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Requirements on Quality (ATMP)

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Summary

- Briefly about GMP
- Terminology – Starting material/Drug Substance/Drug Product
- CTD format of the dossier
- Relevant guidelines
- Risk-based approach
- Development strategy
- Raw materials‘ grade
- Release testing and certification
- Medical device as a part of ATMP

Briefly about GMP

- **GMP = Good Manufacturing Practice**
- System for ensuring that products are consistently produced and controlled according to quality standards

- Covers all aspects of production from the starting materials, premises, and equipment to the training and personal hygiene of staff, as well as documentation practices (SOPs and record-keeping).

Briefly about GMP

- Discuss the project with the NCA (National Competent Authority)
- Initial inspection → Manufacturing/Import Authorisation for Investigational ATMP

Briefly about GMP

- Authorised GMP facility is needed prior to production of a clinical material.
- EudraLex - The Rules Governing Medicinal Products in the European Union - Volume 4 - Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (GMP for ATMP)
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf

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Briefly about GMP

- Premises and equipment
  - Design and construction (individual areas, clean rooms)
  - Qualification (installation → operational → performance)
- Personnel
  - Responsibilities (Qualified Person)
  - Training, hygiene
- Documentation system (instruction and records)
- Production
  - Starting and raw materials
  - Manufacturing process setting and control
  - Process validation
  - Process deviations and quality defects

Briefly about GMP

Important ATMP specific aspects

- **Tissue and cells as starting material**
  - Donation, procurement and testing - Directive 2004/23/EC (or Directive 2002/98/EC) applies
  - Variability
  - Safety
  - Traceability
- **Multi-product facility**
  - Risk of cross-contamination
- **Terminal sterilisation not possible in the most cases**
  - Aseptic manufacture
- **Risk-based approach**
  - Complexity and technological possibility (autologous non-substantially manipulated cells VS allogeneic substantially manipulated product by using cell stock system)
  - Phase of development

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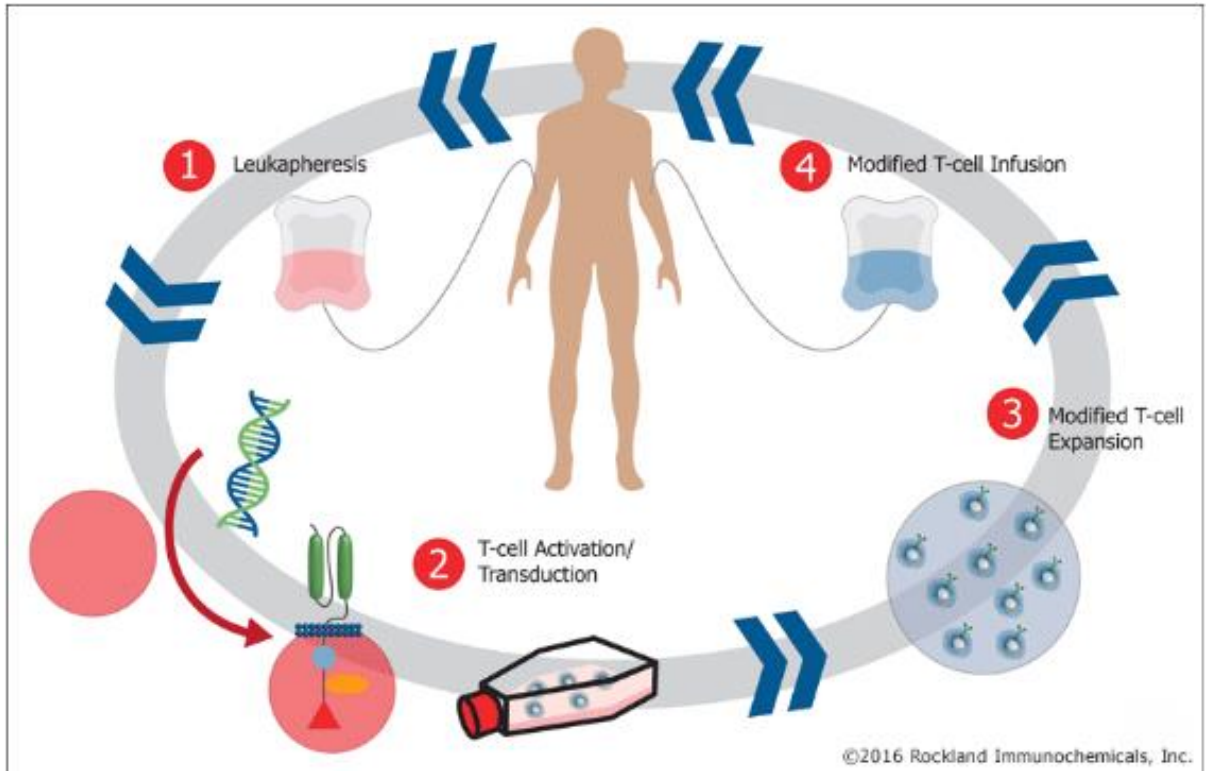
Drug Substance

