Regulatory considerations for ATMP based cancer therapies

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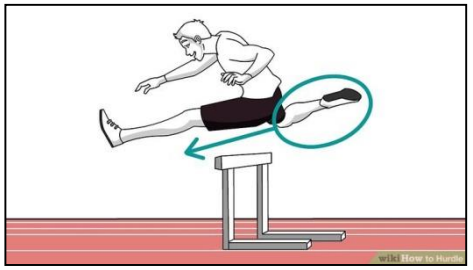
DISCLAIMER: Personal views only, meant to initiate further discussion; may not necessarily reflect views/opinions of MEB, EMA or EDQM.

Outline

- EU regulatory framework for ATMPs
- Manufacturing aspects specific for ATMPs
- Clinical aspects
- Regulatory flexibility
  - Agency Support

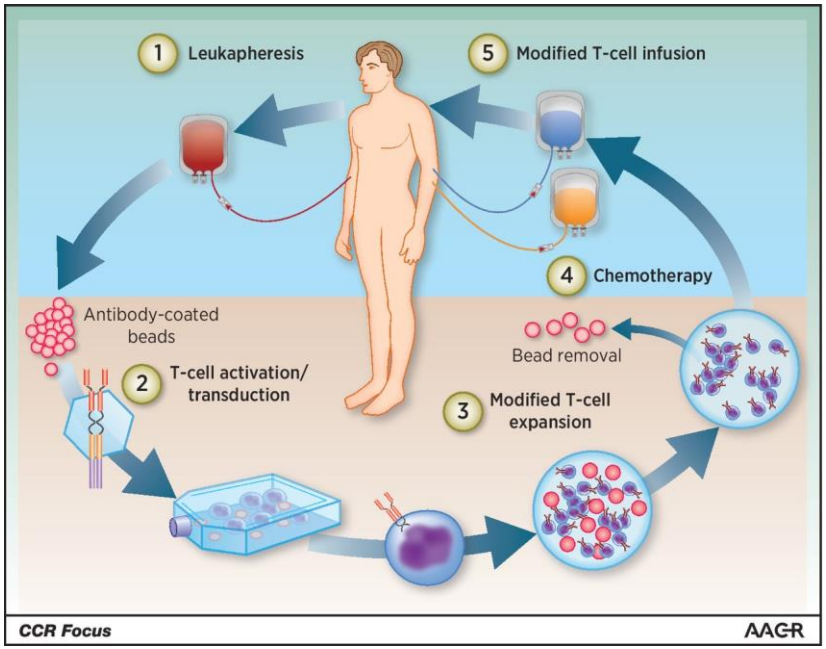
Development phases & manufacturing steps

