Advanced Therapy Medicinal Products

Hospital pharmacists involved in ATMP and in Risk Assessment

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Conflict of interest

- Nothing to disclose

Radboud university medical center

- Bench to bedside
- ATMP cleanroom: celltherapy medicinal products
  - GMP suite 120 m^2
  - 2x class B-rooms (each: 2 LAF-units)
  - QC labs
  - QP, QA, operators, translational scientists

Self assessment questions

1. Should you collaborate with a biosafety officer when organising the reconstitution of a gene therapy medicinal product?

2. Is your pharmacy equipped for receipt and storage of cryopreserved cell therapy medicinal products?

3. Does the production of ATMPs have to comply with Vol. 4 GMP, Part I?

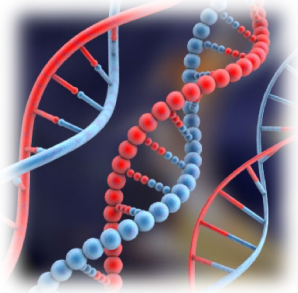
Learning objectives

1. Describe the scope of ATMP regulations
2. Outline the challenges of ATMPs for hospital pharmacists
3. Make out opportunities and threats of ATMPs
4. Anticipate future research and development as related to ATMPs

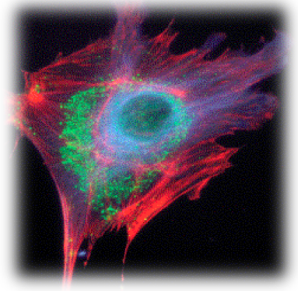
Regulations **Challenges** **Development**

ATMPs: biological medicines

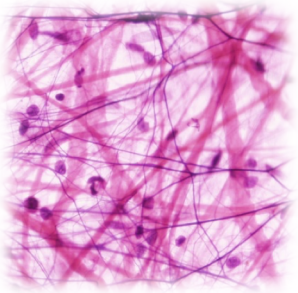
1. **Gene therapy**
   GTMP



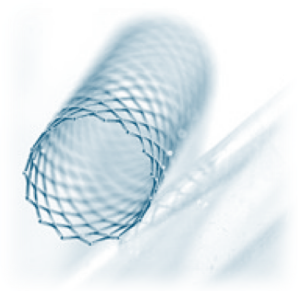
2. **Cell therapy**
   C*TMP*



3. **Tissue engineered product**
   TEP



4. **Combined ATMPs**



EMA reflection paper on classification of ATMPs; 21 May 2015

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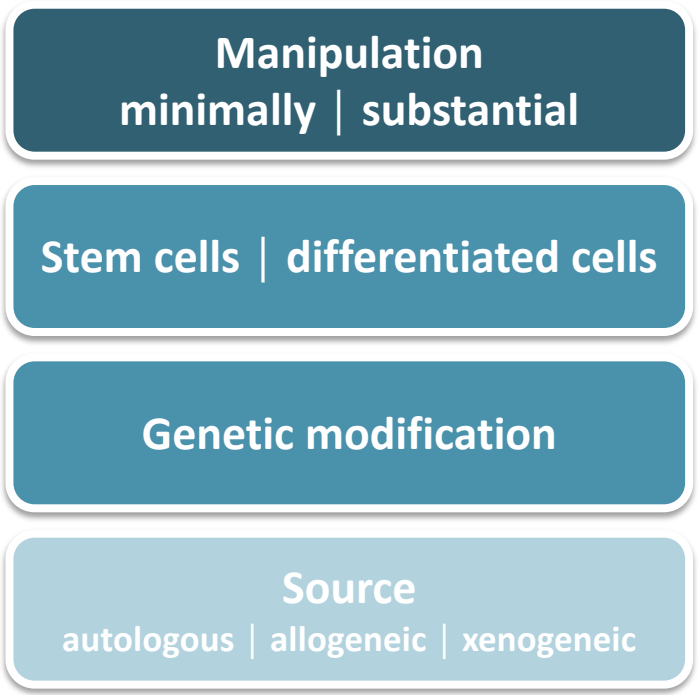
Cell based

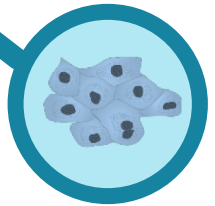
- Hematopoietic stem cells (HSC)
- Dendritic cells (DC)
- T cells
- NK cells
- Chondrocytes
- Mesenchymal stromal cells (MSC)
- Embryonic stem cells (ESC)
- Induced pluripotent stem cells (iPS)



Complexity

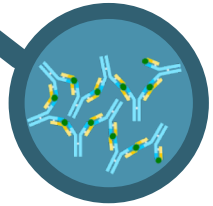
ATMPs

Transfer of cells, tissue or genetic material



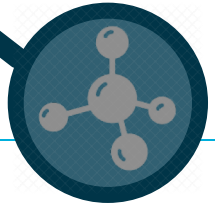
Biologics

Protein engineering



Small Molecules

Chemical engineering



How applied?