Active Ingredient

- Engineered cells or tissues
  - Combined with other materials (matrixes...)
- Recombinant nucleic acid and its viral or non-viral vector
- Genetically modified cells

Drug Product
Final Product

- = drug substance with excipients (in its final combination) in the primary container



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Starting material ... „Where does a GMP start?“

- **Cells and tissues** from a tissue establishment

- In case of products consisting of viruses or viral vectors, the starting materials shall be the components from which the viral vector is obtained, i.e. **the master virus vector seed or the plasmids used to transfect the packaging cells and the master cell bank of the packaging cell line**.
- In the case of products consisting of plasmids, non-viral vectors and genetically modified microorganism(s) other than viruses or viral vectors, the starting materials shall be the components used to generate **the producing cell, i.e. the plasmid, the host bacteria and the master cell bank of recombinant microbial cells.**
- In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, **the vector and the human or animal cells**.
- The principles of good manufacturing practice shall apply from the bank system used to produce the vector or the plasmid that are used as starting materials.

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How to present quality data to the regulatory authority?

1) Manufacturing/Import Authorisation for Investigational ATMP

2) Specific product developed (non-clinical batches manufactured)

1) Clinical trial application – **Submission of IMPD (Investigational Medicinal Product Dossier)**

- **quality** (CMC – Chemistry, Manufacturing, and Controls)

CTD format of the dossier

3.2.S DRUG SUBSTANCE

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

3.2.S.1.2 Structure

3.2.S.1.3 General Properties

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

3.2.S.2.2 Description of Manufacturing Process and Process Controls

3.2.S.2.3 Control of Materials

3.2.S.2.4 Controls of Critical Steps and Intermediates

3.2.S.2.5 Process Validation and/or Evaluation

3.2.S.2.6 Manufacturing Process Development

3.2.S.3 Characterisation

3.2.S.3.1 Elucidation of Structure and other Characteristics

3.2.S.3.2 Impurities

CTD format of the dossier

3.2.S.4 Control of Drug Substance
3.2.S.4.1 Specification
3.2.S.4.2 Analytical Procedures
3.2.S.4.3 Validation of Analytical Procedures
3.2.S.4.4 Batch Analyses
3.2.S.4.5 Justification of Specification
3.2.S.5 Reference Standards or Materials
3.2.S.6 Container Closure System
3.2.S.7 Stability
3.2.S.7.1 Stability Summary and Conclusions
3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment
3.2.S.7.3 Stability Data

Continuous process

CTD format of the dossier

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

3.2.P.2.1.2 Excipients

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

3.2.P.2.2.2 Overages

3.2.P.2.2.3 Physicochemical and Biological Properties

3.2.P.2.3 Manufacturing Process Development

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3.2.P.2.5 Microbiological Attributes

