Regenerative Medicines Regulation and Quality Control in the EU

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Disclaimer

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Background:
Regenerative Medicines Regulation in the EU
Advanced Therapy Medicinal Products: ATMP Regulation 1394/2007
10 + years of experience in the EU

- Gene Therapy Medicinal Product
- Somatic Cell Therapy Medicinal Product
- Tissue Engineered Product
- + medical device
- Therapeutic genetic sequence
- Substantially manipulated cells with medicinal action
- Engineered cells for regeneration, repairing, replacing
- combined ATMP

EMA:
- ATMPs: Centralised Marketing Authorisation Application mandatory
- Biologicals Working Party: Quality
- Committee for Advanced Therapies: Quality, Non-Clinical, Clinical
- Committee on Medicinal Products for Human Use: Final decision
ATMP Regulation to facilitate advancement and incentivise the field

- Reduced fees for EMA scientific advice
- Committee for Advanced Therapies (CAT) as cross-disciplinary committee:
  - For all assessments and advice
  - Guidelines
  - ATMP related discussions
- Recommendations on classification (GTMO, CTMP, TEP, combination)
- Certification of quality and non-clinical data
CAT - Committee for Advanced Therapies composition

- Interdisciplinary (quality, non-clinical and clinical)
- chair - elected by serving CAT members
- five members or co-opted members of the Committee for Medicinal Products for Human Use (CHMP), with their alternates - nominated by the CHMP
- one member and one alternate nominated by each EU Member State that is not represented by the members and alternates nominated by the CHMP;
- one member and an alternate nominated by Iceland and Norway;
- two members and two alternates representing patients' organizations nominated by the European Commission;
- two members and two alternates representing clinicians nominated by the European Commission.
Currently licensed ATMPs in EU

- **Holoclar**: *Ex vivo* expanded autologous human corneal epithelial cells containing stem cells
- **Imlygic**: oncolytic virus immunotherapy
- **Strimvelis**: autologous CD34+ cells expressing ADA for ADA SCID
- **Zalmoxis**: modified allogeneic T-Cells as adjunctive treatment for haploidentical HSC transplant
- **Spherox**: autologous chondrocytes for cartilage repair
- **Alofisel**: stem cells from fat tissue for treatment of complex anal fistulas
- **Kymriah**: anti-CD19 CAR-T cells for ALL and DLBCL
- **Yescarta**: anti-CD19 CAR-T cells for DLBCL
- **Luxturna**: AAV RPE65 for retinitis pigmentosa due to gene defect

Previously licensed ATMPs:

- **Glybera**: Gene therapy for lipoprotein lipase deficiency (AAV vector)
- **MACI**: autologous chondrocytes for cartilage repair
- **ChondroCelect**: autologous chondrocytes for cartilage repair
- **Provenge**: autologous CD54+ cells activated with PAP-GM-CSF for advanced prostate cancer
The EU legal & regulatory framework for ATMPs:

- **Blood Directive**
  - 2002/98/EC

- **Clinical Trials**
  - 2001/20/EC
  - 536/2014

- **Paediatrics**
  - 1901/2006

- **Tissues/Cells Directive**
  - 2004/23/EC

- **PhVig legislation**
  - Dir. 2010/84/EU
  - Reg. 1235/2010

- **GMO legislation**
  - Directives 2001/18/EC and 2009/41/EC

- **Medical Devices**
  - 93/42/EC, 90/385/EC
  - 745/2017 from May 2020

- **GMP**
  - 2003/94/EC
  - GMP for ATMPs

- **Advanced Therapy Regulation**
  - 1394/2007

- **Falsified Med.**
  - Dir. 2011/62/EU

- **Orphans**
  - 141/2000

- **Variations**
  - 1084(5)/2003
  - 1234/2008

- **Centralised procedure:**
  - Reg. 726/2004
EU quality guidance for cell-based products


5.2.12: **Raw Materials** of Biological Origin for the Production of Cell-Based and Gene Therapy Medicinal Product. (PhEUR)

Guideline on xenogeneic cell-based MPs (EMEA/CHMP/CPWP/83508/2009)

Guideline on MPs containing genetically modified cells (CHMP/GTWP/671639/2008)

Potency testing of cell-based immunotherapy MPs for treatment of cancer (CHMP/BWP/271475/06)

ICH Q5A (R1) Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin (CPMP/ICH/295/95)

ICH Q5D Derivation and characterisation of cell substrates used for production of biotechnological/biological products (CPMP/ICH/294/95)

Guideline on the Risk-based approach (CAT/CPWP/686637/2011)

Reflection paper on in-vitro cultured chondrocyte containing products for cartilage repair of the knee (EMA/CAT/CPWP/568181/2009)

Development of non-substantially manipulated cell-based ATMPs: flexibility introduced via the application of the risk-based approach (EMA/CAT/216556/2017)

Risk-based approach (RBA)

