EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Paul-Ehrlich-Institut
Federal Institute for Vaccines and Biomedicines

CMC ASPECTS OF GENE THERAPY MEDICINAL PRODUCTS

SME workshop: Focus on chemistry, manufacturing and controls (CMC) regulatory compliance for biopharmaceuticals and advanced therapies

Presented by Matthias Renner on April 16, 2015
Division Medical Biotechnology, Paul-Ehrlich-Institut, Germany

AGENDA

- Definition GTMPs
- Classification
- Critical aspects of GTMP manufacturing and control
- Guidelines

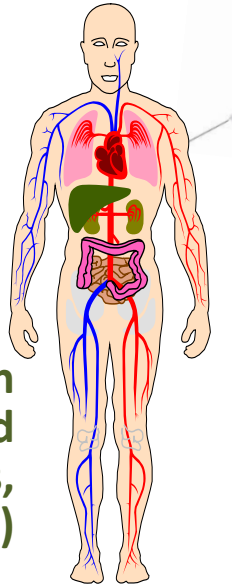
ex vivo GENE TRANSFER *in vivo*

cell line

explantation of target cells

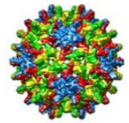
gene transfer

reinfusion of modified cells (autologous, allogenic, xenogenic)



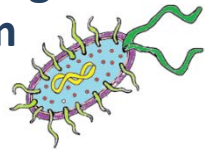
direct application:

virus / viral vector



non-viral vector:
naked DNA, RNA
complexed

(non)-replicating recombinant microorganism

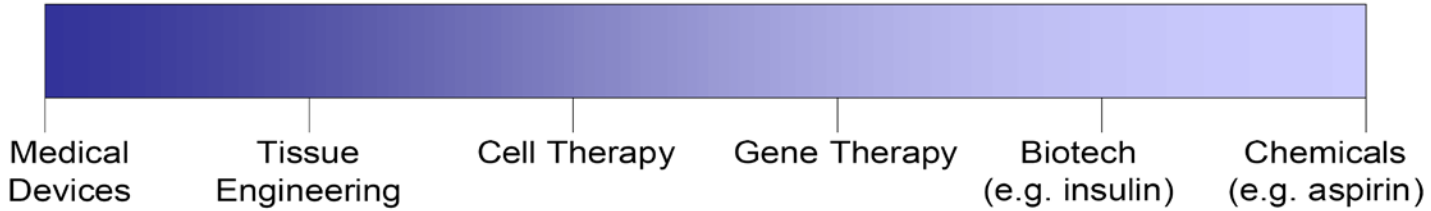


REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

Medicinal Products



Advanced Therapies (ATMPs)

In case a medicinal product may fall within TEP or CTMP and GTMP, then GTMP applies

COMMISSION DIRECTIVE 2009/120/EC

of 14 September 2009

amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products

GENE THERAPY MEDICINAL PRODUCT

means a biological medicinal product which has the following characteristics:

(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence [AND]

(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence

Gene therapy medicinal products shall not include vaccines against infectious diseases.

Classification - Examples

INDICATION	PRODUCT	CLASS.
Intended as adjunct treatment in HSC transplantation	Allogeneic T cells encoding an exogenous TK gene	sCTMP
Intended for prevention and treatment of HPV16 induced pre-malignancies and malignancies	Plasmid encoding a mutation-inactivated E7-E6 fusion protein from Human Papillomavirus 16 linked to the human chemokine hMIP-1a via a dimerization module derived from human IgG3	GTMP
Intended for prevention and treatment of HCV and HCV-induced hepatocellular carcinoma	Adenoviral vector expressing the non-structural region of hepatitis C virus (HCV) in which a mutation has been introduced	Not an ATMP

CAT Classification

- **Is the product classified as ATMP?**
- **Is it classified as TEP, somatic cell therapy, or gene therapy medicinal product?**
- **Is it combined or non-combined?**
- **Classification is**
  - **voluntary**
  - **free of charge**
  - **not legally binding**

