Lääkealan turvallisuus- ja kehittämiskeskus | Säkerhets- och utvecklingscentret för läkemedelsområdet | Finnish Medicines Agency

GLP-vaatimukset ATMP-valmisteiden turvallisuustutkimuksille

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Advanced therapy medicinal products (ATMPs)

- Somatic cell therapy medicinal products
- Tissue engineered products
- Gene therapy medicinal products

Advanced therapy medicinal products

Innovative therapies for diseases and conditions for which limited or no treatment options exist

- Degenerative diseases
  Alzheimer's disease, Parkinson's disease, macular degeneration, diabetes
- Autoimmune diseases
  Chron's disease
- Cancer
- Tissue defects
  bone, cartilage, skin, myocardial infarction, spinal cord injury
- Organ replacement
  artificial liver, bladder

Cell-based medicinal products

- Somatic cell therapy medicinal products
- Tissue engineered products

Somatic cell therapy medicinal products

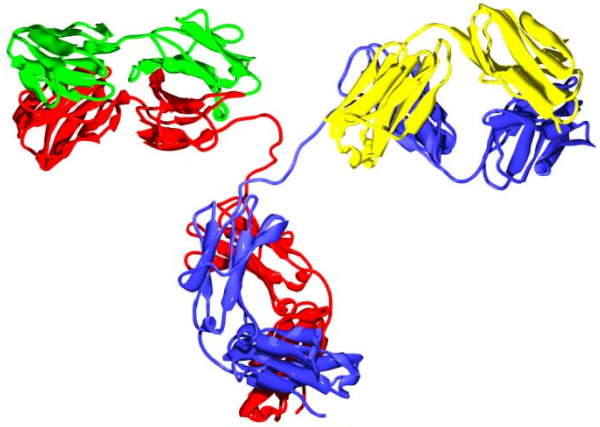
- cells or tissues that have been subjected to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or
- cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor
- to treat, prevent or diagnose a disease through the pharmacological, immunological or metabolic action

Annex I, Part IV of Dir 2001/83/EC

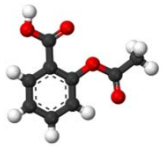
Tissue engineered products

- engineered cells or tissues (see above)
- to regenerate, repair or replace a human tissue

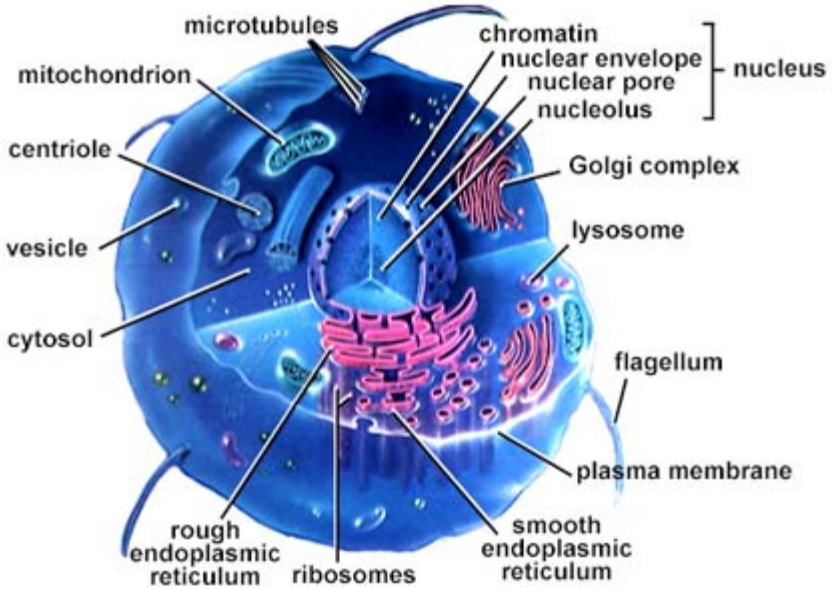
Regulation EC (No) 1394/2007



IgG ~1500 Da (~1400 aa)



