Post-Approval Changes, Change Management Protocols and Comparability for ATMPs

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<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Strimvelis</td>
<td>Autologous CD34+ cells with a retroviral vector containing the adenosine deamidase gene</td>
<td>ADA-SCID</td>
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<td>Holoclar</td>
<td>ex vivo expanded autologous human corneal epithelial cells containing stem cells</td>
<td>limbal stem cell deficiency</td>
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<tr>
<td>Imlygic</td>
<td>Oncolytic virus consisting of attenuated herpes simplex virus type-1</td>
<td>unresectable melanoma that is regionally or distantly metastatic</td>
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<tr>
<td>Kymriah</td>
<td>CD19 CAR-T cells</td>
<td>B-Cells ALL and DLBCL</td>
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<td>Yescarta</td>
<td>CD19 CAR-T cells</td>
<td>DLBCL and B-cell ALL</td>
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<tr>
<td>Spherox</td>
<td>Autologous chondrocytes</td>
<td>Repair of symptomatic articular cartilage defects</td>
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<td>Libmeldy</td>
<td>Autologous CD34+ cells expressing human arylsulfatase</td>
<td>Haemophilia A</td>
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<td>Tecartus</td>
<td>autologous CD4 and CD8 T cell expressing anti CD19 CAR</td>
<td>Mantle Cell Lymphoma</td>
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<td>Abecma</td>
<td>Anti-BCMA CAR-T cells</td>
<td>Multiple Myeloma</td>
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<td>Lisocabtagene maraleucel</td>
<td>Anti-CD19 CAR-T cells</td>
<td>No-Hodgkin Lymphoma, DLBCL</td>
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<tr>
<td>Luxturna</td>
<td>AAV2 expressing hRPE65</td>
<td>inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations</td>
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<td>Zolgensma</td>
<td>AAV9 containing the human SMN gene</td>
<td>Spinal muscular atrophy</td>
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<tr>
<td>Alofisel</td>
<td>Allogeneic fat cells</td>
<td>Complex anal fistulas</td>
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<tr>
<td>Breyanzi</td>
<td>CD19 CAR-T cells</td>
<td>DLBCL, PMBCL, FL3B</td>
</tr>
<tr>
<td>Carvikti</td>
<td>BCMA CAR-T</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td>Upstaza</td>
<td>AAV</td>
<td>aromatic L-amino acid decarboxylase (AADC) deficiency</td>
</tr>
<tr>
<td>Roctavian</td>
<td>AAV factor VIII</td>
<td>Hemophilia A</td>
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Regulatory background
Variations to a Product Licence in EU

- Substantive changes to an approved product licence must be submitted to the EMA as Variations;

- **Type IA**: minor variation, administrative changes,
  - submit within 12 months of implementation, or for changes that impact agency’s ability to supervise: Immediately (Do and Tell)

- **Type IB**: more significant than IA change but not a type II change or an extension,
  - Approval within 30 days if no further questions, otherwise up to 60d extension

- **Type II**: substantial change to a licence
  - 30 – 120 days assessment depending in complexity

- For biologicals including ATMPs, more variations are classed as type II

Post Approval Change Management Protocol (PACMP)

- Introduced in 2012, set out in Variations Guideline, to facilitate the implementation of more complex changes
- step-wise approach in the assessment of changes:
  - evaluation of the strategy (protocol) for the change
  - separate evaluation of the data produced based on the agreed strategy
- Step 1:
  - submission of CMP as a type II variation: very detailed plan of how the change will be implemented and about how the acceptance criteria for any data will be set
- Step 2:
  - submission of the data as type IB variation
- Step to can also be submitted as part of a NAS application!
PACMP – pros and cons

+ Decoupling the plan and the data ensure that regulatory input can be obtained into the plan before it is implemented
+ Final implementation of the change should be faster as it is only data evaluation

- If there are significant changes that need to be made to the plan (e.g. in the acceptance criteria), this will potentially require a further variation or could result in a rejection of the type IB variation if not notified
Common CMC post-approval changes
that don’t require product comparability

- Extension of Shelf-life:
  - Submit data for review; type IB

- Analytical procedure changes
  - Classification depends on change, **equivalence** of the change must be demonstrated, by assay characterisation **bridging studies** between old and new procedure
  - ATMP procedures are often complex, this process may be a commitment from approval, e.g. validation, implementation of new procedures
  - Assay Kit changes due to supplier problems

