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

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Currently Approved ATMPs in the EU

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

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

Rules for the classification of variations:
https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:223:FULL:EN:PDF

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

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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?

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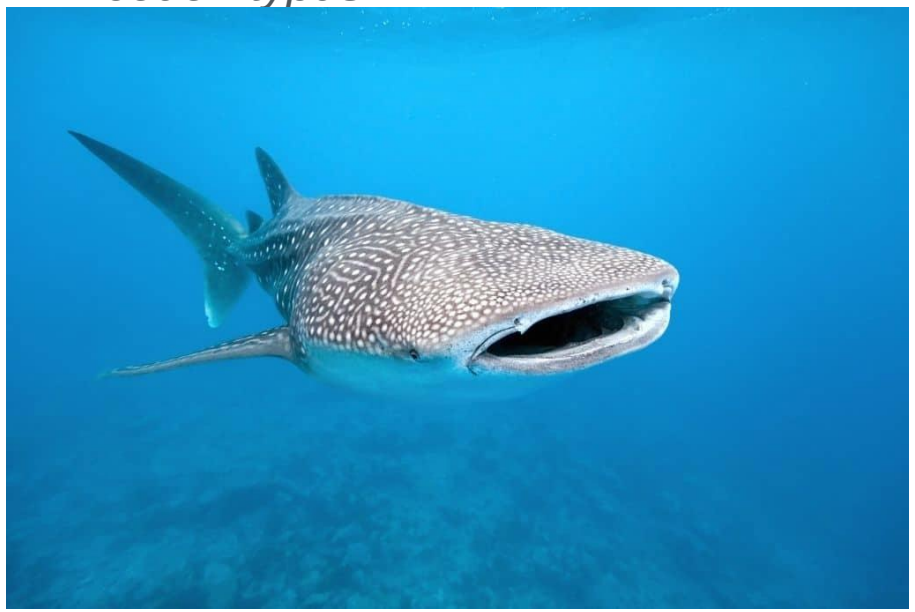
Release data represent the product characteristics that define the quality **when everything else is unchanged**

Changes: verification that the product is still the same

Rhincodon typus



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Carcharodon carcharias

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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

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- 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

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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!