- Licensed products
  - Centrally regulated
- Clinical trials
  - As a manufacturer
    - For ATMPs, mainly academic-based manufacturing
  - As a site in a clinical trial
- Unlicensed medicines
  - Non-routine manufacture (hospital exemption)

ATMPs with marketing authorisation

Chondro Celect	TEP	Autologous cartilage cells expanded ex vivo expressing specific marker proteins	Cartilage defects of the knee	2009	With-drawn
Glybera *Alipogene tiparvovec*	GTMP	LPL-gene in AAV vector	Familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks	2012	With-drawn
MACI	TEP	Collagen matrix with autologous cultured chondrocytes	Cartilage defects of the knee	2013	Suspen ded
Provenge *Sipuleucel-T*	CTMP	Autologous PBMNs activated with GM-CSF	Prostate cancer	2013	Suspen ded

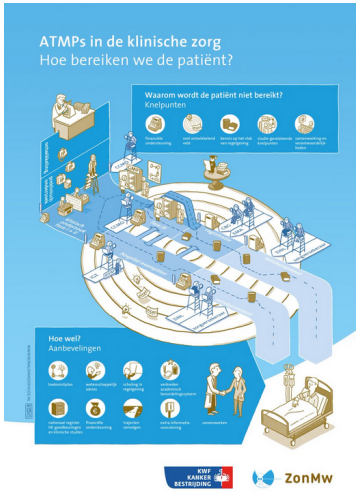
ATMPs with marketing authorisation

Holoclar	TEP	Autolgous ex vivo expanded corneal epithelial cells containing stem cells	Limbal stem cell deficiency due to ocular burns	2015
Imlygic *Talimogene laherparepvec*	GTMP	Attenuated HSV with GM-CSF gene	Unresectable melanoma stage III/IV	2015
Strimvelis	GTMP	Autologous CD34+ cells expressing adenosine deaminase gene	Severe Combined Immunodeficiency (ADA-SCID)	2016
Zalmoxis	GTMP	Allogeneic T cells expressing truncated nerve growth factor receptor and HSV-TK	Adjunctive treatment in haplo-HSCT patients with high risk of hematological malignancies	2016
Alofisel *Darvadstrocel*	CTMP	Expanded, immunoregulatory adipose stem cells	Treatment of complex perianal fistulas in Crohn's disease	2017 pos opinion
Kymriah *Tisagenlecleucel*	GTMP	CAR-T cells CD19	B-cell lymphoma, ALL	2018 submitted

Clinical trials

- Clinical trials, especially first-in-human studies are mostly academia initiated and sponsored
  - Level of knowledge of regulatory requirements
  - How to meet data requirements and quality standards for bridging the product to the clinic?

- Planned: EMA Guideline on Investigational ATMPs



Hospital exemption

- Exemption for ATMPs from the centralised marketing procedure, not for clinical research

- Unlicensed medicine to meet special needs of individual patients
- Individual prescription
- Small scale production, non-routine basis
- Prepared and used in the same member state
- Used in a hospital
- Must comply with principles of GMP

