Current Issues in EU Cell & Gene Therapy Regulation

Christiane Niederlaender, UK CAT Delegate, MHRA
Disclaimer

The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties nor of the Medicines and Healthcare Products Regulatory Agency.
ATMP Regulation 1394/2007: 10 + years of experience in the EU

Substances containing cells which do not fulfil the definition of a medicinal product are regulated under the ‘Tissues and Cells Directive’.

⇒ An ATMP must also comply with the requirements of EUTCD.
Currently licensed ATMPs

- **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

Previously licensed ATMPs:

- **Glybera**: Gene therapy for lipoprotein lipase deficiency (AAV vector)
- **MACI**: autologous chondrocytes for cartilage repair
- **Chondrosphere**: autologous chondrocytes for cartilage repair
- **Provenge**: autologous CD54+ cells activated with PAP-GM-CSF for advanced prostate cancer
Regulatory flexibilities

- Risk-based Approach
- Exceptional circumstances
- Accelerated assessment
- Conditional approval
- Adaptive licensing
- PRIME
Risk-based approach (RBA)

- **Dir 2009/120/EC** to enable a control strategy to adequately manage the risks of the product/manufacturing process – for MA and CT
- 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)
  - scientific advice

**RISK BASED APPROACH GUIDELINE (feb 2013)** to identify the **risks** and associated **risk factors** and to establish a **risk profile** for the ATMP under development

- With the use of the identified **risk profile** the Applicant will be able to justify the extent of data to be included in the MAA (IMPD) dossier - CTD Mod 2.2
- more flexible - less quality centred - include non-clinical and clinical considerations – risk mitigation measures
- GMP guide does not exclude tools for Quality risk management (as in ICHQ9)
- GMP Guide provides examples for RBA
# Q&A on minimally manipulated cells

<table>
<thead>
<tr>
<th>Risk Factor / Quality</th>
<th>Risk</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>
</tr>
</thead>
<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>
<td></td>
</tr>
<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>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Safety of the product could be affected by the potential process-related impurities and microbiological contamination</td>
<td></td>
</tr>
<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></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>
<td></td>
</tr>
<tr>
<td><strong>Structural / functional integrity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Potency assay needs to be established; functional &amp; viability markers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**PRIME**
Major public health interest, unmet medical need.
Dedicated and reinforced support.
Enable accelerated assessment.
Better use of existing regulatory & procedural tools.

**Adaptive Pathways**
Scientific concept of development and data generation.
Iterative development with use of real-life data.
Engagement with other healthcare-decision makers.

**Early Access Tools**

**Accelerated Assessment**
Major public health interest, unmet medical need. Reduce: assessment time: 150 days.

**Conditional MA**
Unmet medical need, seriously debilitating or life-threatening disease, a rare disease or use in emergency situations.
Early approval of a medicine on the basis of less complete clinical data.
Adaptive Pathways

1. Iterative development either of:
   a. staggered approval from initially restricted patient population to increasingly wider populations
   b. confirmation of the benefit/risk balance of a product authorised under Conditional MA with early or surrogate endpoints.

2. Gathering of evidence through real-world data to supplement clinical trial data

3. Involvement of patients and health technology assessment (HTA) bodies in the discussion of the product development program.

‘Safe harbour’ discussions – formalisation of advice via normal SA procedure.
PRIME (Priority Medicines)

- To foster development of medicines with a high public health potential
  - Reinforced scientific and regulatory advice
  - Optimise development for robust data generation
  - Enable accelerated assessment

- Eligibility to PRIME:
  - Potential to address an unmet medical need
  - Scientific justification based on data / evidence from non-clinical and clinical development

Features

- Written confirmation of PRIME eligibility and potential for accelerated assessment;
- Early CHMP/CAT Rapporteur appointment during development;
- Kick off meeting with multidisciplinary expertise from EU network;
- Enhanced scientific advice at key development milestones/decision points;
- EMA dedicated contact point;
- Fee incentives for SMEs and academics on Scientific Advice requests.
PRIME experience

- New procedure since April 2016 - CAT involved in eligibility discussion
- 43 ATMP PRIME eligibility request submitted
- = 29 % of all valid eligibility requests (n=148)
- 14 ATMP PRIME eligibilities granted

Cumulative overview of recommendations on PRIME eligibility requests adopted by 14 December 2017