3.2.P.2.6 Compatibility

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CTD format of the dossier

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

3.2.A.2 Adventitious Agents Safety Evaluation

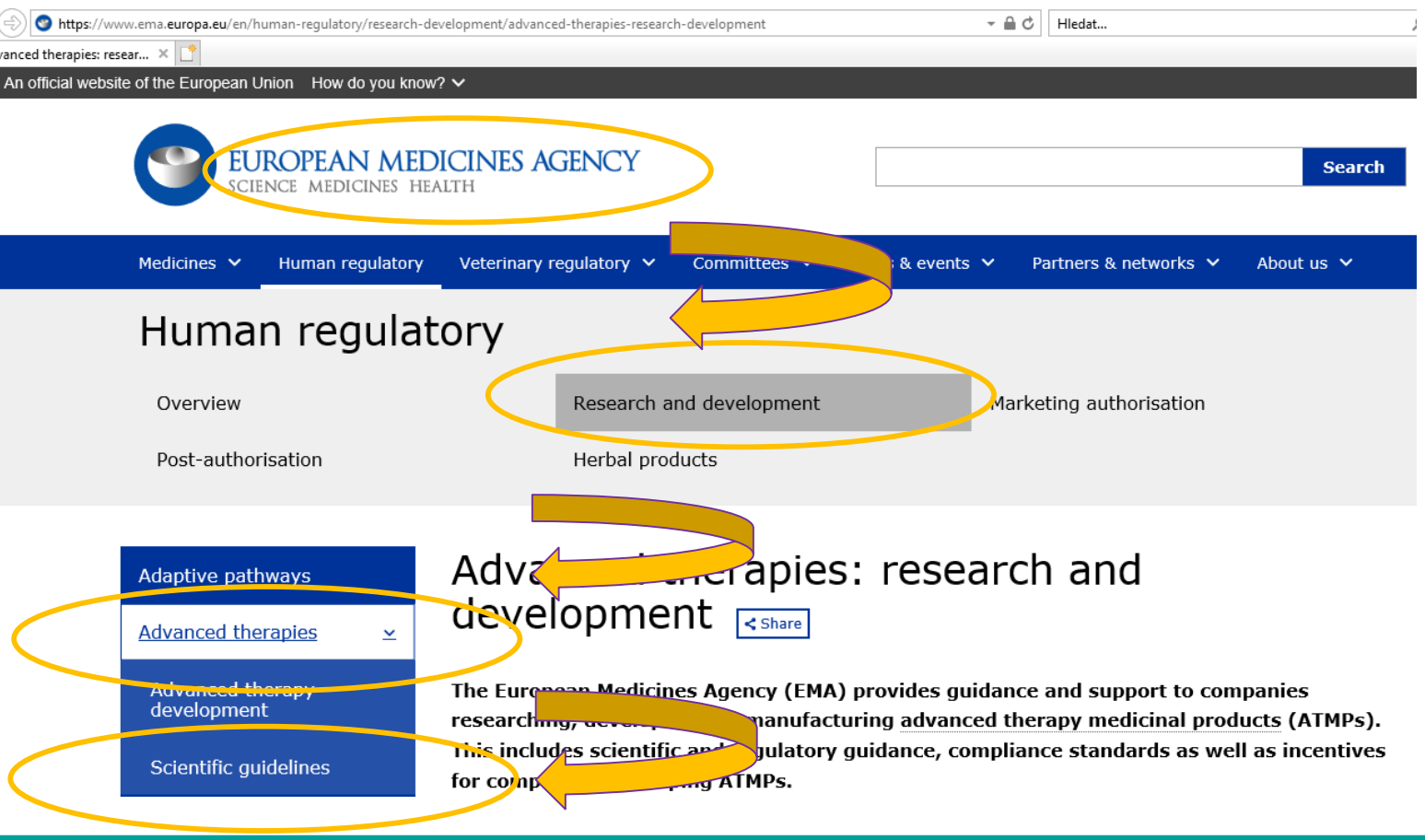
3.2.A.3 Excipients

3.2.R REGIONAL INFORMATION

3.3 LITERATURE REFERENCES

Relevant guidelines

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



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Relevant guidelines

- **Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials EMA/CAT/852602/2018 (draft – closed public consultation)**
- Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)
- Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014)
- Raw materials derived from animal- or human-derived material (blood):
  - Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01)
  - Ph. Eur. 5.2.12 and Ph. Eur. 5.1.7
  - Guideline on 1253 Plasma-Derived Medicinal Products (EMA/CHMP/BWP/706271/2010)
- European Pharmacopoeia
  - 5.2.12 Raw materials for the production of cell-based and gene therapy medicinal products
  - 2.6.27 Microbiological control of cellular products
  - 2.6.1. Sterility
  - … etc.