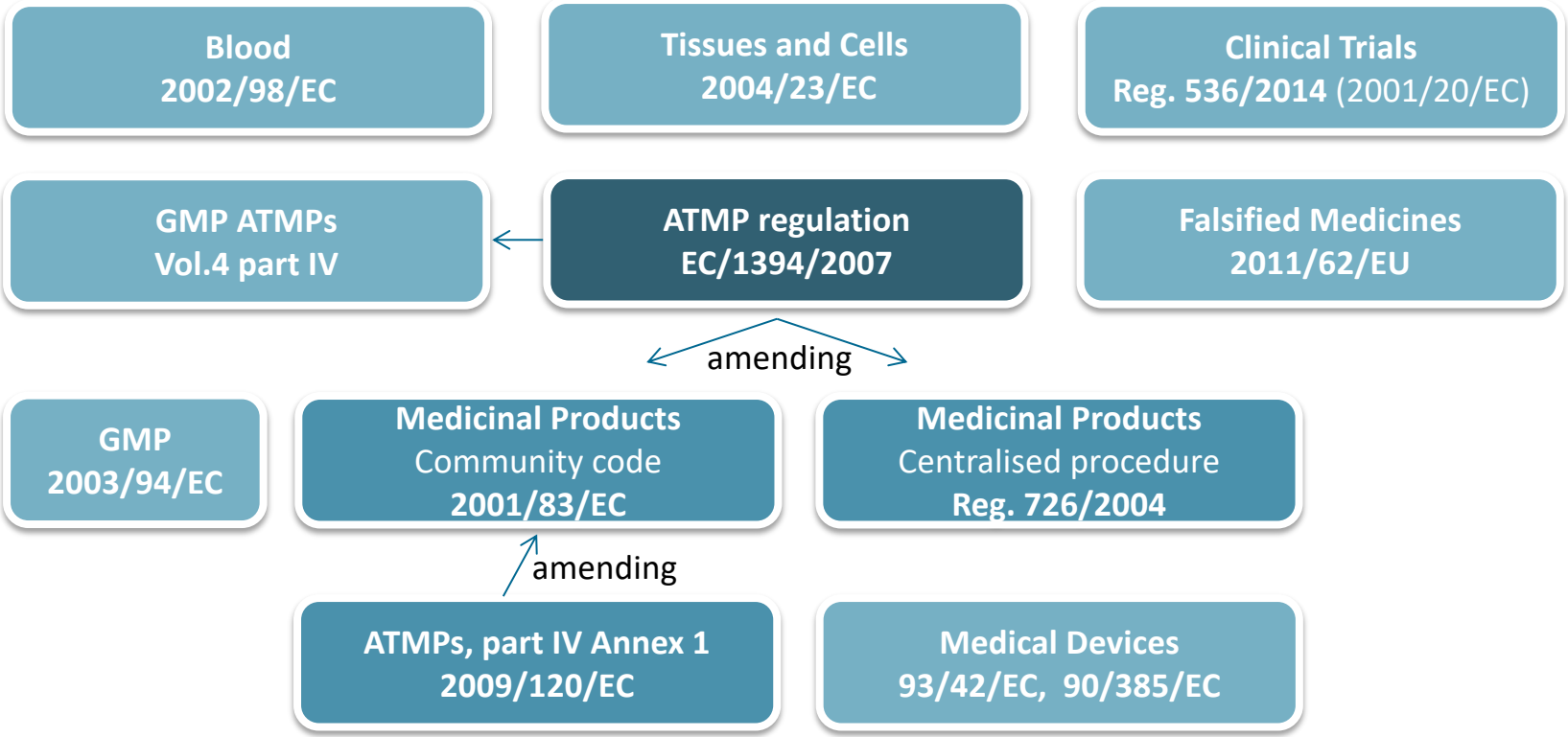
- Implementation in the EU
- Patient access
- Clinical data requirements
- Reimbursement

Regulations

Challenges

Art. 28(2) of regulation 1394/2007

EU regulatory framework



EU guidance

- **Guideline on cell-based medicinal products**
- **Guideline Risk-based approach**
- **ICH / EMA guidelines safety, quality, efficacy**
- **Quality, preclinical and clinical aspects of GTMP**
- **Disease specific guidelines**
- **Ph. Eur. monographs**
  2.6.1, 2.6.21, 2.6.27, 2.6.7, 2.6.14, 2.7.23, 2.7.24, 2.7.28, 2.7.29, 5.1.6, 5.2.12
- **TSE/BSE, bovine serum, porcine trypsin**

GMP ATMPs

- 1394/2007 art.5
- Scope: ATMP with MA as well as ATMP being tested or used as reference in clinical trials.

- Two consultation documents issued
- Stakeholders and PIC/s not in favour of a stand-alone document
- 22 November 2017: Vol.4 part IV GMP ATMPs adopted by EC
- ATMP manufacturers should comply no later than 22 May 2018

GMP ATMPs

- Stand-alone document: includes all topics with relation to ATMPs normally covered in GMP and annexes

- Risk based approach
- Personnel
- Premises
- Equipment
- Documentation
- Starting / raw materials
- Seed lot and cell bank systems
- Production
- Qualification and validation
- QP and batch release
- Quality Control
- Quality defects and recalls
- Reconstitution