- RBA permits the manufacturer to design organisational, technical and structural measures to ensure quality according to the specific risks
  → requires evaluation considering product and state of the art
- Manufacturer to justify approach, and that the totality of measures applied is adequate to ensure address the specific risks of the product and of the manufacturing process
- New information on risks → revisit the control strategy
- Level of effort and documentation to be commensurate with risk
- Alternative approaches to those described in Guideline possible if capable of meeting same objective
### Q&A on minimally manipulated cells

<table>
<thead>
<tr>
<th>Risk factor / Quality</th>
<th>Tumour formation</th>
<th>Unwanted tissue formation</th>
<th>Unwanted immunogenicity</th>
<th>Disease transmission</th>
<th>Treatment failure Lack of efficacy</th>
<th>Toxicity Safety issues</th>
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<tbody>
<tr>
<td><strong>Cell starting material</strong></td>
<td>Autologous cells, not substantially manipulated, are expected to represent no risk for tumourigenicity</td>
<td></td>
<td>Autologous cells are not expected to trigger immune reactions</td>
<td>For autologous product disease transmission to the recipient is not an issue</td>
<td>Quality and consistency of cells has to be ensured; harmonized procedures for procurement, handling, transport. Acceptance criteria for volume and cell numbers</td>
<td>In principle autologous cells are not expected to be associated with toxicity, but altered environment for cells has to be considered</td>
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<tr>
<td><strong>Aspects of the manufacturing process and level of cell manipulation</strong></td>
<td>Autologous cells, not substantially manipulated, are expected to represent no risk for tumourigenicity</td>
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<tr>
<td><strong>Cell population, heterogeneity &amp; differentiation potential</strong></td>
<td>Autologous cells, not substantially manipulated, are expected to represent no risk for tumourigenicity</td>
<td>Autologous cells are not expected to trigger immune reactions</td>
<td>For autologous product disease transmission to the recipient is not an issue;</td>
<td>Quality and consistency of cells/mixture has to be ensured and monitored; Though the manufacturing is very limited, the cell selection process has to be validated</td>
<td>In principle autologous cells are not expected to be associated with toxicity, but altered environment for cells has to be considered</td>
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<td><strong>Structural / functional integrity</strong></td>
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<td>Potency assay needs to be established; functional &amp; viability markers</td>
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Starting and Raw Material Control
EU: Definition of starting and raw materials

Paragraph 3.2.1.1(b) Part I of Annex 1 to 2001/83/EC:

‘..starting materials shall mean all the materials from which the active substance is manufactured or extracted......for biological medicinal products, starting materials shall mean any substance of biological origin such as micro-organisms, organs and tissues...cells or fluids (including blood or plasma) of animal origin, and biotechnological cell constructs...Any other substances used for manufacturing or extracting the active substances, but from which this active substance is not directly derived, such as reagents, culture media, foetal calf serum, additives, and buffers involved in chromatography, etc. are know as raw materials.’

EU Raw Material equivalent to US Ancillary Materials

Paragraph 3.3.1. Part IV of Annex 1 to 2001/83/EC

‘Additional Substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) which are combined with manipulated cells of which they form an integral part shall be considered as starting materials, even if not of biological origin.’
Starting Material Control: Key considerations

Examples: bone marrow, placenta, umbilical cord, iPSC, cartilage biopsy, apheresis, collagen scaffold, membrane,

• ‘meet standards appropriate for intended use’

• Control of adventitious agents

• GMP certification not required (GMP principles in some cases)
• Manufacture responsible for Quality of starting materials.
• QC procedures at Manufacturing site:
  • Documentation checks
  • CoO/CoA
  • Established specifications (Biopsy appearance, size, etc.)
  • Further ‘in-house’ sterility and function testing: growth factors, scaffolds...
• Validated shipping/transport to manufacturing site.
## Examples of Starting Material QC

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<td>Donor Traceability &amp; testing</td>
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<tr>
<th>Cell lines or banks</th>
<th>Development History (‘cell history file’) traceability</th>
<th>Compliance to GMP Risk assessment</th>
<th>Characterisation and control ICH Q5A/B/D</th>
</tr>
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<tr>
<th>Scaffold/membrane</th>
<th>CoA and CoO Specifications</th>
<th>Suitability of animals</th>
<th>TSE compliance</th>
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Integral devices

• Cell-based medicinal products may incorporate structural components as starting materials which independently are medical devices or active implantable medical devices → should meet essential requirements on medical devices as per current legislation

• New EU Medical Device Regulation requires CE marking also for integral devices which are not independent of the product (2020) – guidance will be issued

• Cell-based medicinal products may also incorporate structural components which are not used in the same way as in a CE marked medical device → to be appropriately characterised and evaluated for suitability for intended use – obtain CE mark?