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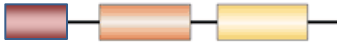
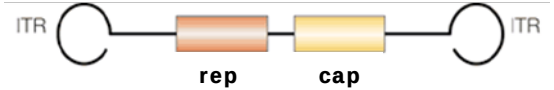
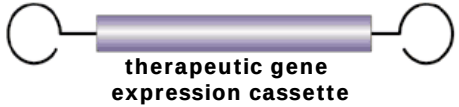
Virus vector production principle



packaging genes

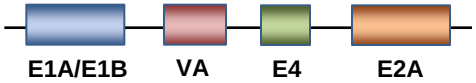
AAV genome



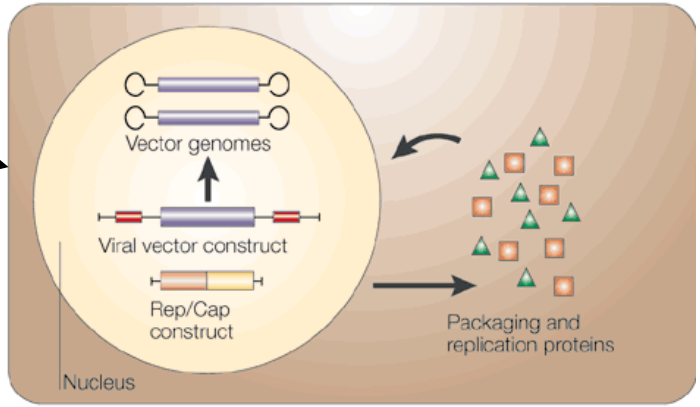


vector genome

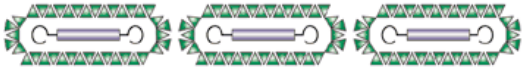
Adenovirus helper function



- **transient as virus**
- **transient / stable as plasmid**



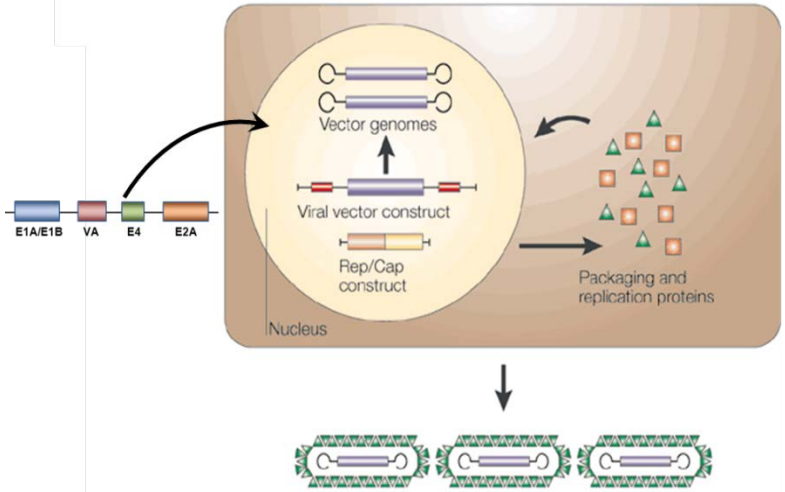
packaging cell



gene-therapy.net
(modified)

Characterisation of vector producer cells

- ✓ Adventitious agents/sterility
- ✓ Generation of wt-virus
- ✓ Cell viability
- ✓ Morphology / growth characteristics
- ✓ Genetic stability of the cell
- ✓ Genetic integrity of the inserts
- ✓ Transgene expression



State-of-the-art vector design

Use of non-state-of-the-art vector and packaging cells should be avoided,

- **to allow manufacture of consistent and safe product.**

  Sponsor Statement: "There are molecular strategies by which the generation of RCVs during manufacture can be reduced or potentially eliminated, for example the use of cell lines and vectors which lack overlapping […] nucleotides, thus preventing homologous recombination. However, such a system is not currently employed by the Sponsor."

- **to avoid later changes in vector design and subsequent `comparability´ exercises**

  Use of non-SIN retroviral vectors, use of WPRE with destroyed X-reading frame

Change in GTMP design

- Change of cell line for vector production could be change in product composition (enveloped viruses)
- Change in nucleotid sequence of therapeutic gene (codon optimisation)
- Change in vector backbone (non-SIN to SIN vector, use of mutated WPRE)

Vector design

Information needed on

- history
- genetic manipulation
- establishment and
- characterisation and control of viral vector seed
    - (sequencing data)

GTMP release criteria

Does the agency agree that the tests and acceptance criteria for DS and DP are adequate at the clinical stage of development with the GTMP? Could the Agency provide feedback on further tests that they deem will be necessary to support a Marketing Authorisation Application?