GMP ATMPs

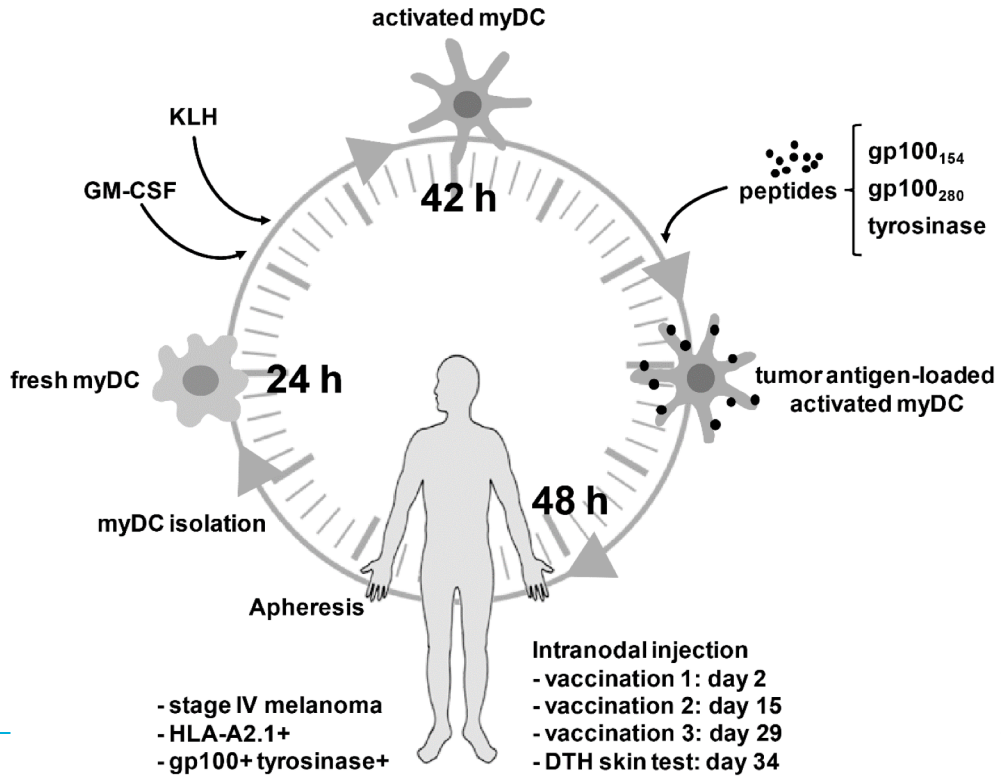
Investigational ATMPs

- May be produced in a class-A area with a surrounding C-class area.
- Routine activities such as self-inspection, calibration, and so forth may be performed at "appropriate intervals", based on risk analysis.
- The level/detail of documentation may be adapted to the stage of development.
- Wider acceptance criteria may be applied in very early phases of clinical development.

Genetically modified organisms

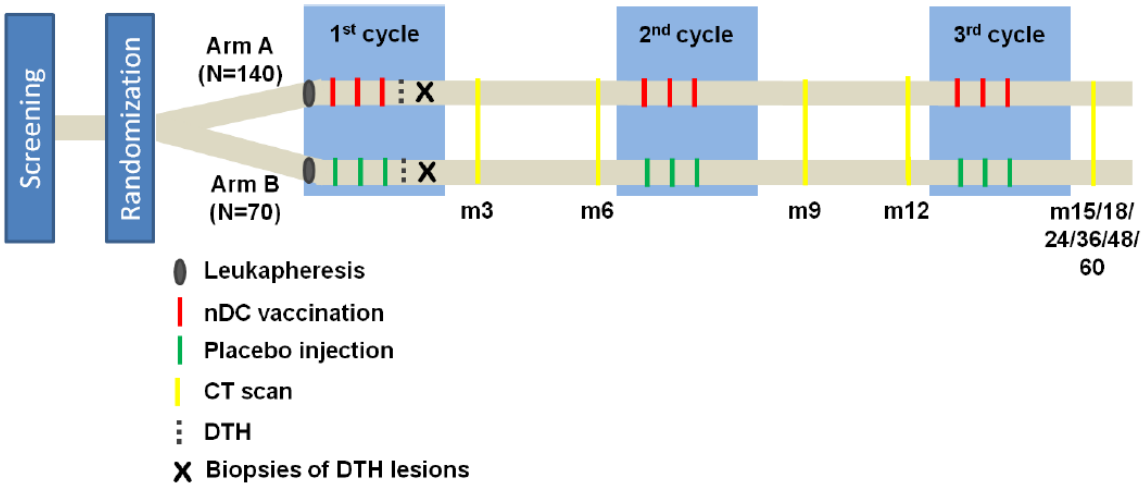
- Appointment of Person Responsible for Biosafety