Risk-based approach

- Identification of risks and associated risk factors
- Development (and amount of presented data) is adjusted to the specific profile of these risks

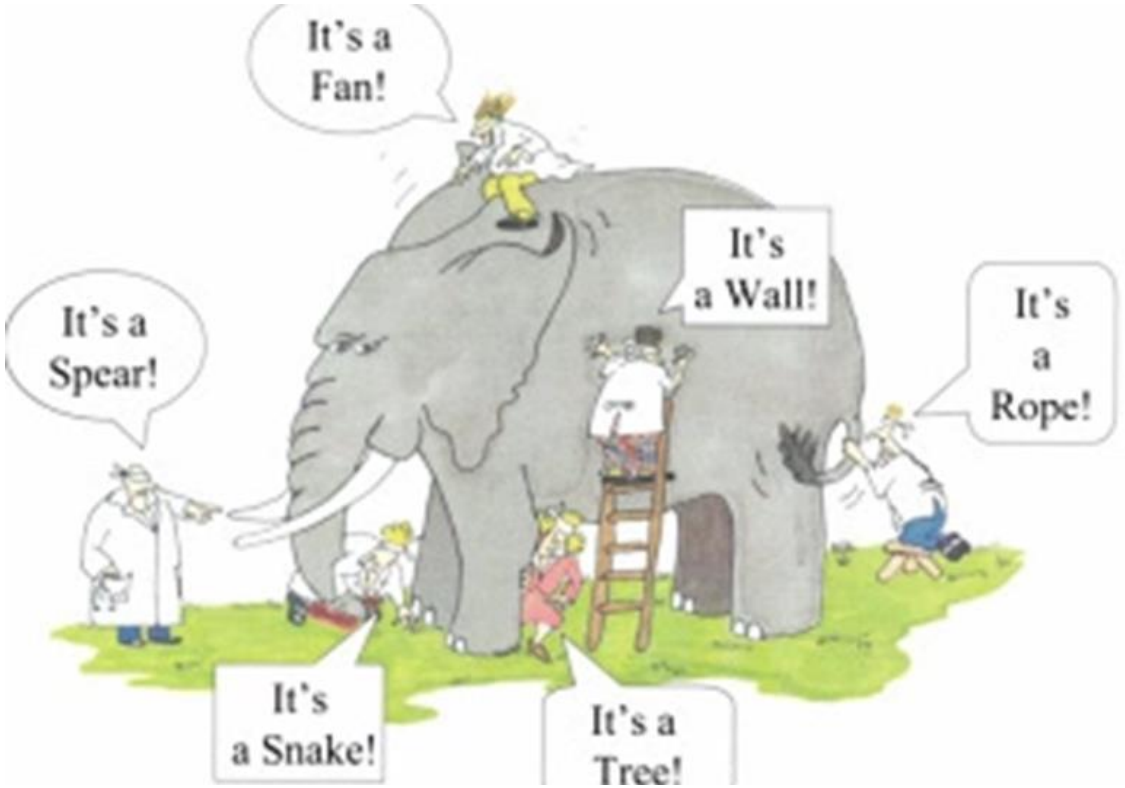
unfavourable effect attributed to the clinical use of ATMP and of concern to the patient and/or to other populations

- Risks caused by character of the starting and raw materials, by level of manipulation during the manufacturing process, by control strategy, by level of manipulation prior to administration, by level of knowledge of the product itself.

Risk-based approach

Risk profiling

- Critical and multi-disciplinary view is needed.
- Evaluation of critical quality attributes. What is critical parameter and what is irrelevant?
- Amended during the development.
- Safety of the patient is a priority.