Aspirin MW 180



Eukaryotic cell 10 µm

fimea

Non-clinical requirements for cell-based products

- ✓ **Proof-of-concept**
  - Relevant animal model(s)
- ✓ **Pharmacological and toxicological effects**
  - Biodistribution
  - Unintended differentiation
  - Ectopic engraftment
  - Tumourigenicity
  - Immune related effects

- ✓ **Provide estimate for selection of safe and efficacious dose in clinical studies**
- ✓ **Support the route of administration and feasibility of application procedure**
- ✓ **Identify target organs for toxicity**
- ✓ **Identify parameters to be monitored in clinical studies**

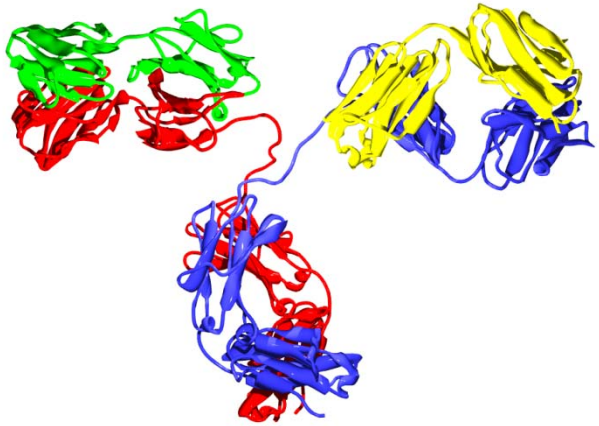
Gene therapy medicinal products

Gene therapy medicinal products

- active substance contains or consists of a recombinant nucleic acid which therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence, or to the product of genetic expression of this sequence

- to regulate, repair, replace, add or delete a genetic sequence

Part IV of Annex I to Directive 2001/83/EC



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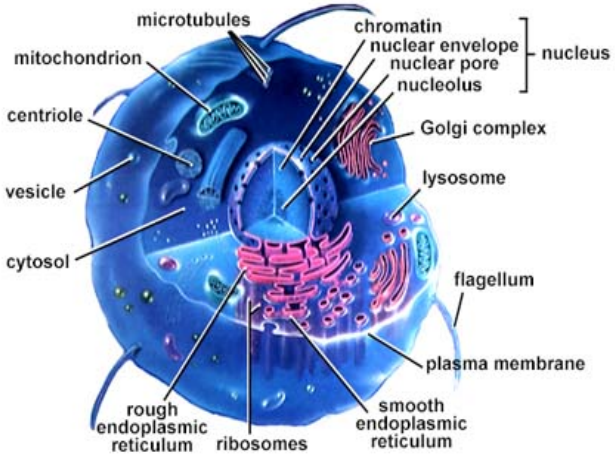
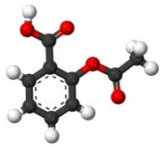


Eukaryotic cell 10 µm



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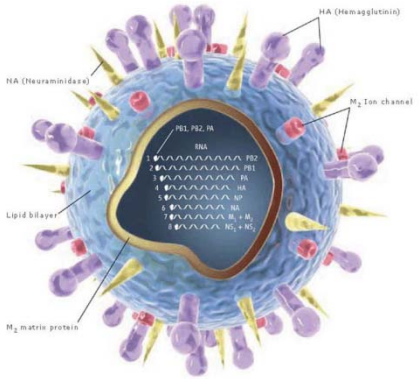


Virus particle 20-300 nm

Non-clinical requirements for gene therapy products

- ✓ **Proof-of-concept**
  - Relevant animal model(s)
- ✓ **Pharmacological and toxicological effects**
  - Biodistribution
  - Persistence
  - Ectopic transgene expression
  - Recombination and mobilisation of a vector
  - Induced cellular changes
  - Insertional mutagenesis
  - Germline transmission
  - Immune related effects of a transgene and a vector
  - Virus shedding

- ✓ **Provide estimate for selection of safe and efficacious dose in clinical studies**
- ✓ **Support the route of administration and feasibility of application procedure**
- ✓ **Identify target organs for toxicity**
- ✓ **Identify parameters to be monitored in clinical studies**

GLP requirements

Legal background

ATMP (advanced therapy medicinal products) are medicinal products the marketing of which necessitates a Marketing Authorisation recommended by the European Medicines Agency (EMA) and issued by the European Commission.