• companies do not need to CE mark matrices, etc. if they are integral with the cells but will need a NB report post-MDR implementation.
GMP for ATMP’s

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EUROPEAN COMMISSION

EudraLex
The Rules Governing Medicinal Products in the European Union
Volume 4
Good Manufacturing Practice

Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

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<tr>
<td>Adoption by the European Commission</td>
<td>22 November 2017</td>
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<tr>
<td>Date for coming into operation</td>
<td>ATMP manufacturers should comply with these Guidelines no later than 22 May 2018.</td>
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These Guidelines are specific to ATMPs. Other documents developing GMP requirements for medicinal products which are contained in Volume 4 are not applicable to ATMPs, unless specific reference thereto is made in these Guidelines.
# Examples of Raw Materials used in ATMP Manufacture

<table>
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<tr>
<th>Chemicals</th>
<th>Recombinant Biological origin</th>
<th>Non-recombinant Biological origin&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Buffers • Culture media • Synthetic peptides • Beads • DMSO • Glycerol</td>
<td>• Mabs • Trypsin • Nuclease • Growth Factors • Cytokines • Composite media • Collagenase</td>
<td>• Antibodies • Porcine trypsin • Bovine serum • Albumin • Growth factors • Insulin • Feeder Cells • Antibiotics&lt;sup&gt;2&lt;/sup&gt; • Autologous plasma</td>
</tr>
</tbody>
</table>

<sup>1</sup> Human, animal, plant, microbial

<sup>2</sup> Antibiotics are classed as chemicals but can be of biological origin
Raw Materials Control for ATMPs

- Consider risk: **Suitability for intended use.**
  - origin of RM (animal, human, recombinant)
  - Degree of contact
  - Potential to affect safety
  - Effect on potency

- Low risk items (e.g. chemicals): CoA

- ‘best quality’ reagents at licensing stage
  - Ph.Eur. grade expected where available: Chemicals, recombinant growth factors, Bovine serum monograph, Porcine trypsin monograph
  - possible to use research grade with appropriate understanding of risk/justification (not usual at time of MAA) – commensurate with development stage

- Reproducible quality from batch-to-batch.

- Avoid animal or human derived material where possible (adventitious agent safety)

- Minimise the number of raw materials used

- Comparability issues when significant changes to raw materials
Ph.Eur. Raw Material Monograph

5.2.12: Raw Materials of Biological Origin for the Production of Cell-Based and Gene Therapy Medicinal Products

Covers specific groups of raw materials:

• Sera and Serum replacements
  including platelet lysates and other undefined growth additives, conditioned media, blood and other cellular components

• Proteins produced by recombinant DNA technology
  include growth factors, cytokines, hormones, enzymes and monoclonal antibodies

• Proteins extracted from biological material
  e.g. porcine derived Trypsin and endonucleases.
Control of Drug Substance and Drug Product
Specifications: Biological variation & Product Efficacy

Patient heterogeneity and product variability mean that predicting effectiveness can be difficult.

- Do statistical data suggest there is a correlation with specific factors, in terms of safety and efficacy?
- Sufficient product characterisation to ensure that variability is justified.
- Wide margins can be acceptable, but must be justified by manufacturing and backed by clinical use.
Testing approaches:

• Where it is not possible to perform release tests on the active substance or finished product for technical reasons or due to limited product, alternative strategies can ensure adequate control:

  – Testing of **key intermediates or in-process controls** - relevance of results to critical quality attributes of finished product to be demonstrated
  – **Real time testing** in case of short shelf-life materials/products
  – **Increased reliance on process validation** where scarcity of materials or very short shelf-life limits possibilities for release controls
  – Investigational ATMPs: process validation is not expected but may be important when routine release testing is limited or not possible
Testing strategy - examples

- Sterility test (Ph. Eur. 2.6.1) on finished product not always possible due to the scarcity of materials or time constraints (short shelf-life, medical need)
  - Alternative methods for preliminary results, combined with sterility testing of media or intermediate product at relevant time points
  - Validated alternative rapid microbiological methods; if suitable
  - Mitigation measures if results of sterility test are not available at release

- Cells in suspension are no clear solutions → particulate matter test replacement with appearance test (e.g. color) acceptable

- On-going stability program could be waived for products with shorter shelf-life
QP and batch release

- Re-testing of imported products is often not possible – justify strategy
- Combined investigational ATMPs: QP to verify that quality specifications (set by manufacturer) are adhered to
- Batch release prior to results of QC testing:
  - Internal procedure to describe measures to be taken in case of out-of-specification
- QP can be responsible for more than one site
- QP may rely on audits of third parties or responsibility can be shared with more than one QP
- Decentralised manufacturing must be addressed
Reconstitution

• ATMPs tend to have special instructions for use to ensure product quality, maximise safety and minimise the potential for adverse reactions

• Reconstitution activities can be performed at the administration site outside a GMP environment (substantial manipulation excluded) and cannot be considered as a manufacturing step

• Authorized ATMPs – need to validate the reconstitution processes

• The manufacturer/sponsor/MA holder should describe the reconstitution process, including equipment to be used and requirements at the site of administration

→ Are supporting data/instructions relevant and sufficient?
Outlook on investigational ATMP Guideline (ATiMP GL)

- Multidisciplinary guideline for all iATMPs (SC, TE, GT)
- Quality, preclinical and clinical guidance
- Considering device aspects

- Focus on requirements for first-in-human and exploratory studies, but guidance for later development will also be included
- Common text where applicable and split into cell therapy / gene therapy where needed
- Specific considerations for genetically modified cells and integral medical devices are included
- Consultation opens early 2019
Thank you!