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3.2.S.1 General information

- Description of the active substance
  - Cell composition (their phenotype)
  - Description of gene construct and individual sequences
  - Mechanism of action, rationale for using the specific strategy

CTD format of the dossier

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3.2.S.2 Manufacture

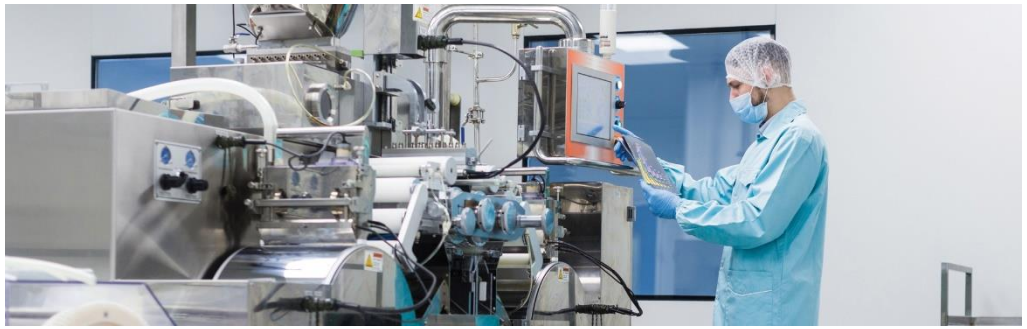
- Detail description of the process and its control
  - Clearly defined limits/conditions
    - Process parameters and in-process controls
  - Holding times, transport

- Microbiological safety
- Process variability
- Cell purity/viability
- Virus replication

Alternative approach?

Critical parameter?

ATMP Manufacture



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Manufacturing process – ATMP's specificity

- Variability of the starting materials
- Direct effect of raw materials on quality and safety of the final product
- Limitations with regards to sterilisation or viral inactivation steps
- Aseptic production
- Limited amount of material (including ethic aspect)
- One product = one batch

Starting materials

- Tissue and cells – donation, procurement and testing under Directives 2004/23/EC and 2002/98/EC
  - Donor testing – additional serological tests?
  - Standardised procedures
- Cell banks/ cell stocks
  - In accordance with principles of ICH guideline Q5D
  - Testing – identity, virus safety, genetic stability
  - Capacity?
- Vectors
  - Detailed description of development
  - Genetic identity and integrity
  - Safety

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Quality grade of raw materials

Raw material	Step	Function	Origin	Quality
Saline, 0.9%	2	Diluent in cell processing	Chemical	Approved medicinal product 76/ 172/03-C
Isolymph	2	Separation medium in density gradient centrifugation used to isolate mononuclear cell fraction	Chemical	Research grade
Recombinant Epidermal Growth Factor, 10 µg/mL	3 to 9	Supplement in culture medium	Recombinant using microbial production cells	GMP grade
Fetal Bovine Serum (FBS)	3 to 9	Neutralizes enzymatic activity of Trypsin	Bovine	CoA + virus safety declaration + CEP
Dimethyl sulphoxide (DMSO)	7, 12	Constituent cryopreservation of medium	Chemical	USP

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Quality grade of raw materials

- Ph.Eur. 5.2.12 Raw materials for the production of cell based and gene therapy medicinal products
- Ph. Eur. 5.1.7 Viral safety

- Materials derived from human plasma
  - Requarements the same as for plasma used as medicinal product
  - Traceability – from donor to recipient and vice versa (aggreement)
  - Pooling – limitations of human donors (16 per product?)
- Bovine materials - CEP … Certificates of Suitability (CEPs) issued by EDQM (European Directorate for the Quality of Medicines & Health)
- – database https://extranet.edqm.eu/publications/recherches_CEP.shtml

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https://extranet.edqm.eu/publications/recherches_CEP.shtml

EP 5.2.12 - Hledat Googlem | Certificates catalogue

Search Database online | Certification

edqm

- You can search the certification database by:

  - Name of the certified substance or
  - Monograph number or
  - Holder of the certificate or
  - Certificate number or
  - Issue date of certificate or
  - Expiry date of certificate
  - Status of the certificate

- The substance name is equal to the monograph name and the subtitle for chemical, herbal and double certificates and is the substance name for TSE certificates

If you are interested in all types of certificates , please select the button beside "all". If you are only interested in TSE or herbal certificates, please select the button beside your required choice and only TSE or herbal certificates will be displayed as a result of your choice.

Search a [Substance Name]

that [Contains]

foetal

Search | Clear

○ all
◉ TSE Only
○ Herbal Only

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Research grade

- Manufacturer/vendor waives responsibility for clinical usage of their product
- ATMP manufcaturer is responsible for quality of used materials

GMP-grade

- Not sufficient claim
- What does it ensure?

Raw materials

What is its source and related risks with respect to microbial, viral and TSE/BSE safety?