- *Dir 2001/83/EC as amended*
  - *Annex I Part IV (Dir 2003/63/EC)*
  - *Reg 1394/2007*

- General requirements for all medicinal products
  - Non-clinical (fpharmacological-toxicological) studies should be conducted according to the good laboratory practise (GLP
    - *Annex I Part I (Dir 2003/63/EC)*

- Additional specific requirements for ATMP products
    - *Annex I Part IV (Dir 2009/120/EC)*

Legal requirements

Proteins | **Cell-based products** | **Gene therapy products**

(EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

Biotech and advanced therapy products to be authorised by the EMA

Directive 2001/83/EC Community code relating to all medicinal products for human use

Directive 2003/63/EC (Annex I of 2001/83/EC)
Analytical, pharmaco-toxicological and clinical requirements

(EC) No 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation 726/2004

Directive 2009/120/EC (Annex I, part IV of 2001/83/EC)
Technical requirements for testing of ATMPs

Dir 2004/23/EC setting standards of quality and safety for donation, procurement, testing, processing, preservation, storage and distribution of human tissues/cells,
*Technical requirements in **Dir 2006/17/EC** and **Dir 2006/86/EC***

Clinical trials

- **Regulation 536/2014** on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

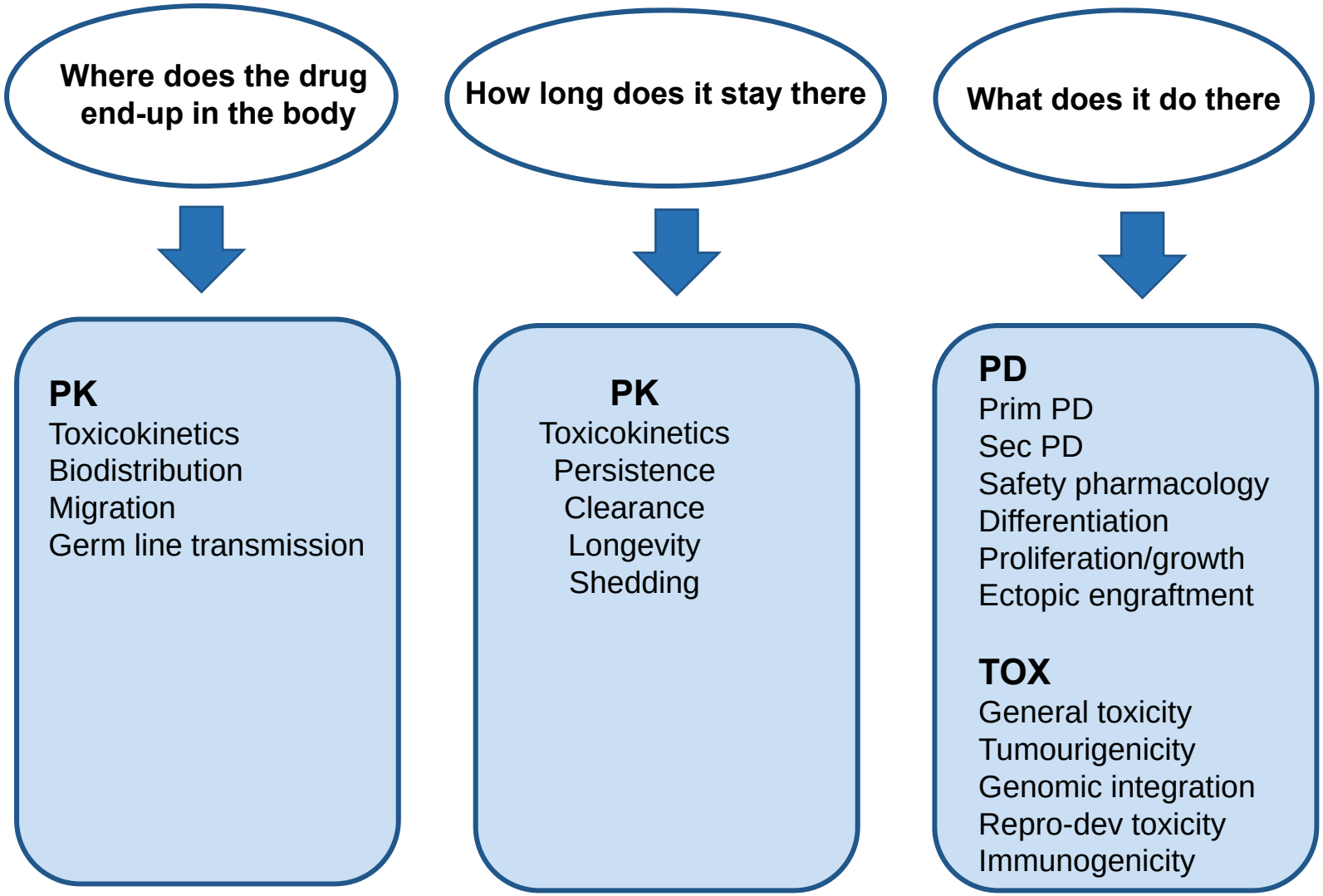
"Non-clinical information submitted in an application dossier shall be based on data derived from studies complying with Union law on the principles of good laboratory practice"

