set up at 7 days approved by health autorities

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Next step

September 2021 – Optimization of BacT for detection of mold and yeast

December 2021 – Validation of Mold and Yeast

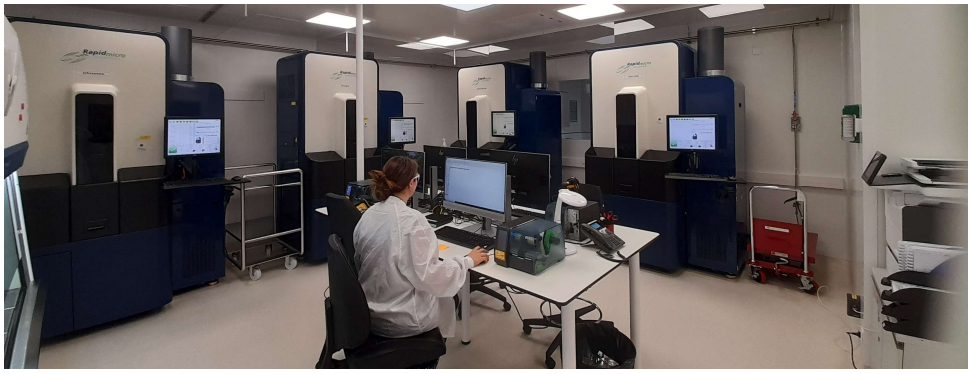
March 2022 – Validation report approval

July 2022 – Submission to the EMA

September 2022 – Waiting for EMA feedback

Validation of incubation time at 5.7 days

Challenge: EP 2.6.27 indicate that « *The sample are [...] incubated for not less than 7 days* »



Optimization of EM analysis

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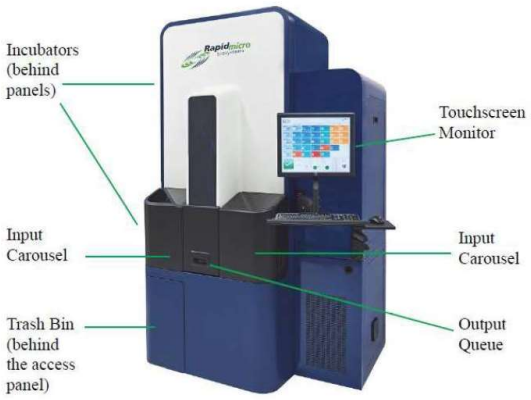
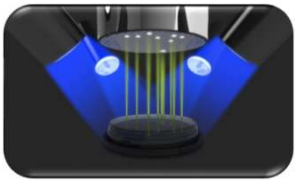
Context

- **Previous situation** - outsourcing of all EM samples for analysis
  - Incubation 72h minimum at 20-25°C then 48h minimum at 30-35°C according to USP <62>
  - Reading by one qualified operator with visual count followed by one verification
- **Current situation** – internalization of EM samples analysis by the implementation of Growth Direct
  - Automatic incubation and reading
  - Fast detection of micro-colony

Growth Direct

- Growth Direct, What is it ?
  - Automatic system for incubation and reading of EM sample
- How are microorganisms detected ?
  - Micro colonies auto fluorescence
  - Locates, tracks and counts colonies
  - Automatically counts at scheduled intervals
  - No Human intervention





Strategy of implementation

- **In step 1: Definition of incubation temperature**
  - Objective: defined temperature allowing the detection of all types of microorganism (environmental bacteria, skin bacteria, mold and yeast)
  - Incubation temperature defined: 25-30°C
- **In step 2: Determination of Time To Result (TTR)**
  - Objective: determination of incubation time
  - Study done at the defined temperature previously
  - Incubation time defined: 56 hours
- **In step 3: Analytical validation**
  - Objective: demonstration of non inferiority of alternative method in comparison to compendial method according to USP <1223>, Eur. Pharm 5.1.6 and PDA TR 33
  - Study done with 56 hours
  - Validation of GDS and 14 hours at 4°C for time holding time