Ask for maximum information from the manufacturer/vendor. Include inactivation steps, if possible.

How is it tested (parameters, methods, criteria)?

Own release testing prior its usage.

What should ATMP manufacturer know?

Is the manufacturer/vendor reliable?

Inspection at the site of its manufacture.

Does an alternative material exist?

Market monitoring.

Is there a risk of its shortage or changes in production?

Agreement with the vendor.

Process validation

- Process validation is not required
  - Except validation of aseptic processing (media-fill)
  - Except validation of viral inactivation steps
  - Except specific situation of ATMP
    - Usage of processes with limited in-process controls
    - Usage of model systems (scale-down, alternative material)

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Process development

- Manufacturing site/process/analytical methods
- Describe clearly:
  - Which modification was introduced and why?
  - Since which date/batch number is it applicable?
  - What is its potential effect on quality, safety, potency?
    - Are validation data still relevant?
- Was comparability evaluated?

Process development – comparability study

- Changes require prior approval (substantial amendment)

- Comparability study
  - Comparison of process parameters
  - Comparison of produced material
    - Characterization methods, release data, stability data
  - Side-by-side analysis and split samples when possible
- Extent of studies depends on introduced change, phase of development and technical/ethical possibilities
  - Non-clinical/clinical data may be needed

https://parexel-academy.com

The more reflective CQAs are of clinical outcome, the easier it is to establish the product comparability

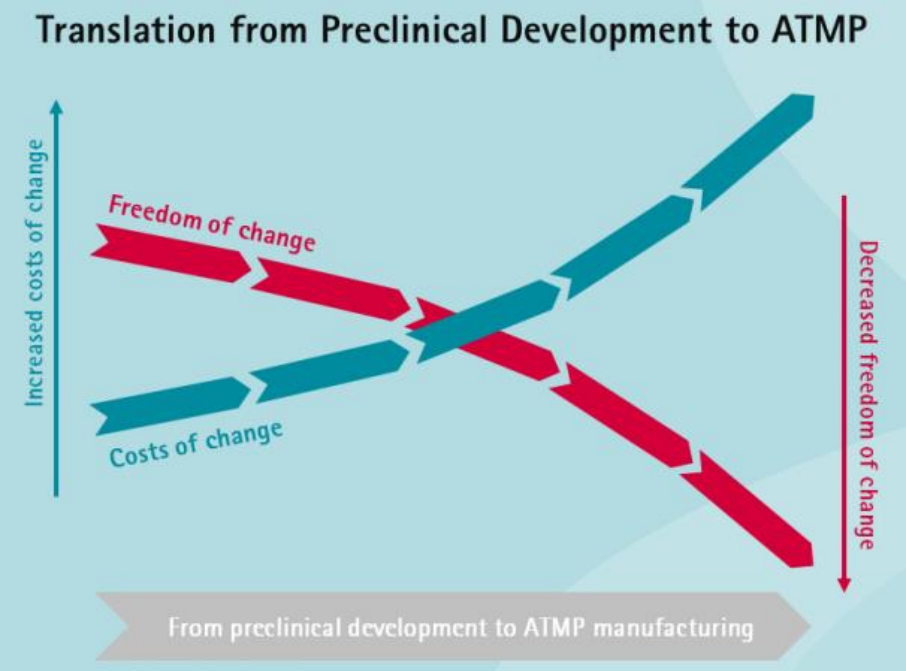
Process development

- Demonstration of needed level of comparability
  - Improvement or change?
  - Relevancy of previously obtained data?

Critical steps:

- **Toxicity studies and dose definition → FIM**
- **Pivotal CT→ registration**

Planning – crucial for success of the whole development



zdroj: https://cellgenix.com

Manufacture – automatic processes

- Specific model of „closed“ systems for production
- Approval of the production machine (CE mark for medical devices) does not mean approval of the ATMP manufacture
- Need to demonstrate safety of used materials and suitability of the process – responsibility of the ATMP manufacturer

- **Advantage:** consistency of the production, possibility of manufacture close to the patient (in time and place)
- **Disadvantage:** limited possibility for process control and optimalization, risk for loss of consistent control (decentralization)

