Non-clinical assessment of early phase trials : ATMPs

FAMHP

BRUSSELS

15.09.2023

Claire BEUNEU

famhp

federal agency for medicines and health products

.be

Content

- Introduction
- Guidelines
- NC assessment
  - Pharmacology
  - Biodistribution
  - Toxicology
- Conclusions

Specific challenges with ATMPs

- Highly complex and diverse products
- Complex manufacturing proces
- Often personalised
- Route of administration
- Often single administration
- Risk-based approach

Risk-based approach

- Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products (EMA/CAT/CPWP/686637/2011)

- To identify the risks and associated risk factors, and to establish a risk profile for an ATMP under development

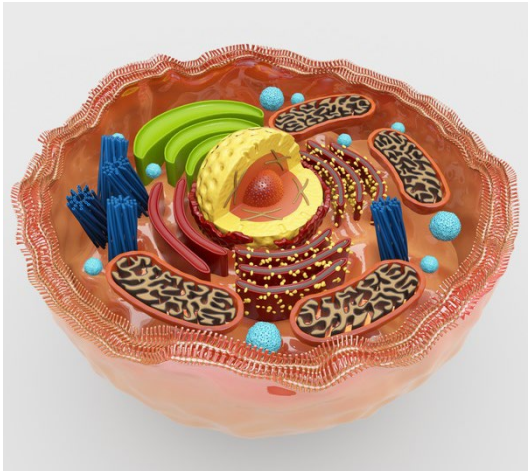
- Based on this risk profile, the Applicant will justify the extent of data included in the MAA dossier