Manufacturing of a CTMP



Treatment schedule nDC melanoma

- Placebo-controlled: 2:1 nDCs : placebo
- Immune monitoring by skintest
- Conditionally reimbursed



Production process

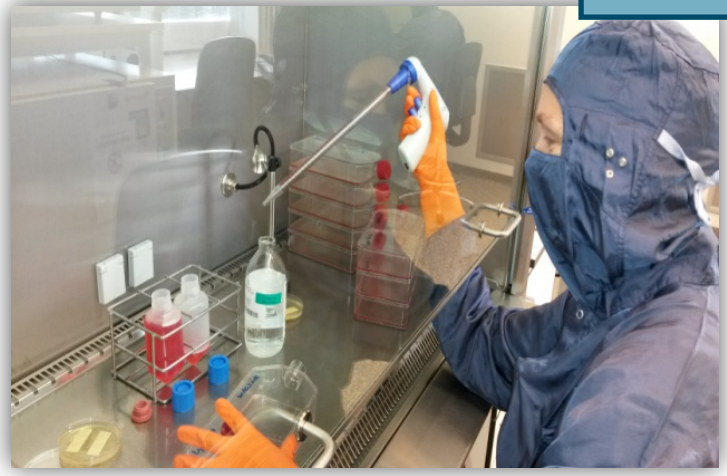
- Difficult to standardise
  - Open systems
  - Long duration
  - Many interventions / preparatory activities
- Cells: dependent and reactive to environment, are fragile
- Autologous products or patient-specific, small batches
- Filtration / sterilisation not possible
- Biosafety and environmental issues
- Rapidly evolving field

  → danger of continuous process modification

Challenges

Equipment

- Open vs fully closed
- Automation
  - Reduce manufacturing variabilities
  - Increase throughput
  - How to integrate in the process, how to connect?
- Biocompatability of materials of disposables
- Extractables / leachables

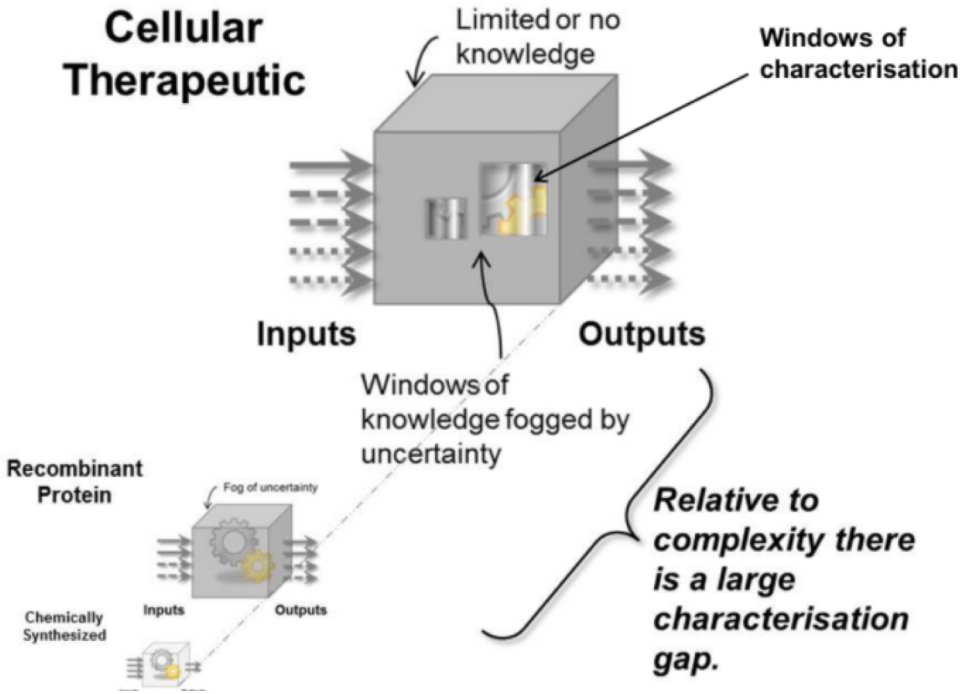


Raw materials and excipients

- Starting material: procurement
- Raw / ancillary materials
- GMP-compliant reagents for manufacturing are rarely available
- Control strategies to assure quality
  - Risk assessment to understand impact of raw material on quality of endproduct
  - Production within recognized quality system, qualified production facilities