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3.2.S.3.2 Impurities

3.2.S.3 Characterisation

- Detailed description of the active ingredient → **identity**
- Expected mechanism of action, biological activity → **potency**

- Product- and process-related impurities
  - undesirable cell types, residuals of culture media, used antibodies, endotoxins …
- Parameters evaluating potential instability of the material
  - such as differentiation status or tumourigenicity for cells and sequence integrity, transduction efficacy or particle to infectivity ratio for gene therapies
- Non-cellular components
- **The manufacturer´s own results of characterization studies**
  - number of used batches, used analytical methods, results and their discussion

3.2.S.3 Characterisation

- Characterization methods
  - Basis for release testing strategy
  - Necessary for demonstration of comparability

CTD format of the dossier

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

3.2.P.2.1.2 Excipients

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3.2.P.2.2.3 Physicochemical and Biological Properties

3.2.P.2.3 Manufacturing Process Development

3.2.P.2.4 Container Closure System

3.2.P.2.5 Microbiological Attributes

3.2.P.2.6 Compatibility

3.2.P.1 Description and Composition of the Drug Product

- Quantitative amount of active ingredient(s) and excipients
- Route of administration?
- Manipulation prior to administration?
  - In agreement with information for invetigator/pharmacy manual
  - Medical device needed?

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3.2.P.2 Pharmaceutical Development

- Include everything (usually sufficient in summary)
  - with regards to phase of development
- Formulation development (FBS, DMSO …)
- Manufacturing process development
  - Manufacturing site/ manufacturing process/ analytical methods / storage conditions

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3.2.P.5 Control of Drug Product

Specifications = defined list of cotrols performed routinely at the time of product release (and stability)

1. Identify parameters that assures the quality
   (incl. safety and potency)
2. Select a suitable analytical method
3. Propose acceptance criteria based on:
   a) Characterization and development studies
   b) Available results (release and stability)

3.2.P.5 Control of Drug Product

Parameter	Analytical method	Acceptance criteria
Appearance, volume	Visual control	Min. 5 ml of yellow suspension without extraneous particles
Cell concentration	Ph. Eur. 2.7.29	2-6 x 10^6 cells/ ml
Identity	Microscopic evaluation	Spheroid cells ….
Purity	Flow cytometry In-house SOP.XX.YY	CD … ≥ 95 % CD … ≥ 95 % CD … ≤ 2 %
Mycoplazma	Ph. Eur. 2.6.21	No contamination
Sterility	Ph. Eur. 2.6.27	Sterile
Potency assay 1*	*In vitro* inhibition of proliferation In-house SOP.XX.YY	More than … when compared to reference standard
Impurities	Flow cytometry In-house SOP.XX.YY	CD … For information only

* … Tested on intermediate at day 8.

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3.2.P.5 Control of Drug Product

- Description of analytical methods
- Confirmation of their suitability
  - Basic validation parameters (specificity, accuracy, linearity, limit of detection …)
  - Usage of negative and positive samples
- Check for relevant pharmacopoeial monographs

3.2.P.5 Control of Drug Product

- Possible specific situation (described in GMP for ATMP):
  - Batch release prior to obtaining the results of quality control tests
  - Administration of the product with results out of specifications

Risk of analysis

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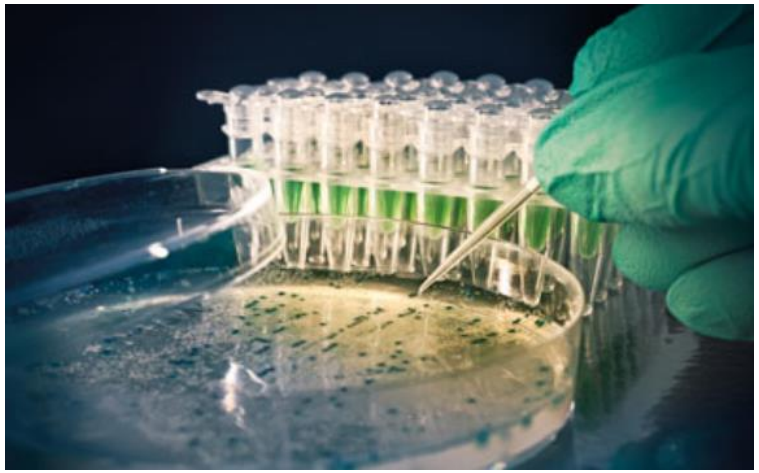
Batch release prior to obtaining the results of quality control tests

- Justification, why different strategy is not possible
  - Stability data, patient conditions
- Justification, why this strategy is possible
  - Risk evaluation, supportive validation data

- Action when results are outside of the acceptance criteria?

