The risk-based approach for ATMPs – a new paradigm with 3Rs opportunities

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federal agency for medicines and health products

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ATMPs and legal framework

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

➔ Centralised EU marketing application

➔ 1 single application and opinion (EMA, Amsterdam)

➔ RISK-BASED APPROACH

Annex 1 part IV of Directive 2001/83/EC

Due to the specific nature of advanced therapy medicinal products, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application […]

The risk analysis may cover the entire development […]

Relevant available non-clinical and clinical data or experience with other, related advanced therapy medicinal products may also be considered in the risk analysis.

Any deviation from the requirements of this Annex shall be scientifically justified […]

NC studies: general principles

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

Risk-based approach guideline

- 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

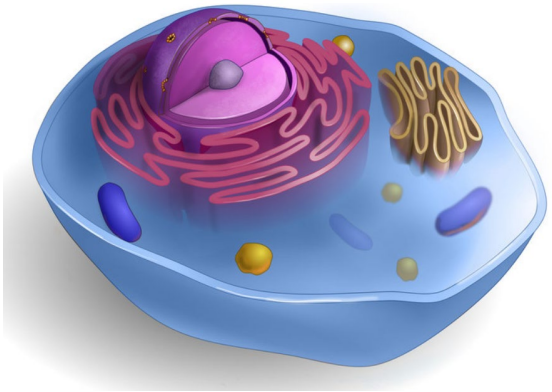
- Based on this risk profile, the Applicant will justify the extent of data included in the MAA dossier

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

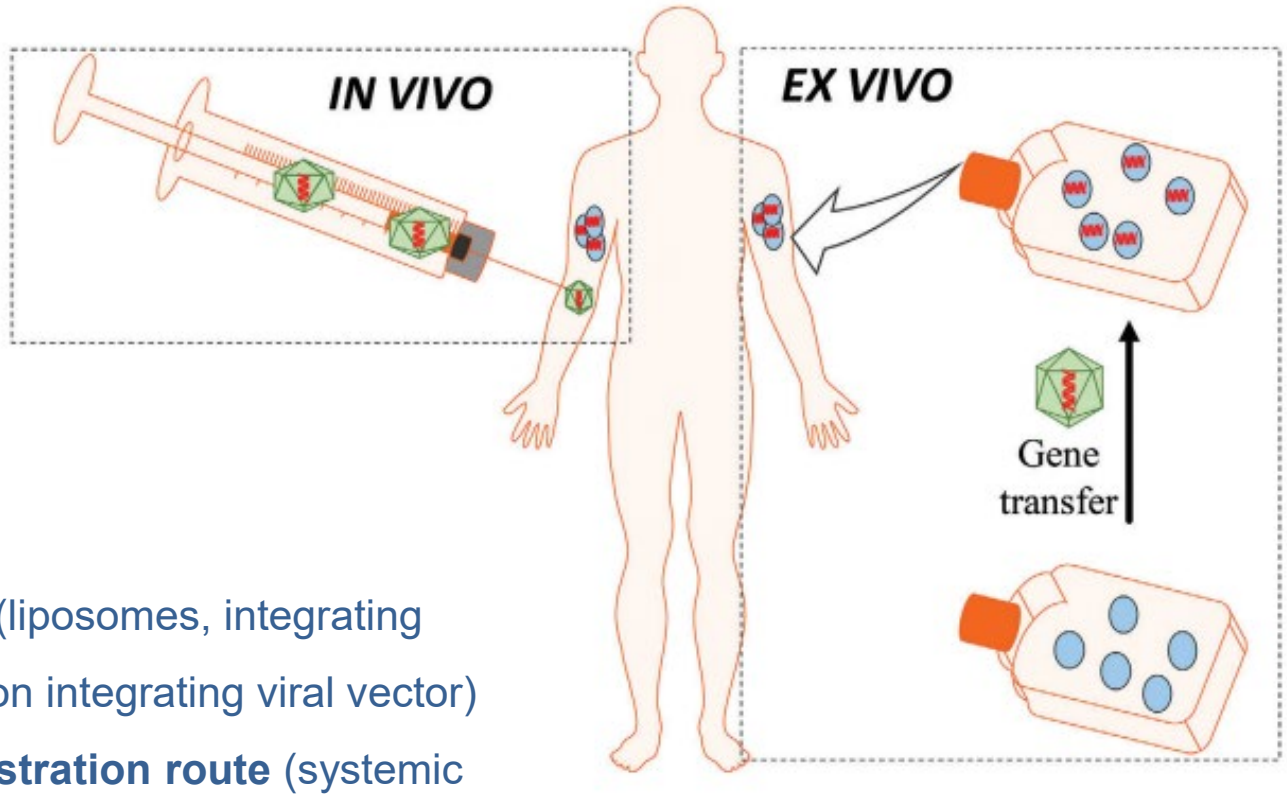
+ ability to initiate an immune response

+ mode of administration

+ persistence

From *www.medicalgraphics.de*

Gene therapy medicinal products



- **Vector** (liposomes, integrating versus non integrating viral vector)
- **Administration route** (systemic versus local)
- **Persistence**

From *Wang Y, et al. Adv Healthc Mater. 2021 Jan;10(1).*

Risk profiling methodology

- *1st step*: To identify risks associated with the clinical use of the ATMP (unfavourable effect)
- *2nd step*: To identify product specific risk factors contributing to each identified risk (product characteristic)
- *3rd step*: To map the relevant data for each identified risk factors against each of the identified risks
- *4thstep*: To conclude on the risk factor – risk relationships

⇒ data generated/collected to address this risk

⇒ Scientific justification for omitted studies

Examples

- Risk of tumorigenicity linked to risk factor long term culture ex vivo: if in vitro genome stability studies (QL) do not raise concerns, no need for an in vivo study

  ⇒ tumorigenicity studies in mice are most of the time unnecessary

- Risk of tumorigenicity linked to risk factor of biodistribution: if cells are locally contained (i.e. medical device), no need for a full biodistribution study

- Risk of tumorigenicity linked to risk factor of integration: e.g. with an AAV vector

  ⇒ risk analysis based on relevant literature data and clinical monitoring

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

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

What to do (justification required when not applicable)

Conclusions

- Use of the risk-based approach : explain and justify all choices
- Use of data from litterature / similar products : explain to which extent they are relevant
- 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

Your medicines and health products, our concern

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