Ph.Eur. 5.2.12 “raw materials of biological origin for the production of cell-based and gene therapy medicinal products”

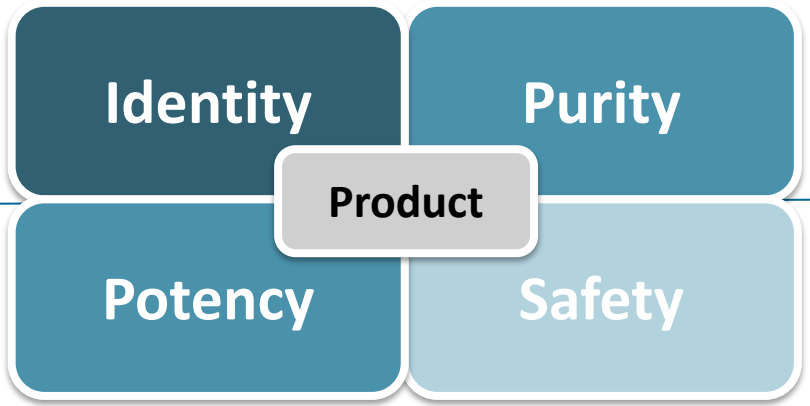
Quality Control



Challenges

Quality Control

Surface marker
DNA fingerprint
Species
Morphology
Biochemical marker



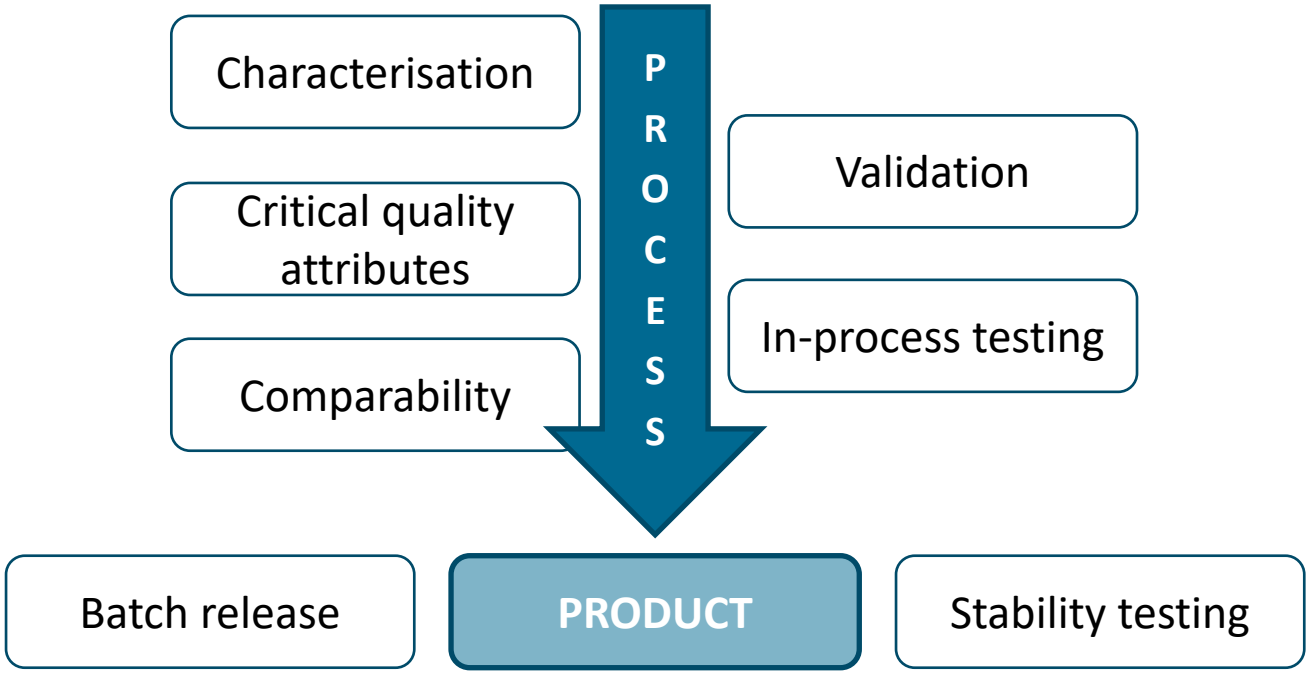
Surface marker
Viability
Transduction efficiency
Transgene expression
Process contaminants

Viability
Titer
Bioassays
Target cell lysis
Cell activation
Colony formation
Transgene expression