QC control of virus vector DS/DP

Identity	▪ Physical titer ▪ Therapeutic gene expression
Potency	▪ Infectious titer ▪ Particle to infectivity ratio ▪ Therapeutic gene expression ▪ Biological activity
Purity	▪ Process-related impurities: Benzonase, Resins, etc. ▪ Residual Plasmid DNA (TAT) ▪ Residual HC-DNA (SV40 T-Ag, E1A) ▪ Residual HCP
Safety	▪ Sterility, Endotoxin, Mycoplasma ▪ Replication-Competent Virus

Aspects of potency testing of virus vector-based GTMPs

- Infection efficiency one aspect of potency but not sufficient
- Expression of therapeutic gene might be considered acceptable for early clinical trials
- At MAA functional assay based on activity of the therapeutic protein and reflecting clinical efficacy should be in place (if feasible)

Reasons for quality comparability exercise

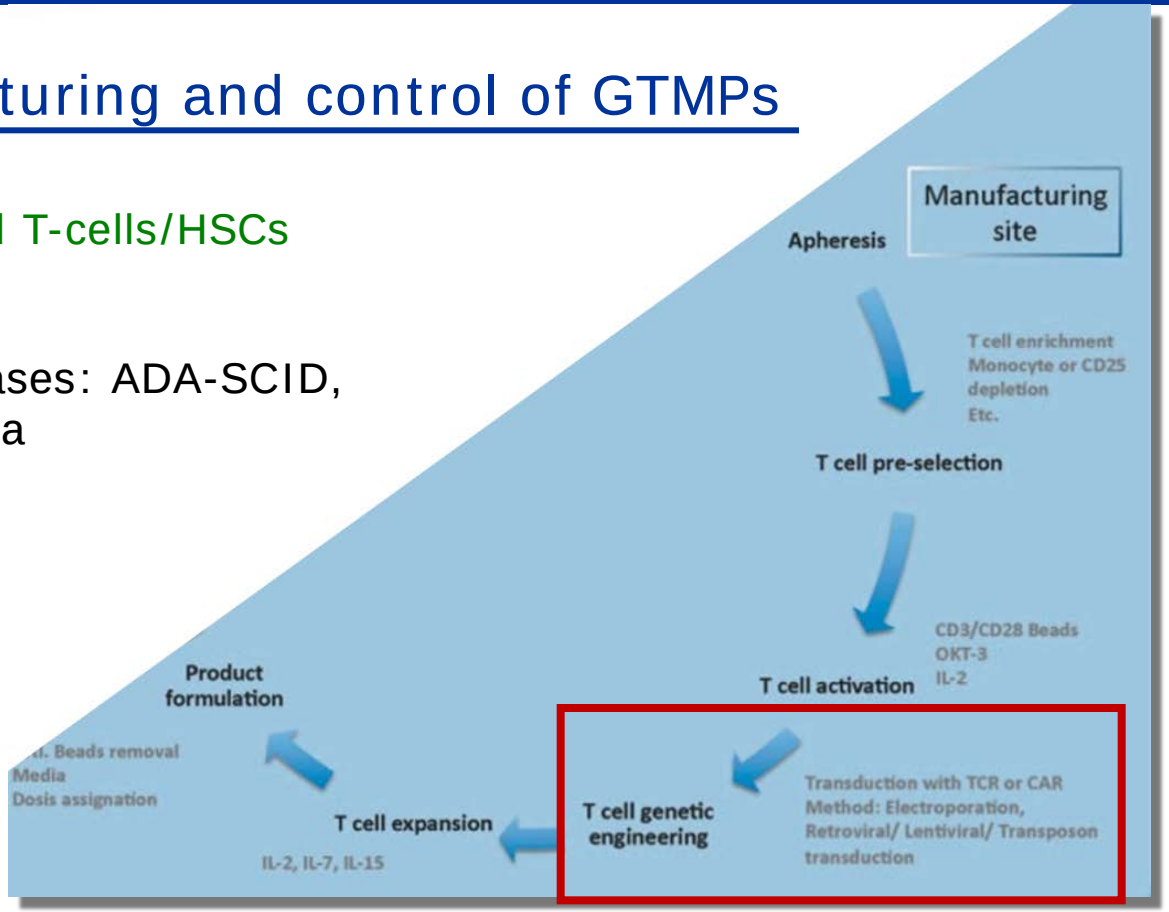
- Use of „early development batches“ for non-clinical analyses and clinical batches when significant changes have been implemented
- Change in manufacturing process during clinical evaluation
- Manufacturing process upscaling
- Change in manufacturing sites, change in analytical procedures

Challenges in manufacturing and control of GTMPs

Example: Genetically modified T-cells/HSCs

Indication:

- inherited monogeneic diseases: ADA-SCID, X-SCID, ALD, ß_thalassemia
- tumor, virus infection



modified from Wieczorek and Uharek (2013)

Challenges in manufacturing and control of GTMPs

Is the manufacturing process of the lentiviral vector and the proposed process validation strategy considered acceptable?