Non-clinical pharmaco-toxicological requirements

Pharmacodynamics
- Primary pharmacodynamics (PD)
- Secondary PD
- Safety pharmacology
- PD drug interactions

Pharmacokinetics
- ADME
- PK drug interactions

Toxicology
- General toxicity: single and repeat-dose
- Genotoxicity
- Carcinogenicity
- Developmental and reproductive toxicity
- Local tolerance
- Immunotoxicity
- Immunogenicity
- Environmental risk assessment


Where does the drug end-up in the body
How long does it stay there
What does it do there
PK
Toxicokinetics
Biodistribution
Migration
Germ line transmission
PK
Toxicokinetics
Persistence
Clearance
Longevity
Shedding
PD
Prim PD
Sec PD
Safety pharmacology
Differentiation
Proliferation/growth
Ectopic engraftment
TOX
General toxicity
Tumourigenicity
Genomic integration
Repro-dev toxicity
Immunogenicity

General requirements	Special requirements for biologicals and ATMPs		
	Proteins	Gene therapy	Cell-based therapies
Pharmacology Prim PD Sec PD Safety pharmacology	Proof-of-concept Prim PD Sec PD Safety pharmacology	Proof-of-concept Tropism (Safety pharmacology)	Proof-of-concept Tissue integration Tissue interaction Bioactive molecules (Safety pharmacology)
Pharmacokinetics ADME TK	Absorption Biodistribution (Excretion)	Biodistribution, persistence, clearance, mobilisation, germ line transmission	viability, longevity, distribution, growth, differentiation and migration
Toxicology Single and repeat-dose toxicity	Single and repeat-dose toxicity	Can be included in POC studies	Can be included in POC studies
Genotoxicity	(-)	(-)	(-)
Carcinogenicity	Included in chronic tox studies	Insertional mutagenesis	Tumourigenic potential
Repro-dev toxicity	Repro- dev toxicity	Fertility, reproductive potential	(-)
Other toxicity	Immunogenicity (Immunotoxicity)	Immunogenicity shedding	Immunogenicity, immunotoxicity, xenopathogen transmission
ERA	(-)	GMO ERA	(-)

GLP requirements

- **GLP requirements the same regardless of the product class!**

- Nonclinical studies according to the GLP requirements
  - All pivotal studies to which nonclinical safety is based on
  - Safety pharmacology and toxicology studies

- Pharmacological characterisation and proof-of-concept studies generally non-GLP
  - When pivotal safety end-points are included in a POC study the study should be conducted under GLP

- Full GLP compliance may not always feasible
  - Deviation may be justified due to product related issues
  - GLP principles must be followed to the extent possible
  - Non-GLP and possible impact to the overall safety assessment need to be justified
  - Acceptance on a case by case basis