Sterility testing

- Ph. Eur. 2.6.1 Sterility



- Ph. Eur. 2.6.27 Microbial examination of cell-based preparations

- General monograph... Ph. Eur. 5.1.6 Alternative methods for control of microbiological quality

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Ph. Eur. 2.6.27 Microbial examination of cell-based preparations

- Test suitability for the specific sample/matrix
- Growth promotion test of culture media

- A “negative-to-date” result as a release parameter?
  - Justification
  - Consider the control of microbiological safety in a complex view
  - In case of positive result, MO and its sensitivity to antibiotics is identified and the treating physician is contacted immediately

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Administration of the product with results out of specifications

- Exceptionally possible, if the administration of the product is **necessary to avoid an immediate significant** hazard to the patient and taking into account the alternative options for the patient and the risk of losing the cells/tissues contained in the product.
- When the request of the treating physician, the manufacturer **should provide the treating physician** with its evaluation of the risks and notify the physician that the out of specification product is being supplied at his/her request. The confirmation of the treating physician to accept the product should be recorded by the manufacturer. The manufacturer should immediately notify **the sponsor and the sponsor should inform the relevant competent authority**.

How to comunicate this event to the NCA?

What information the NCA wants to collect?

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CTD format of the dossier

3.2.P.5 Control of Drug Product
3.2.P.5.1 Specification(s)
3.2.P.5.2 Analytical Procedures
3.2.P.5.3 Validation of Analytical Procedures
3.2.P.5.4 Batch Analyses
3.2.P.5.5 Characterisation of Impurities
3.2.P.5.6 Justification of Specification(s)
3.2.P.6 Reference Standards or Materials
3.2.P.7 Container Closure System
3.2.P.8 Stability
3.2.P.8.1 Stability Summary and Conclusion
3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment
3.2.P.8.3 Stability Data

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3.2.P.8 Stability

- Confirm stability and obtain information on degradats
- Define conditions and maximum storage time
  (including in-use stability after thawing or reconstitution)

- Usage of surrogate materials?
  (such as cells from healthy donors)
- Suitable panel of methods?
- Sterility at the end of stability testing
- Discussion of results

CTD format of the dossier

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

3.2.A.2 Adventitious Agents Safety Evaluation

3.2.A.3 Excipients

3.2.R REGIONAL INFORMATION

3.3 LITERATURE REFERENCES

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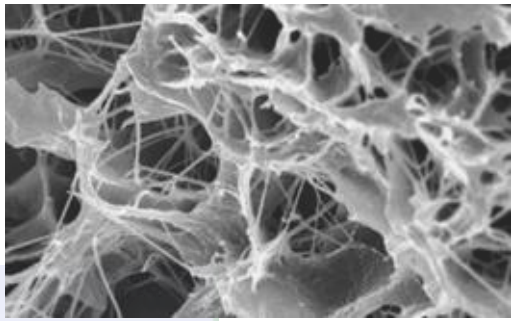
ATMP and medical devices



<u>Information on medical device</u>

… it is a part of the submiited IMPD
Identification, source (manufacturer)
CE mark (yes or no)
Quality control
Compatibility

Medical device is an **integral part of the product**
Medical device is starting material
Included in manufacturing process
Effect: cells (groth, aktivity) ↔ acelllular material (function, integrity)
Medical device used as an **excipient**
Medical device is a **part of the container or administration set**

In-vitro diagnostics
… it is a part of the submitted IMPD
Method has to be validated to be acceptable, for example for patient selection.

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Take home message

- Documentation:
  - Logic presentation
  - Unambiquious
  - In detail

- Risks analysis, planning (be aware of comparability)
- Critical evaluation of your own data, dicussion
- Safety of the patient is a priority
- Early contact with national competent authority (or EMA through ITF meetings or Scientific Advice)

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