In step 1: Definition of incubation temperature

- Verification of microorganisms growth at 25-30°C
  - Test of microorganisms defined in EP 2.6.1
  - Test of in-house strains
- **Risk to use one temperature (25-30°C)**
  - Slow growing of skin microorganism → Impact on incubation time
- **Opportunity to use one temperature (25-30°C)**
  - Better detection of environmental bacteria and mold

In step 2: Determination of TTR

- TTR correspond to the time point allowing the detection of 85% of CFU
  - About 600 sampling done in production unit and QC lab (passive air, surface, active air, gowning)
- Assessment of 1 TTR per sampling
- Definition of final TTR as the longest TTR results = 52 hours + 1 additional reading → **56 hours**

4.7. Cumulative TTR

In total, 11601 CFU were analysed and the TTR was calculated as 44 hours

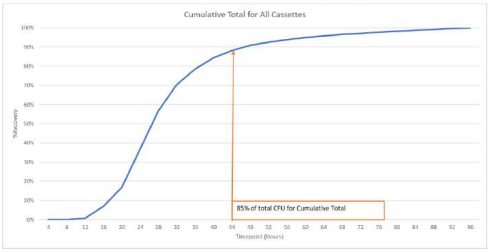
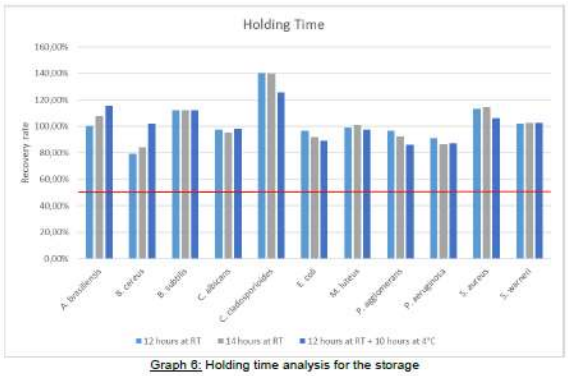


Figure 7 Summary Graph showing 85% Cumulative TTR across all samples

Extraction from Rapid Micro Biosystem report analysis

In step 3: Analytical validation

- **Partial validation** done and use of other Novartis site results
  - Validation of **specificity** and **holding time** only
- **Specificity**
  - Tests all microorganisms defined in EP 2.6.1 and in-house strains
  - GD counts not statistically different as compared to visual count
- **Holding time**
  - Tests all microorganisms defined in EP 2.6.1 and in-house strains
  - No difference between condition stored at RT and incubated directly in GDS
- **Results : Validation compliant, Incubation time of 56 hours, storage at RT during 14 hours**



Graph 6: Holding time analysis for the storage

Growth Direct in routin

Opportunities

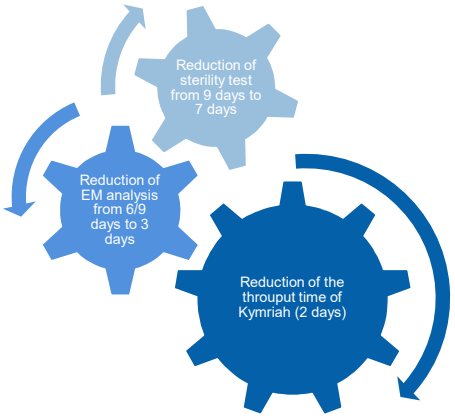
- Improvement of data integrity
- Reduction of incubation time

Challenge

- No distinction between mold and bacteria → visual check required
- Detection of false positive by GD
- Plate size 57mm² → impact on settling plate

Conclusion

- Sterility test validated for 7 days
- Waiting the feedback of EMA to reduce at 5.7 days
- Implementation of GD
  - Incubation time: 56 hours
  - Incubation temperature: 25-30°C
  - Partial validation done
- In total, 2 days less for Kymriah release



Thank you

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