Review of the New EU/EMEA Cell and Tissue Regulations

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EU Regulatory Structure

- **European Commission – executive branch**
  - Governing body (executive branch) of the European Union
  - Composed of EC member states (represented by commissioners) and a president

- **European Parliament – legislative branch**
  - Legislative body (785 Members of European parliament, apportioned to the population, elected for 5-year terms)

- **European Medicines Evaluation Agency**
  - Agency for the evaluation and licensing of medical products
  - Created by legislation crafted by the European Parliament and approved by the European Commission

- **National Competent Authorities (NCAs)**
  - Agencies in each member state that evaluate and license medical products
Definition

- **Advanced Therapy Medicinal Product (ATMP)**
- **ATMP is the European legal terminology for:**
  - Gene Therapy Product (previously defined under 2001/83/EC)
  - Somatic Cell Therapy Product (previously defined-2001/83/EC)
  - Tissue Engineered Product (consists of engineered cells or tissues)
    - Is intended to regenerate, repair or replace a human tissue
    - May contain cells or tissues of human or animal origin (or both)
    - May contain cells and tissues may be either viable or non-viable
    - May contain other elements (e.g., scaffolding, biomolecules, matrices, chemical substances)
Advanced Therapy Medicinal Products (ATMP)

- **Legal history of ATMP regulation in the EU:**
  - Original EMEA Directive 2001/83/EC did not cover ATMP
  - EMEA Directive 2003/63/EC:
    - Amended the original 2001 directive
    - Covers ATMP development, except tissue-engineered products (TEP’s)
    - *Currently* in force for regulation of ATMP development in the EU
  - **Directive 1394/2007**
    - Ratified by EU Parliament and Council on 13-Nov-07
    - Specifically covers ATMP including TEP’s
    - *Will be effective on 30-Dec-08*

- **Key guidance document for cell-based therapy**
  - Guideline on Human Cell-Based Medicinal Products (EMEA/CHMP/410869/2006)
  - Website:  www.emea.europa.eu
Product Characterization

- **Factors to be considered in a characterization scheme**
  - Tissue source (*e.g.*, allogenic vs. autologous)
  - Concurrent use of matrices, scaffolding, biologically active molecules, membranes in the final product

- **Characterization is a function of intended activity(ies) of transplanted cell product in humans**
  - Biochemical action
  - Immunological action
  - Metabolic action
  - Structural replacement of damaged tissue
  - Other

- **Types of characterizations to be employed**
  - Morphology
  - Karyotype
  - Immunological markers
  - Metabolic or synthetic products
  - Other
Comparability (Lot-to-Lot and Donor-to-Host)

- Data on the behavior and characteristics of the prototypes needs to be retained throughout process development
  - Characterization should be complete enough to demonstrate consistency among batches both early and late in development to commercial scale manufacturing
- ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process
  - Product characterization encompasses
    - Physiochemical properties
    - Biological activity
    - Immunochemical properties
    - Purity, impurities, contaminants
    - Release specifications
    - Stability
Potency of Cellular Products

• **Factors to be considered**
  - Activity of implanted cells in relevant disease-based animal models
  - Scaling of cell dose to humans based on animal models
  - Fraction of viable cells implanted into a patient
  - Secretion of biologically active molecules per tissue mass or functional assay (application-dependent approach)
    - Example: TNF-\(\alpha\) inhibition in mesenchymal stem cells for the treatment of acute graft-versus-host disease
    - Up-regulation of co-stimulatory molecules
Good Manufacturing Practices

- Design of GMP should be validated in order to ensure product consistency
  - *A priori* specifications need to be defined and justified
  - Specific issues:
    - Manufacturing area physically separated from tissue collection and procurement facility
    - Avoidance of cross-contamination with collected materials
    - Aseptic conditions should be suitable and validated
    - Dedicated product-specific and single-use equipment
    - Characterization of manipulation of cells during manufacturing process
    - Characterization of transportation and storage conditions and materials associated with these conditions
Registration of Tissue Establishments

- Currently a blend of **early** (tissue collection) and **late** (medicinal products) regulations
  - Tissue collection, processing and storage (2004/23/EC)
  - Facility licensing of tissue establishments
    - 2006/17/EC
    - 2006/86/EC
- No EU-approved **stem cell** products to date
- Marketed “scaffold-based” products may not have been approved under updated guidance for manufacturing
Qualified Person

• A “qualified person” is an expert in an area of pharmaceutical development or pharmacovigilance who:
  ▸ Is permanently and continuously at the disposal of the marketing Authorization Holder (MAH)
  ▸ Is responsible and accountable for the MAH’s practices in his or her area of discipline (e.g., manufacturing, pharmaceutical development, pharmacovigilance)
  ▸ Liaises with the National Competent Authority and EMEA on issues related to his/her discipline
EU in Guidance Phase vis-à-vis US FDA

- Two options exist for scientific advice in the EU
  - Scientific advice at the national agency level
    - More informal, less expensive, not uniformly available in all countries, procedural details differ among countries
    - Useful for country-specific CTAs
    - Advice not binding
    - Advice retained in dossier
  - Scientific advice at the EMEA level
    - Review by the Committee for Advanced Therapies
    - More formal, more complex scheduling, documentation more rigorous, higher fees for advice
    - More preparation needed
    - Advice not binding
    - Advice retained in the dossier
    - Advice applicable to/accessible in EU applications
## List of Draft EU Cell-Based Guidance Documents

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Status</th>
<th>Title</th>
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| Cell - Xenogeneic  | Concept Paper   | Points to Consider Xenogeneic Cell Therapy Medicinal Products –Effective June 2004  
revision of the Points to Consider on Xenogeneic Cell Therapy Medicinal Products –May 2007 |
| Cell               | Draft Guideline | Human cell-based medicinal products January 2007                      |
# List of Planned EU Cell-Based Guidance Documents

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Title</th>
<th>Timeframe</th>
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<tr>
<td>All</td>
<td>Detailed guidelines relating to the application of the traceability provisions in Article 16</td>
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<tr>
<td>All</td>
<td>Detailed guidelines relating to the application of the provisions on follow-up of efficacy and adverse reactions, as well as Risk management</td>
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<td>All</td>
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<tr>
<td>All</td>
<td>Guideline on GCP for advanced therapy medicinal products</td>
<td>No Date Provided</td>
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<tr>
<td>Cell</td>
<td>Guideline on human cell-based products</td>
<td>Finalize and Publish 1-2 Qc2008</td>
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<tr>
<td>Cell – Xenogeneic</td>
<td>Finalize revision of Points to Consider document: Xenogeneic cell-based medical products</td>
<td>Issue First Half 2008</td>
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<tr>
<td>Cell</td>
<td>Concept Paper on Post-Marketing Surveillance of cell-based medicinal products</td>
<td>1Q2008</td>
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<tr>
<td>Cell</td>
<td>Reflection paper on stem cell products</td>
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Glossary of Key EU Documents for Cellular Therapies

- **Tissue collection, processing and storage**
  - 2004/23/EC

- **Facility licensing of tissue establishments**
  - 2006/17/EC
  - 2006/86/EC

- **Current legal framework for cellular therapies**
  - 2003/EC/EC

- **Future legal framework for cellular therapies**

- **Key guidance document for cell-based therapy**
  - Guideline on Human Cell-Based Medicinal Products (EMEA/CHMP/410869/2006)