COMMISSION DIRECTIVE 2009/120/EC

of 14 September 2009

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In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells. The principles of good manufacturing practice shall apply from the bank system used to produce the vector onwards.

QC control of virus vector starting material

- Manufacture compliant to GMP
- Full control of manufacturing process
- Release of starting material equivalent to release of DS/DP except
  - Potency by infectivity and therapeutic gene expression might be sufficient
  - Some process related impurities may be addressed in characterisation studies

of active substance (vector related)

- Transduction rate
- Copy number
- Transgene expression
- Biological activity

Process / batch validation

Is use of cell apharesis material from normal donors for process validation acceptable?

- Mobilisation should be performed in same manner before apharesis
- Consideration of potential differences in
  - Cell type composition before and after expansion
  - Cell growth potential during expansion phase
  - Transduction efficiency and transgene expression
- Challenging to address potency with healthy donor cells in diseases based on mutated gene

Validation strategy based on combination of historical data, process development, characterization and comparability studies, cells from healthy individuals, and a continued process verification on patient samples is acceptable

How to deal with short shelf life of the final product?

A real time release strategy is required for the drug product due to the short shelf life. The intention is to have a two stage release process: Stage 1 being release for infusion based on a subset of the release tests that can be performed prior to infusion and stage 2 being the final product release once all release testing has been completed.

Provided that

- process validation demonstrates robust production
- characterization and validation batches meets reliable release criteria

two-stage release process is acceptable.

Regulatory guidance on quality

Quality, preclinical and clinical aspects of GTMPs	04.2001
Design modifications of GTMPs during development	02.2012
Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to ATMPs	03.2013
CHMP/CAT position statement on Creutzfeldt-Jakob disease and ATMPs	06.2011
Questions and answers on gene therapy	12.2009
Quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors	03.2009
Quality, preclinical and clinical aspects of medicinal products containing genetically modified cells	05.2012
Development and Manufacture of Lentiviral Vectors	11.2005
Management of clinical risks deriving from insertional mutagenesis	08.2013

Regulatory guidance on quality

EUROPEAN PHARMACOPOEIA 6.0

5.14. Gene transfer medicinal products for human use

01/2008:51400
corrected 6.0

5.14. GENE TRANSFER MEDICINAL PRODUCTS FOR HUMAN USE

London, 20 April 2009
Doc. Ref. EMEA/CHMP/VWP/141697/2009

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON QUALITY, NON-CLINICAL AND CLINICAL ASPECTS OF LIVE RECOMBINANT VIRAL VECTORED VACCINES

➢ **Ph. Eur. 5.2.3. Cell substrates for the production of vaccines for human use**

Table 5.2.3.-1 – *Testing of cell lines*

Test	Cell seed	Master cell bank (MCB)	Working cell bank (WCB)	Cells at or beyond the maximum population doubling level used for production
1. IDENTITY AND PURITY				
Morphology	+	+	+	+
Identification: nucleic acid fingerprinting and a relevant selection of the following tests: biochemical (e.g. isoenzymes), immunological (e.g. histocompatibility), cytogenetic markers	+	+	+	+
Karyotype (diploid cell lines)	+	+	+(1)	+(1)
Life span (diploid cell lines)	–	+	+	–
2. EXTRANEOUS AGENTS				
Bacterial and fungal contamination	–	+	+	–
Mycoplasmas	–	+	+	–
Spiroplasmas (insect cell lines)	–	+	+	–
Electron microscopy (insect cell lines)	–	+(3)	–	+(3)
Tests for extraneous agents in cell cultures	–	–	+	–
Co-cultivation	–	–	+(2)	+(2)
Tests in animals and eggs	–	–	+(2)	+(2)
Specific tests for possible contaminants depending on the origin of the cells	–	–	+(2)	+(2)
Retroviruses	–	+(3)	–	+(3)
3. TUMORIGENICITY				
Tumorigenicity	+(5)	–	–	+(4)

ICH harmonisation for better health

Considerations:

CHMP/ICH/607698/08 Oncolytic Viruses

Thank you for your attention

The views expressed in this presentation are in part the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the Paul-Ehrlich-Institut or the EMA committees or working parties

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