- Specification
  - Tightening is easy (maybe based on commitment)
  - Widening must be based on batch data and clinical experience, more likely scenario for ATMPs than for other biotech
Comparability for ATMP post approval changes:

- Changes to the manufacturing process of the drug substance or drug product occurring at any stage of the development
  - Change to a raw/starting material supplier
  - New manufacturing process site
  - Removal of a key raw material (e.g. FBS, antibiotic)
  - Changes to seed stocks (MCB/WCB or VSB)
  - Changes to equipment/procedures (e.g. clarification/chromatography)
  - Introduction of new unit operations (e.g. filtration steps)
  - Manufacturing Scale-up/out : 2d to 3d culture
  - DP formulation (excipient)

- Critical changes to the manufacturing of the starting material with impact on the manufacturing of the finished product
  - E.g. Cell source changes, pre-transport processing, freezing
  - Vector scale up, plasmid change, additional purification, changed purity of enzyme, mRNA
Why comparability?

Release data represent the product characteristics that define the quality when everything else is unchanged.

Changes: verification that the product is still the same

*Rhincodon typus*  
*Carcharodon carcharias*
Comparability protocol must be provided – what is sufficient

- nature of the change and **risk assessment**
- step in the manufacturing process
- Stage of development: pre- or post- licensing approval, pivotal clinical trial
- key attributes identified in the original characterisation studies
- Risk-based approach: testing based on effect of change on CQA (justify reduced testing)

**Establish comparability acceptance criteria:**

- Current specification
- IPCs
- Stability
- Historical batch data
- Statistical analysis
- What level of extended characterisation is decided based on nature of change and risk
Batches

- Side-by-side testing preferred over comparison of post-change data with pre-change historical data.
  - manufacture using Process A and B.
  - Side-by-side characterisation testing using representative material from old and new process.

- Split samples of starting material help minimise variability

- Surrogate material may help: is the surrogate material sufficiently representative of patient material? – can be more ethical but also economical advantage

- Retention samples where possible – use wisely
Surrogate material

- Material used instead of the actual raw and starting materials to be used in manufacture process development and comparability and as part of process validation
- i.e. normally voluntary donor material instead of patient material
- Examples:
  - Umbilical cord blood cells
  - Donor blood or blood components
  - Cadaveric material
- Must be sufficiently justified and demonstrated that the data are relevant
Examples and Approaches to non-comparability

- Different phenotypic or genotypic profile
- New product or process related impurity
- Existing product or process-related impurity outside specifications limits
- Multiple vs single parameter differences
- Improvements in purity

Justifications

- Original specifications were not appropriate (based on limited data)
- Impurity removed during manufacture
- Risk assessment for potential impurity (worst-case administration per dose)
- Evidence from literature: no safety concern
Further non-clinical and clinical bridging studies

- analytic difference with unpredictable (unknown) effects on efficacy and safety
  need to establish new proven specs

- Animal toxicity studies
- Animal efficacy models
- Bio-equivalence, PD/PK
- Immunogenicity testing
- Human safety and efficacy
- Pharmacovigilance monitoring

Case-by-case, indication and posology dependent.
Regulatory guidance

➤ Comparability considerations for Advanced Therapy Medicinal Products (ATMP) Q&A (EMA/CAT/499821/2019)

➤ Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/2008 Rev. 1)

➤ ICH Q5E (CPMP/ICH/5721/03) not applicable but some principles may apply:
   - stepwise conduct of the comparability exercise;
   - focus on the manufacturing process steps that are most appropriate to detect change;
   - use of suitable and sufficiently sensitive analytical methods;
   - generation of data enabling to reach a conclusion on the comparability.

➤ Most relevant for vectors
Conclusion

- Post-approval changes are common and for ATMPs of part of commitments that are made at approval
- Some changes are less complex and do not require comparability
- More complex changes can be managed with a PACMP
- Changes made to the production process, materials, etc. could lead to clinically significant changes in the final product
- Comparability for ATMPs normally required where manufacturing process is changed in any way
- A comparability protocol should be established based on risk assessment and the nature of the change
- For approved products tests must go beyond release tests
Thank you!