Stability: real time, closure integrity, leachables. → may be product exhausting

Sterility
Mycoplasma
Endotoxins
Cellular impurities
Adventitious virus
Residual virus
Viral replication competency
Tumorigenicity
Immunogenicity
Engraftment

Quality development



EMA. Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials (EMA/CHMP/BWP/534898/2008)

Validation

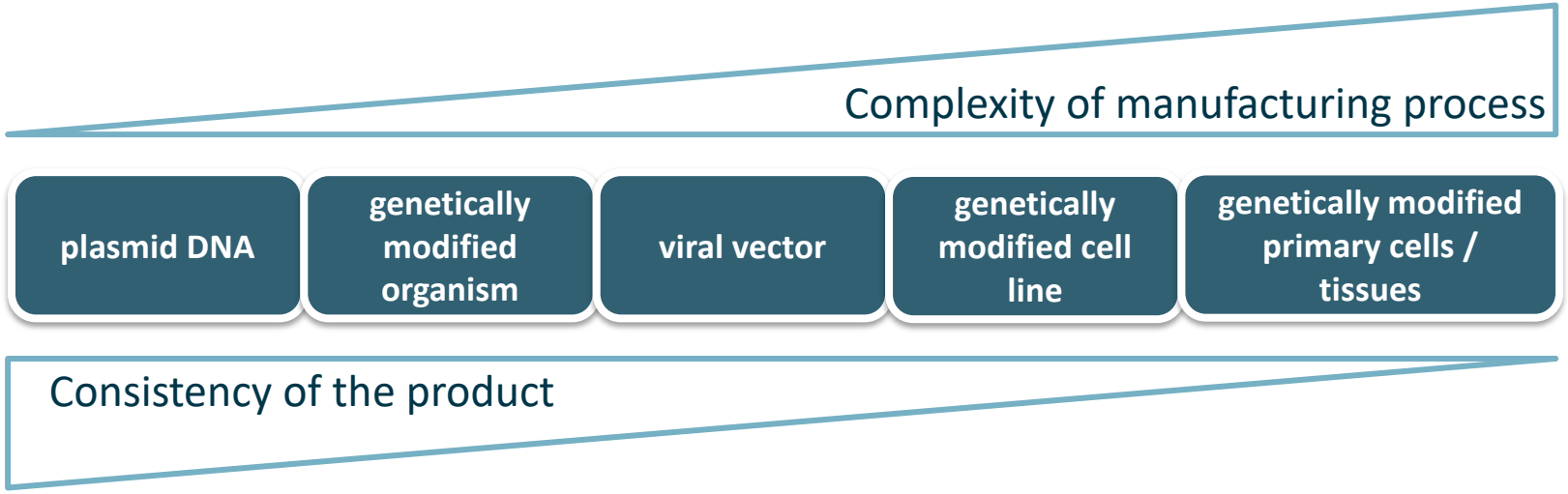
Process validation

- Demonstration that process ensures consistent production
- Key items of equipment must be qualified (risk-based approach)
- Sterilisation processes must be validated
- Aseptic process must be validated (media fills)

Validation of test methods

- Sterility tests must be validated
- Potency assays should be validated throughout clinical development
- Other tests must be shown suitable for intended purpose

Validation


Complexity of manufacturing process
plasmid DNA
genetically modified organism
viral vector
genetically modified cell line
genetically modified primary cells / tissues
Consistency of the product

Batch release

- Short shelf life
- Variability of starting material, quality of raw materials, variability of the production proces → higher level OOS-results, deviations expected?
- Impact of OOS-results and deviations difficult to evaluate because effect on product quality often not clearly understood
- Involvement in manufacturing and quality operations

Challenges

Transport, receipt

- Fragility
- Short shelf life
- Sensitity to changes in temperature, light, vibration, pH shifts
- Qualification of shipping contractor