Each phase and step has its regulations

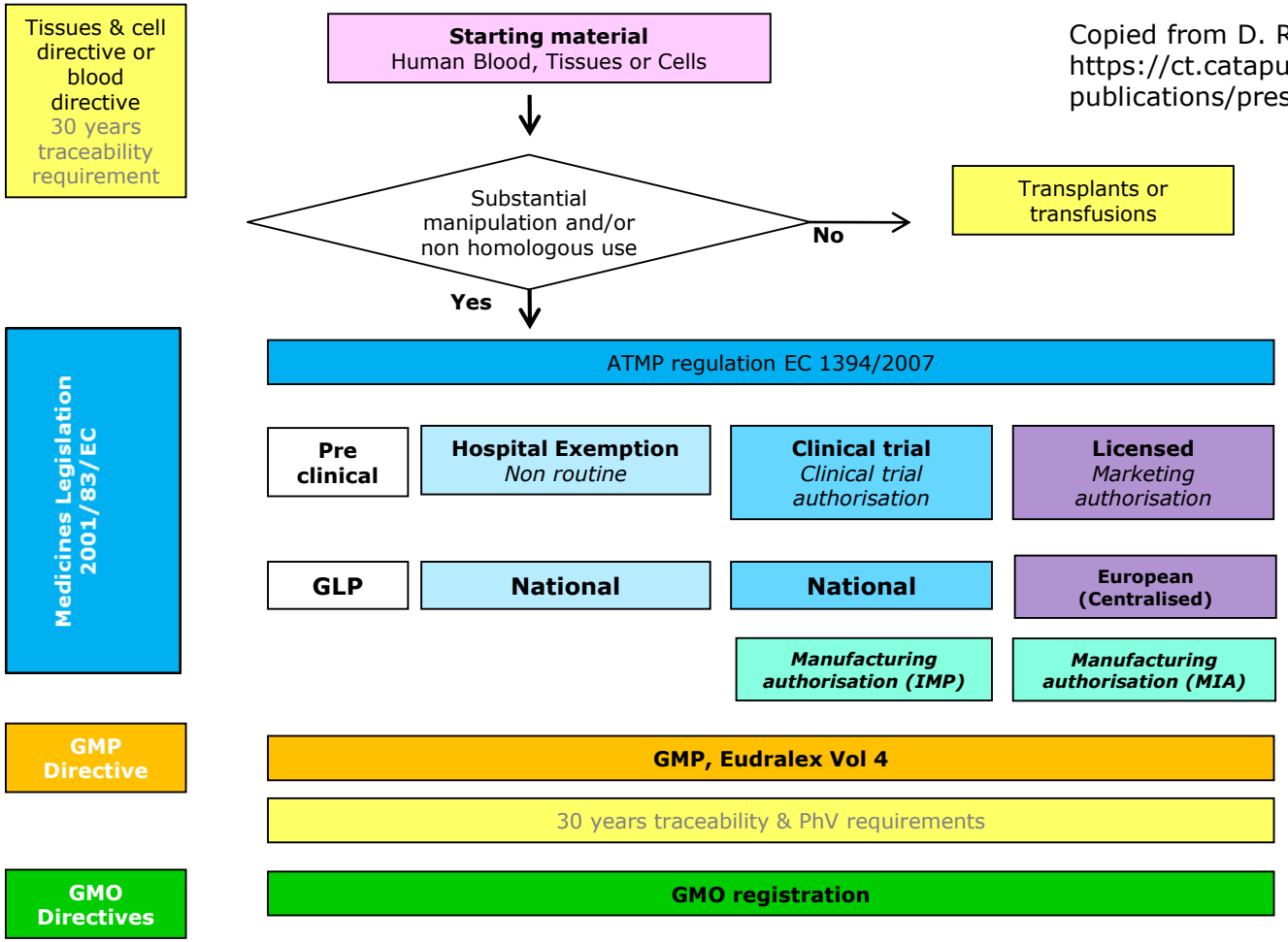


- Non-clinical studies
- Clinical trials
- Marketing Authorisation
- Manufacturing process
  - Patient/donor derived cells

  e.g. TIL, modified TCR-T cells
  - Genetically modified cells
  - Oncolytic viruses
  - Transport
- Environmental risk assesssment