Cell based medicinal products

Autologous

Allogeneic **Origin**

Xenogeneic



stem cell

Differentiation progenitor

Proliferation

terminally differentiated

Bioactive molecules **Other components**

Structural components

Manipulation genetic modification

culture

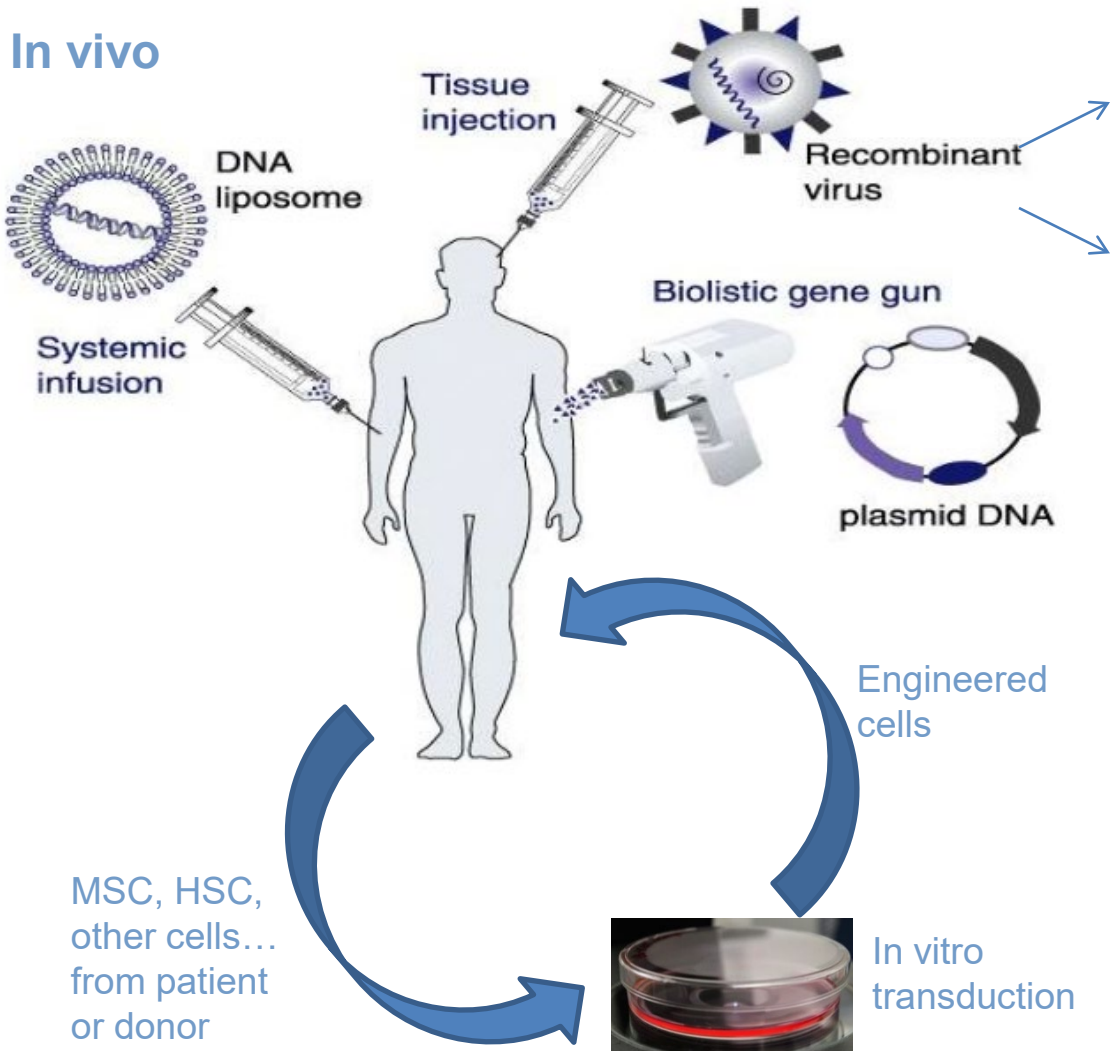
differentiation

+ ability to initiate an immune response?

+ mode of administration ?

+ duration of exposure ?

Gene therapy medicinal products



Main guidelines

- Guideline on the quality, non-clinical and clinical aspects of **gene therapy** medicinal products (EMA/CAT/80183/2014)
- Guideline on human **cell-based** medicinal products (EMEA/CHMP/410869/2006)
- ICH guideline S12 on nonclinical **biodistribution** considerations for gene therapy products (EMA/CHMP/ICH/318372/2021)
- DRAFT Guideline on quality, non-clinical and clinical requirements for **investigational** advanced therapy medicinal products in clinical trials (EMA/CAT/852602/2018)

EMA webpage:
https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products

Non-clinical studies: general principles

- Demonstrate proof-of-principle
- Define pharmacological and toxicological effects predictive of the human response
- Provide information to select safe and efficient doses
- Support the duration of exposure and duration of follow-up
- Sequential non-clinical development is not generally applicable for ATMPs
- 3R: combined studies

Pharmacology

- Should provide evidence supporting **the potential clinical benefit** or at least the related biological effect/molecular mechanism of action

- In vivo **animal models** and/or in vitro studies
  - Route & regimen should reflect the intended clinical use
  - Immunocompromised, knock out, trangenic, in vitro
  - Homologous versus heterologous
  - Relevant markers of biological activity

- Should support route of **administration**, treatment **dose** and **regimen**

Biodistribution

- Tissue **distribution** and **persistence** (ICH S12 for GTMP)
- Target tissue **selectivity** (ectopic engrafment, tropism…)
- Cell based products: viability, phenotype, integration with surrounding tissue
- Viral vectors: **integration** to the host cell genome (e.g. in gonads)
- Observation time should cover persistence

Toxicology (1)

- Administration route and regimen should mimic clinical use
- One single relevant species may be sufficient
- Single dose: extended follow up period (long term effects)
- Repeated dose toxicity studies only where multiple dosing is intended in clinics
- Endpoints as in the guideline on repeated-dose toxicity studies (CPMP/SWP/1042/99) unless otherwise justified
- Viral vectors: integration potential (both intended and non intended)

Toxicology (2)

- In vivo tumourigenicity = on a case by case basis, with cells at the limit of routine cell culturing or beyond that limit

  QL part: analysis of e.g. proliferative capacity, dependence on exogenous stimuli, response to apoptosis stimuli, genomic stability…

- Germline transmission (prior to fist clinical use)

  results of BD studies, types of target cells within the gonadal compartment

- Shedding (protection of third parties)

