Regulatory perspective (I)

Dr Carla Herbergs, Medicines Evaluation Board, CT-TRACS Co-Chair, Netherlands
Safety assessment of cell therapy products

CTG Catapult and HESI – CT-TRACS Workshop

Carla Herberts

Clinical assessor, NL alternate CAT
Medicines Evaluation Board
ca.herberts@cbg-meb.nl

14 February 2018
Disclaimer

The contents of this presentation represent the personal views of the speaker only; the contents do not necessarily reflect current or future opinions of the MEB, the EMA, and/or their committees/working parties.
Cell therapy falls within the regulatory framework for ATMPs

- EU Regulation 1394/2007
- GTMP, CBMP, TEP
- Committee for Advanced Therapies
- EMA Procedures
  - Scientific advice
  - Protocol assistance
  - **Classification**
  - **Certification (Q, Q/NC)**

**Exception:** *homologous use* of *non-substantially manipulated* cells
Cell therapy poses new challenges
It is not just size

- Manufacture and characterisation
- Plasticity
- Species (or patient) specificity
- Detection
- Dosing
- Persistence
- ...
EU Guidelines

- **Human cell-based medicinal products** (CHMP/410869/06)
- Safety and efficacy follow-up and risk management of advanced therapy medicinal products
- Reflection paper on *in-vitro* cultured chondrocyte containing products for cartilage repair of the knee
- Reflection paper on stem cell-based medicinal products
- Risk-based approach
- ...


For product development

• Guidelines are only a starting point

Non-clinical safety assessment

• Accept limitations of animal studies
  - When using homologous model also characterise animal cells
• Tailored scientific approach
• In vitro studies

Remember: Non-clinical studies are performed to support the clinical development and use of a medicinal product
Most discussed issues in SA

- Choice of animal model
  - homologous, heterologous
  - small vs large
- Biodistribution
- Design of safety studies (which, species, GLP)
- Carcinogenicity/tumourigenicity
- Reduced non-clinical package

⇒ Analysis performed in 2014
Biodistribution

- SA’s on biodistribution
  - Lack of biodistribution should be shown (not assumed)
  - Main focus on persistence
- Often many questions remain unanswered because
  - Limitation of used technique
  - Limitation in study design
- Multitude of techniques
  - Immunohistochemistry
  - Flow cytometry
  - (q)PCR
  - Imaging (19F MRI, fluorescence, SPECT/PET, ultrasound, photoacoustics)
Biodistribution

- provide information on delivery, engraftment and cell retention, distribution, viability, proliferation, persistence
- Better understanding thus supporting RoA, dose, activity/MoA
- Interpretation of observed effects

⇒ Information on biodistribution could be highly valuable for development of cell therapy
Examples

J. Sharkey et al 2016

intracoronary  transendocardial

Vrtovec et al. 2013

De Vries et al 2005
Tumourigenicity

- Inherent concern with cell therapy
- But risk depends on many factors
  - Potency of the cells (pluripotent, multipotent, ...)
  - Proliferation potential
  - Autologous vs allogenic
  - Manipulation
  - ...

SA’s on Tumourigenicity

• No standard carcinogenicity studies
• Testing strategies may include
  • *In vitro* testing (growth rate, karyotyping, senescence, cell differentiation, cell adhesion, growth factor independent growth, expression of oncogenes)
  • *In vivo* evaluation of hyperplasia/cell proliferation

• **Risk assessment**
  But: How to interpret the data and estimate risk?
Finally

- Safety assessment of cell therapy product requires a case by case approach
- Accept limitations of animal models
- Integrative approach and tailored studies
- Biodistribution studies can be informative
  - but need to be further developed
- Tumourigenicity is a concern
  - but assay interpretation and risk assessment is an issue

- Studies are means to an end, not an end in themselves
Thank you

Questions?