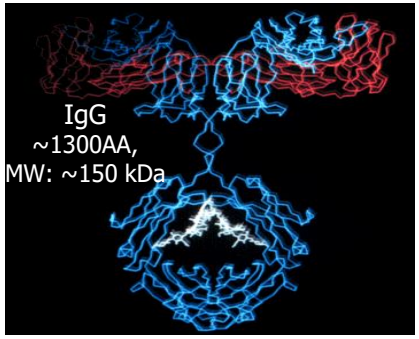
EU regulatory framework for ATMPs

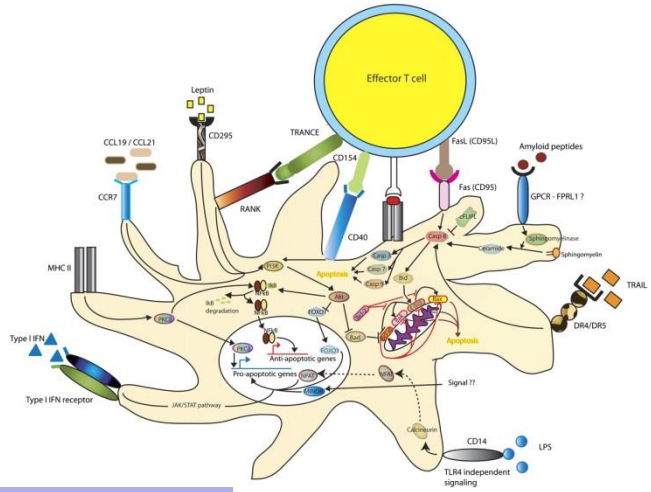


Copied from D. Rabbie, Catapult
https://ct.catapult.org.uk/resources/publications/presentations/all

Manufacturing Aspects

- Pharmaceutical Regulation initially for chemicals
- ATMP are not chemicals nor well-defined biologicals
- Starting material variation
- Biological manufacturing system
- Attributes impacting product safety, efficacy and potency
- Risk-based approach

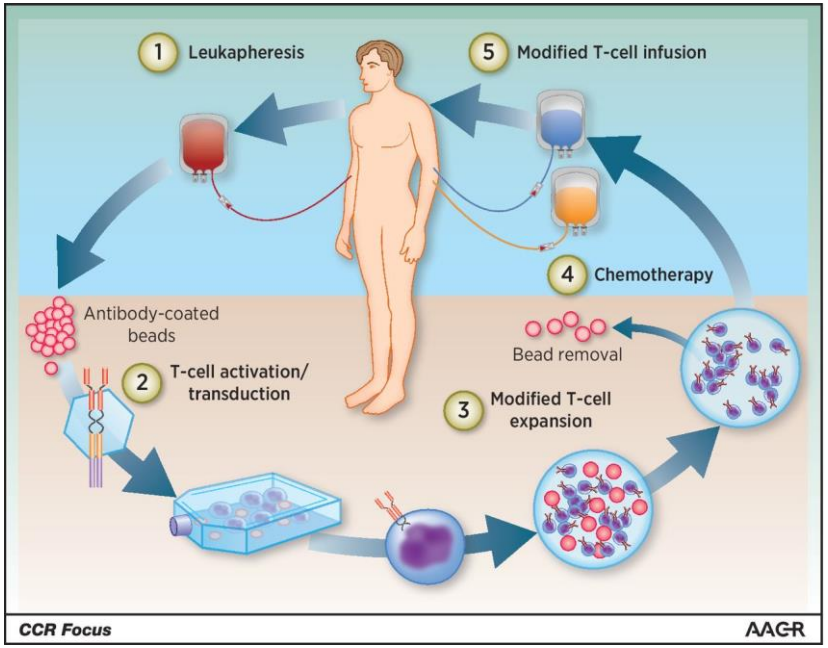




Product is the process

Manufacturing Aspects (2)

- Variability and testing Starting materials
- Quality Ancillary Materials
- Product/Process Characterisation
- Mode of Action
- Critical Quality Attributes
- Potency
- Process validation
- Comparability
- No terminal sterilisation



Product is the process

Risk-based approach (RBA)

- Dir 2009/120/EC to enable a control strategy to adequately manage the risks of the product/manufacturing process (Marketing Authorisation & Clinical Trials)
- Prospectively planned strategy to justify the need for data in the MAA, proportionate requirements based on risk)
- How to do the risk/risk factor profiling?
  - GL on risk-based approach (EMA/CAT/CPWP/686637/2011)
- More flexible
  -less quality centred
  -include non-clinical and clinical considerations
  –risk mitigation measures
- GMP guide allows tools for Quality risk management
- **Formalised common sense**