- GLP requirement for ATMPs
  (https://www.ema.europa.eu/en/documents/other/good-laboratory-practice-glp-principles-relation-advanced-therapy-medicinal-products-atmps_en.pdf)

ERA for GMOs

- Authorisation needed either under contained use (Directive 2009/41/EC) or deliberate release (Directive 2001/18/EC)

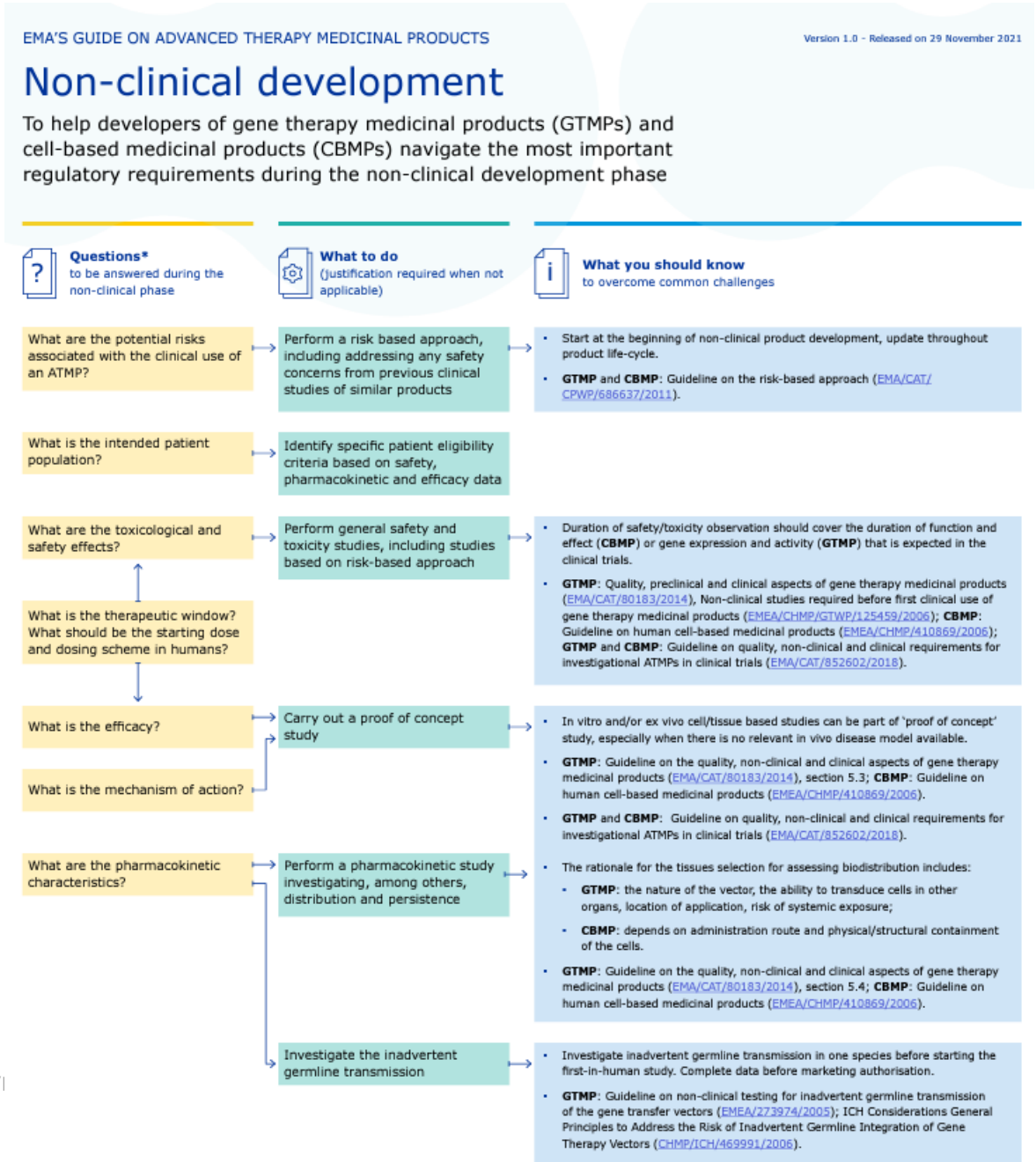
- European Commission webpage on ATMPs:
  - repository of national requirements
  - In vivo gene therapy: Good practice document + Common application form (for AAVs) + Common application form for viral vectors
  - Genetically modified human cells: Good practice document + common application form
  - Oncolytic viruses: considerations for the evaluation of shedding