Storage

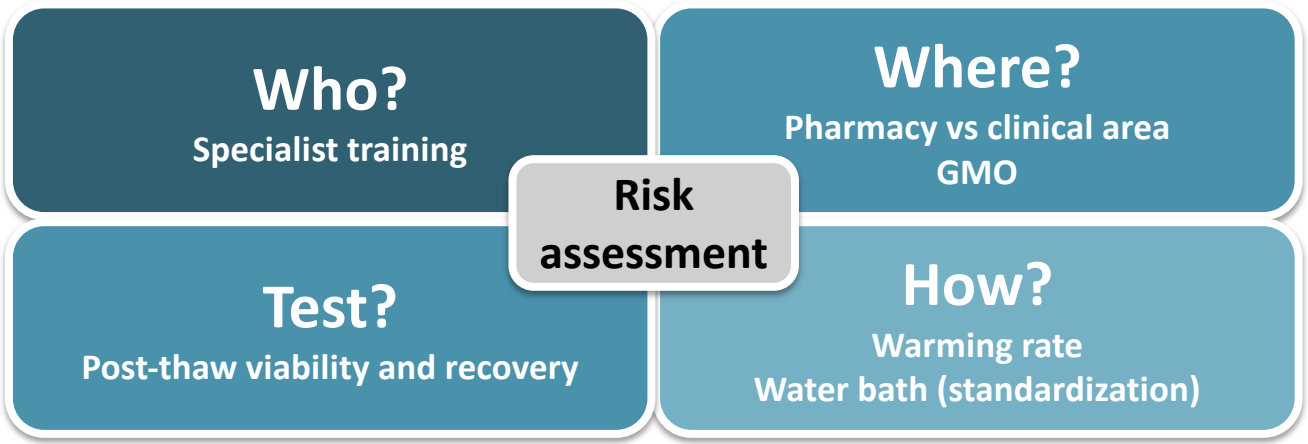
- Validated and monitored -80 °C, -150 °C, LN2, dryshippers
- Trained to deal with this equipment and its hazards?

Challenges

Reconstitution GMP ATMPs Ch. 16

- Activities required after batch release and prior to administration and which cannot be considered a manufacturing step. → EDQM: activities in accordance with SmPC.
- Thawing, washing, buffer exchange, centrifugation steps, removal of process related impurities
- (Re)suspension, dissolution or dilution
- Mixing with patient's own cells, adjuvant, other substances.
- Aliquoting, adaptation of dose
- Loading into delivery system / surgical device
- **Never** reconstitution: substantial manipulation, mixing gene vector with cells
- Must be carried out at administration site, *i.e.* cannot be outsourced to a non-GMP third party

Reconstitution



Challenges Development

Administration

- Register batch numbers

- GMO
  - Introduction into environment
  - Containment
  - Waste
    - Disposables
    - Excreta
  - Desinfection

  → biosafety professional

Role of the pharmacist

- Responsible and accountable for preparation, supply and use of ATMPs
- Hospital pharmacist must ensure that:
  - ATMPs used are of appropriate quality for intended use,
  - Robust governance is in place for the introduction of ATMPs,
  - Staff with appropriate skills and expertise undertake handling en processing of ATMPs, and
  - Appropriate technical and pharmaceutical advice is available.

Threats – academic research

- Science-driven instead of product-driven
  - Progress from exploratory studies to standard patient care

    → draft target product profile
  - GMP-facilities do not aim at MA production/compliance

    → regulatory expertise
- Limited funding
  - How can early investment made by hospital sites / academia into ATMPs be returned within pricing and reimbursement
- Unrealistic timelines

S. de Wilde et al. Drug Discovery Today 2016

Threats – Hospital Pharmacist

- Expertise, training not present in pharmacy
- Required equipment for storage and handling not available in pharmacy
- Limited guidance for engagement in reconstitution

Opportunities - academic research

- Excellent translational research programs
- Core-facilities operational for procurement, processing and storage of human cells and tissues
- Decentralized production in (small) academic GMP-compliant facilities
- Reagents for manufacturing (raw materials)
- Exchange of SOPs and reagents

Opportunities – Hospital Pharmacist

- Take responsibility for the safe use of ATMPs
- Use disease specific expertise
- Use quality-assurance expertise for risk-assessment
- Form multidisciplinary teams: tissue and cell procurement department, biosafety officer, clinicians
- Increase manufacturing knowhow
- Fill the knowledge gap
- Develop systems for pharmacy oversight

Self assessment questions - answers

1. Should you collaborate with a biosafety officer when organising the reconstitution of a gene therapy medicinal product?

   → Yes.

2. Is your pharmacy equipped for receipt and storage of cryopreserved cell therapy medicinal products?

   …

3. Does the production of ATMPs have to comply with Vol. 4 GMP, Part I?

   → No. Vol. 4 GMP, Part IV: GMP requirements for ATMPs, as of 22-May-2018

Take home messages

1. ATMPs are innovative and complex pharmaceuticals, many are patient specific and developed by academic investigators
2. Hospitals will be part of the supply chain

   → requires dedicated staff, facilities and training
3. Hospital pharmacists are essential components of the healthcare professional team providing patient access to new, safe and effective treatments with ATMPs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