Autologous /patient-specific ATMPs

- Autologous cell batches vary in size/quality
- How to set control ranges during manufacturing? (e.g. Transduction efficiency)
- Patient material to validate process and stability
- Continuous process innovation is imperative & challenge
- Manufacturing logistics (e.g. timing & shipping)
- Scale-out/Scale up/Multiple manufacturing sites
- Limited material or time for testing
- Short shelf life
- Test results after product release
- Shipping/handling
- Reconstitution at bedside
- Release of OoS batches? (ref. GMP for ATMP)

Quality of materials used in manufacturing

- Biological Materials (Viral/microbiological safety)
- Traceability (donor & patient)
- Ancillary materials
- – come in contact with cells
- - not intended to be in final formulation
- Container closures
- Criticality/Risk assessment
- Specifications: lot to lot consistency
- Grade (pharmaceutical/research)
- Certificate of Analysis (CoA)
- Test methods
- Ph.Eur. monograph 5.2.12

Viral Vectors

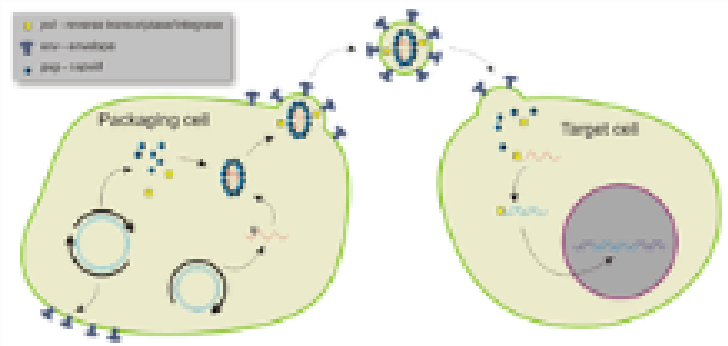
EUROPEAN PHARMACOPOEIA 7.0

01/2010:51400

5.14. GENE TRANSFER MEDICINAL PRODUCTS FOR HUMAN USE

This general chapter is published for information.

- Infectivity/transduction efficiency (using relevant cell type)
- Integration site analysis
- Vector Copy Number (per cell /distribution)
- Characterisation (incl. Capsid Proteins)
- Number of Empty Capsids
- Plasmid RNA/DNA integrity



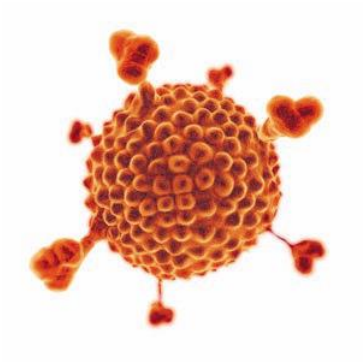
Specific for *Ex vivo* use

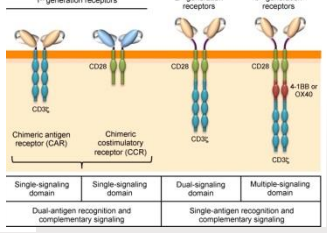
- Replication competent virus RCV
- End of production cells (latent viruses)
- Expression of therapeutic sequence

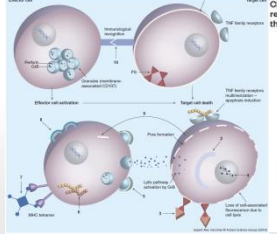
Manufacturing changes & Comparability

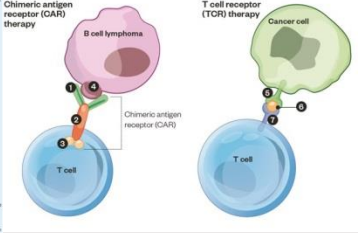
Example Transduced cells

- Preferably before pivotal clinical trial
- Critical process steps /parameters
- Immunophenotypic profile
- Cell number, viability
- Transduction efficiency
- Vector copy number
- Transgene sequence
- Biological characterisation
- Potency
- Stability
- Confirmation with patient cells









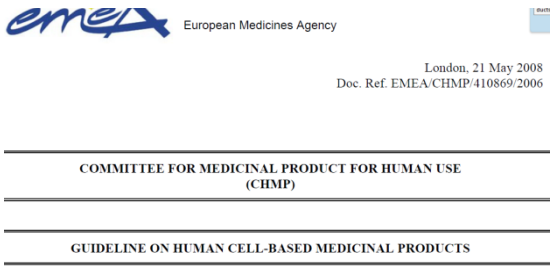
POTENCY

Cell-based medicinal products: the new biologicals

Potency is a key parameter for complex products which are difficult to characterise.