https://health.ec.europa.eu/medicinal-products/advanced-therapies_en

Conclusions (1)

- Use the risk-based approach : explain and justify all choices
- Use of data from litterature / similar products : explain to which extent they are relevant
- Starting dose is often critical
- Consult documents meant to help: GLP statement, harmonised GMO documents, training material, Non-clinical development flowchart

https://www.ema.europa.eu/en/documents/other/guide-advanced-therapy-medicinal-products-non-clinical-development-flowchart_en.pdf



EMA'S GUIDE ON ADVANCED THERAPY MEDICINAL PRODUCTS

Version 1.0 - Released on 29 November 2021

Non-clinical development

To help developers of gene therapy medicinal products (GTMPs) and cell-based medicinal products (CBMPs) navigate the most important regulatory requirements during the non-clinical development phase

Questions* to be answered during the non-clinical phase	**What to do** (justification required when not applicable)	**What you should know** to overcome common challenges
What are the potential risks associated with the clinical use of an ATMP?	Perform a risk based approach, including addressing any safety concerns from previous clinical studies of similar products	• Start at the beginning of non-clinical product development, update throughout product life-cycle. • **GTMP** and **CBMP**: Guideline on the risk-based approach (EMA/CAT/CPWP/686637/2011).
What is the intended patient population?	Identify specific patient eligibility criteria based on safety, pharmacokinetic and efficacy data	
What are the toxicological and safety effects? What is the therapeutic window? What should be the starting dose and dosing scheme in humans?	Perform general safety and toxicity studies, including studies based on risk-based approach	• Duration of safety/toxicity observation should cover the duration of function and effect (**CBMP**) or gene expression and activity (**GTMP**) that is expected in the clinical trials. • **GTMP**: Quality, preclinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014), Non-clinical studies required before first clinical use of gene therapy medicinal products (EMEA/CHMP/GTWP/125459/2006); **CBMP**: Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006); **GTMP** and **CBMP**: Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials (EMA/CAT/852602/2018).
What is the efficacy? What is the mechanism of action?	Carry out a proof of concept study	• In vitro and/or ex vivo cell/tissue based studies can be part of 'proof of concept' study, especially when there is no relevant in vivo disease model available. • **GTMP**: Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014), section 5.3; **CBMP**: Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006). • **GTMP** and **CBMP**: Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials (EMA/CAT/852602/2018).

What are the pharmacokinetic characteristics?	Perform a pharmacokinetic study investigating, among others, distribution and persistence	• The rationale for the tissues selection for assessing biodistribution includes:
		  ▪ **GTMP**: the nature of the vector, the ability to transduce cells in other organs, location of application, risk of systemic exposure;
		  ▪ **CBMP**: depends on administration route and physical/structural containment of the cells.
		• **GTMP**: Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014), section 5.4; **CBMP**: Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006).

	Investigate the inadvertent germline transmission	• Investigate inadvertent germline transmission in one species before starting the first-in-human study. Complete data before marketing authorisation. • **GTMP**: Guideline on non-clinical testing for inadvertent germline transmission of the gene transfer vectors (EMEA/273974/2005); ICH Considerations General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors (CHMP/ICH/469991/2006).

Conclusions (2)

- **Early interactions with regulators**

- ITF briefing meetings
(***https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines#itf-briefing-meetings--section***)

- EU scientific advices
(***https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance***)

- National scientific advices
(***https://www.famhp.be/en/human_use/medicines/medicines/scientific_technical_advice***)

Thank you for your attention

Questions?

Your medicines and health products, our concern

famhp

.be