Risk-Based Approaches to Comparability

The Opportunity
Comparability – the regulatory perspective

* Regulators’ concerns and expectations around comparability
* Planned changes – PACMP
* Risk based approach to:
  * manufacturing changes during ATMP development
  * post-approval
* Role of characterisation data
* Understanding of regulatory process
  * How much emphasis? At what stage?
  * US vs EU
    * GMP requirements
    * Potency assay development timing
    * Characterisation at each stage
    * Progressive development vs full compliance
* The later you leave it the harder it is to recover – can’t go back
[The goal of the comparability exercise is to]

ensure the quality, safety and efficacy of drug product produced by a changed manufacturing process, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to manufacturing process changes

* As valid in pre-approval development
Why does it become an issue?

- Generally accepted that for biological medicinal products “the product is the process”: it is not possible to fully evaluate quality, and by extension safety and efficacy, by application of simple physico-chemical tests.

- Additional data required to evaluate the impact of changes in materials or processes.

- Not sufficient to test to a routine specification.

Changes can result in unplanned and (routinely) undetectable alterations in product quality, safety or efficacy.
Development process – when to think about comparability?

- Transition from research
  - Process development
  - Preliminary safety studies
  - Preliminary characterisation

- Product development
  - Process development (late)
  - Potency assay development
  - Detailed characterisation

- Pivotal non-clinical safety studies
  - Assay methodology fully developed
  - Process stable and validation planned
  - Phase I/IIa clinical studies

BE AWARE
BE ACTIVE
BE CRITICAL
The comparability issue

* Obligation to demonstrate relevance/applicability of data on prior iterations
  * Regulators accept there will be changes during development
  * MUST consider the impact of changes on the validity of previous data
  * Becomes more critical as development proceeds
  * How far can you stretch the argument?
Comparability must be built systematically

- Similarity to previous iteration
- Consideration of all changes – cumulative
- Comparability protocol – consider all outcomes when determining acceptance criteria
- Acceptance criteria MUST be pre-specified
Systematic description of product and manufacturing process used to manufacture key batches – eg pivotal non-clinical safety, and all clinical lots

Differences in product characteristics, process conditions must be highlighted and their impact assessed

Adequacy of data will be critically assessed:
- How much
- Suitability and sensitivity of methods
- Extent of characterisation: phenotypic only? Genomic? Functional assays?

Application of ICH Q5E principles
- Can comparability be determined from Q data only?
- Were non-clinical bridging studies adequate?
- Should clinical bridging studies have been undertaken?
Post-Approval Lifecycle Management (PALM) Plan (EU/US)

The optional PALM plan is included in the initial BLA/MAA. Based on risk-based concepts (ICH Q 5E, 8, 9, 10, 11), it provides commitments to monitor product/process quality, manage process and control strategy changes. In US and EU the PALM is supplemented with Comparability/Change Management Protocols to facilitate streamlined regulatory management of planned changes e.g. changes to site & scale, raw material, working cell bank replacements, planned process improvements or other changes outside the design space.

Acceptability for ATMPs? Need for non-clinical or clinical data to support comparability?
**Change Management Protocol**

- For predicted/likely changes post-approval
  - Eg introduction of new donor Master Cell Banks?
    - Justification for change
    - Description
    - Studies to be performed
    - Supporting data to be supplied– including scale-up justification
  - **For biologics – comparability**
  - Risk assessment
Variations

* B.I.e.2 Introduction of a post approval change management protocol related to the active substance – Type II
* B.II.g.2 Introduction of a post approval change management protocol related to the finished product – Type II
* B.V.c.1 Update of the quality dossier to implement changes, requested by the EMEA/National Competent Authority, following assessment of a change management protocol (biological/immunological) – Type IB
* Changes made under a PACMP – Type IB
“Cells are much more complex entities than small molecules and therapeutic proteins” Salmikangas et al. Regen Med (2015) 10(1) 65-78

* Case-by-case “standard” for ATMPs
* Risk-Based Approach – a tool from 2001/83/EC

2001/83/EC Annex Part IV
A risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application.

* Concept of RBA developed to provide a flexible approach to managing variety of risks associated with the clinical use of ATMPs

* Intent is to determine the extent of data to be included in the MAA, and justify any deviation from the standard requirements for medicinal products

* Based on identification of various risks associated with the clinical use of an ATMP and risk factors inherent to the ATMP with respect to quality, safety and efficacy.

* Use of the RBA in the MAA dossier is optional
Stepwise approach using 4 stages:

1. Identify risks associated with the clinical use of the ATMP
2. Identify product specific risk factors contributing to each identified risk
3. Map the relevant data for each identified risk factors against each of the identified risks
4. Make conclusions on the risk factor – risk relationships

* Include matrix and locations of supporting data in MAA
* Risk = hazard for the patient
* Risk factor = aspect of product that could contribute to a risk
<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>(1) Transformation/tumour formation</th>
<th>(2) Disease Transmission</th>
<th>(3) Treatment Failure</th>
<th>(4) Immunogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting/raw materials</strong></td>
<td>Cell transformation due to growth factor use</td>
<td>Non-sterile medium components</td>
<td></td>
<td>Residual animal proteins residuals in DP</td>
</tr>
<tr>
<td><strong>Culture conditions</strong></td>
<td>Risk for cell transformation due to culture conditions.</td>
<td>Expression of latent virus in extended culture. Adventitious contamination during culture. Potential for mycoplasma contamination.</td>
<td>Influence of cell culture on cell senescence / dedifferentiation may result in treatment failure.</td>
<td>Removal of animal-derived materials and antibiotics. Up-regulation of Class II HLA and/or co-stimulatory molecules during expansion?</td>
</tr>
<tr>
<td><strong>Genetic stability (DS cells)</strong></td>
<td>Potential for genetic instability due to extended culture.</td>
<td></td>
<td>Decreasing potency or growth potential</td>
<td>Up-regulation of Class II HLA and/or co-stimulatory molecules during expansion?</td>
</tr>
<tr>
<td><strong>Genetic stability (MCB)</strong></td>
<td></td>
<td></td>
<td>Decreasing potency or growth potential</td>
<td></td>
</tr>
<tr>
<td><strong>Scaffold material</strong></td>
<td>Non-sterile scaffold. Animal viruses in scaffold</td>
<td>Unsuitable mechanical properties leading to site damage</td>
<td></td>
<td>Animal-derived proteins eg collagen</td>
</tr>
</tbody>
</table>
Sources of variability

* Donor characteristics
* Raw material quality*
* Manufacturing equipment, conditions and facilities
* Manufacturing process
* Reagents and equipment for analytical methods
* Preservation methods
* Distribution conditions
* Preparation for use

Risks

* Variability in materials, process etc
* Manufacturing plant transfer
* Change in acceptability status of materials
* Donor change
* Scale up/out – new logistics
* Characterisation absolutely critical
* What is “safe” to look at and what not to investigate in detail – know the results by having detailed characterisation – balance between this and regulatory expectations
Conclusions

* Regulatory risk vs commercial risk: “safe route” with extensive bridging studies **TOO SLOW / TOO EXPENSIVE**
* Can’t divorce the two, balance different in different situations
* Thorough and critical risk assessment vital – use of RBA helps formalise process and justify development data
* Key is in minimising risks of rejection of comparability argument
* Scientific advice critical but...
* Ultimately MAA is the determinant – don’t know risks (of individual aspects) until dossier is assessed