A combination of **multiple methods** may be needed to adequately define the potency of these products **during the development**. Certain assays may be needed to **control process changes**, whereas **others are more suitable for release testing**.

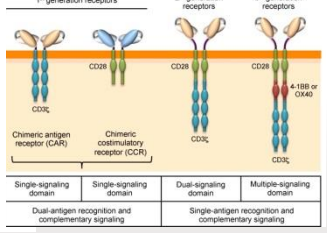
Preferably, the potency assay should reflect the clinical Mechanism of Action.

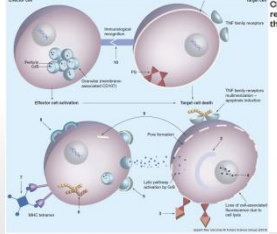

European Medicines Agency

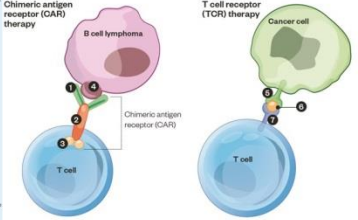
London, 21 May 2008
Doc. Ref. EMEA/CHMP/410869/2006

COMMITTEE FOR MEDICINAL PRODUCT FOR HUMAN USE (CHMP)

GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS







Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer (EMA/CHMP/BWP/271475/2006)

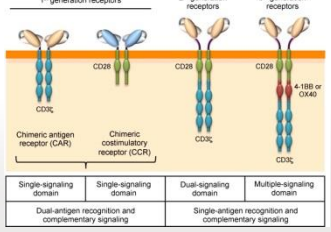
Potency assays for immunotherapy products will be based on complex immune mechanisms which are often **poorly or incompletely understood** and which may be complicated by multi-antigen formulations and **inherent variability of the starting material**.

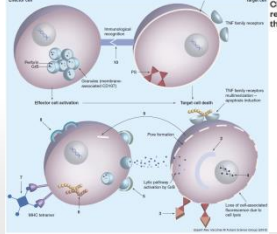
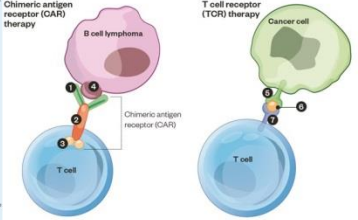
To **assure a consistent functional activity** of the medicinal product in the recipient, the potency of the product **within justified limits** should be demonstrated by a bioassay based on a defined biological effect as close as possible to the **mechanism(s) of action/clinical response**


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/CHMP/BWP/271475/2006 rev.1
Committee for medicinal products for human use (CHMP)

Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer

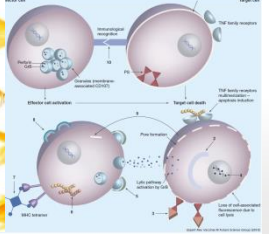


Challenges for Potency tests of Cell Based Products

- Functionality should be demonstrated
- Viability and cell markers not sufficient
- Often exact Mode of Action not fully known
- Often ≥ 1 suspected/suggested MoA
- Sometimes *in vitro* assay does not correlate with *in vivo* situation
- Animal results not necessarily representative for human
- (Semi-)Quantitative
- Release assay based on surrogates due to practical limitations (time, sample size)