By therapeutic area:
- Oncology: 12
- Neurology: 2
- Haematology-haemostaseology: 7
- Infectious diseases: 2
- Cardiovascular diseases: 8
- Immunology-rheumatology-transplantation: 2
- Gastroenterology-hepatology: 2
- Vaccines: 1
- Pneumology-allergology: 1
- Dermatology: 1
- Endocrinology-gynaecology-fertility-metabolism: 2
- Ophthalmology: 1
- Psychiatry: 1
- Other: 1

By type of applicant:
- SME: 15
- Other: 19
- Academic: 3

13 GTMP + 1 CTMP
- 8 Oncology
- 4 Haematology
- 1 Transplantation
- 1 Neurology

*This indicates eligibility requests received but not started by EMA as they were deemed outside the scope of the scheme or with a format and content inadequate to support their review. These are not included in the breakdown by type of applicant or by therapeutic area.
Regulatory Challenges and new developments
Orphan legislation revised

Incentivize development of drugs for rare diseases: many ATMPs

"similar medicinal product" in the context of the orphan legislation:
Article 3 (3) of Commission Regulation (EC) No 847/2000 outdated

Q&A document addresses questions that have been raised by developers of ATMPs regarding the application of the concept of “similar active substance” in an ATMP setting.
**GMO**

GMO aspects need to be addressed in Environmental Risk assessments (ERA)

Clinical Trial Regulation will harmonise clinical trial applications across EU, but does not address ERA harmonisation for investigational medicinal products.

Differences between Member States:
- Definitions (Deliberate Release, GMO)
- Timelines
- Requirements

Dissemination of information about national regulatory requirements in respect of GMO aspects is expected to facilitate the development of gene therapy medicinal products in the EU.

A repository of national regulatory requirements has been created to this effect

---

Joint meetings of Medicines and GMO authorities promoted by the European Commission for streamlining clinical development:
- procedures,
- definitions,
- criteria for GM cells
GMO regulatory domain - controversies

- Human cells – organisms?
- Genetically modified human cells exempted?
- GM cells or the viral vector or both are the GMO?
- Plasmids are GMO?
- Human edited cells … *genetic material has been altered in a way that does not occur naturally* … GMO?
- Animal or plant cells are micro-organisms? … only in culture … for contained use?
Revision of the GMP framework for ATMP’s

- Stand alone document built on general GMP guide + relevant annexes
- Applicable to investigational and commercial product
- Aiming to introduce flexibility to favour development
- To clarify / harmonise inspectorate interpretation
- Integrated in Eudralex vol. IV as Part IV
<table>
<thead>
<tr>
<th>Hospital exemption</th>
<th>The “specials” scheme (UK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The ATMP must be prepared and used in the same EU Member State</td>
<td>Products meeting the requirements of the scheme can be manufactured in the UK or imported to the UK</td>
</tr>
<tr>
<td>The ATMP must be commissioned by a medical practitioner</td>
<td>Products can be prescribed by doctors, dentists and supplementary prescribers</td>
</tr>
<tr>
<td>The ATMP must be custom made to meet an individual prescription and preparation must be on a “non- routine basis”</td>
<td>There is a special needs test (interpreted to mean the absence of a pharmaceutically equivalent and available licensed product)</td>
</tr>
<tr>
<td>The ATMP must be used in a hospital</td>
<td>There is no stipulation as to location</td>
</tr>
</tbody>
</table>
Manufacturing challenges
Automated manufacturing and closed systems

- Definition of a closed system and background requirements: is it really closed?
- In-process controls for automated manufacture
- Operator training
- Standardised protocols
- System suitability tests
- CE mark not sufficient
- Qualification DQ / IQ / OQ / PQ as ATMP-GMP
- Process validation reduced if used as recommended by the device manufacturer
Multiple manufacturing sites

- Standardisation
- Comparability
- Supervision
- Release testing
EU guidance

- GMP for ATMP – EC published in 2017
- Revision of Parental Gene Therapy Guideline - adopted Feb 2018
- Application of GLP through development – EMA published in Jan 2017
- Q&A for minimally manipulated – EMA published in 3 July 2017
- Revise definition for orphan designation – EC published 28 May 2018
- Revised Risk Management Plan / FV guideline – ongoing
Thank you!