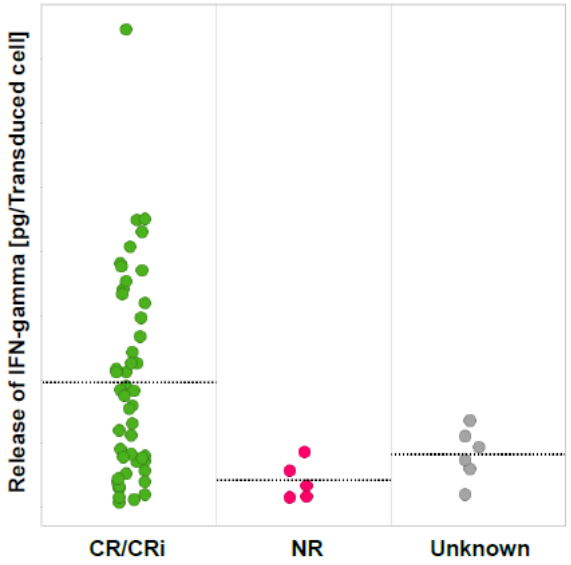


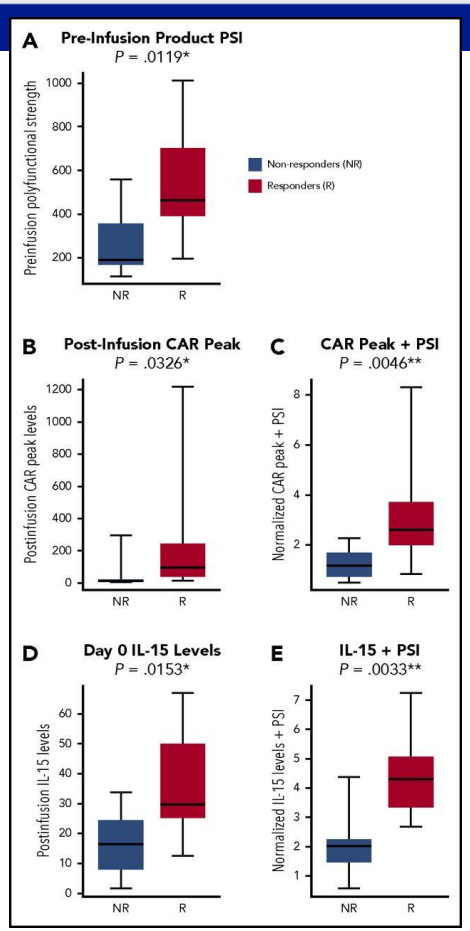
Considerations for (CAR-)T cell potency tests

- Anticipated MoA involves tumour recognition & cell death
- Potency assays based on cytotoxic potential of antigen-specific T cells are most evident
- Biological relevance & correlation with in vivo functionality need to be substantiated with sufficient product-specific (non-)clinical data.
- Can detect clinically relevant defects & sub-potent batches
- How to set specifications?
- Avoid rejection of good batches
- Link clinical data/outcome and potency test
- Establish correlation with clinical response based on potency characterisation studies of **clinical batches**

Correlation potency and clinical response

Response vs product in vitro potency Study B2202





Rossi, Blood 2018

https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM567385.pdf

Clinical considerations for ATMPs

- B/R treated the same as for other products
- Long term effects (Safety & Efficacy)
  - Efficacy: how long will the cells be around and prevent recurrence
  - Safety: e.g. Insertional mutagenesis
- Patient numbers
  - Promising/breakthrough products
  - Historical data
  - Complexity patient group
- Patient survival during manufacture
  - ITT Intention to treat (basis for B/R)
  - Modified ITT (actually treated)
- Clinical trial requirements (CT regulation)

Early Access Tools & Agency Support

- PRIME (Priority medicines); Support during development
- Accelerated Assessment (150 d assessment)
- Conditional MA (less complete clinical data)
- Scientific Advice (also with HTA)
- EMA Website https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies-research-development
- NL: Collaboration MEB, Inspectorate, GMO office, CCMO