Session 3: Complexity of innovative manufacturing and the associated challenges for comparability

European regulators views

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Comparability is an essential part of the evolving process to ensure that data gathered is valid through development, for marketing authorization and beyond.

Understand critical process steps and set predefined acceptable ranges required for consistency – acceptable level of variability.

Meaningful set of QA should be identified to be suitable for control (assay accuracy and precision) and comparability.

Comparability supporting manufacturing changes should not be confounded with similarity.
ICH Q5E on comparability should be considered as broadly applicable

- comparability exercise should start with quality data and then continue as appropriate with non-clinical and clinical studies.

- the product should be evaluated at the process step most appropriate to detect a change in the quality attributes. This may entail evaluating the product at multiple stages of manufacture.

- extent of studies will depend on:
  - the production step where the changes are introduced;
  - potential impact on the purity as well as on the physicochemical and biological properties of the product, particularly considering the complexity and degree of knowledge of the product (e.g., impurities, product related substances);
  - suitability of analytical techniques to detect potential product modifications and results;
  - relationship between quality attributes and safety and efficacy, based on overall nonclinical and clinical experience.
Comparability exercise includes:

- **Extended characterisation**;

- assessing **critical control points in the manufacturing process** that affect product characteristics (e.g., intermediate, drug substance, and drug product);

- need for **stability data**, including from accelerated or stress conditions, to identify differences in the degradation pathways of the product and, hence, potential differences in product-related substances and product-related impurities;

- demonstration of **manufacturing consistency**;

- redefine **in-process controls** including critical control points to maintain the quality

- historical data to provide insight into potential “drift” of quality attributes with respect to safety and efficacy

- Consider nonclinical or clinical characteristics of the drug product and its therapeutic indications
PROCESS CHARACTERISATION

1. process development – setting the process:

Justified by risk based approach / scientific knowledge

for each step - identification of:

– INPUTS – material attributes (starting, raw), process parameters
- OUTPUTS – quality attributes, process performance indicators

all changes during development to be clearly identified

risk evaluation to assess impact on safety and efficacy
INPUTS – material attributes

**Starting materials - changes**

- Plasmid – ex. AAV redesign – new promotor
- cell substrate – cell factory change
- viral vector - retroviral vector safety improvement
- Human cells – expected for autologous gene therapy
INPUTS – material attributes

Raw material - Supplier qualification
Start early from development to validation
Small scale studies – enable acceptance criteria
Reagent functionality addressed

Non critical - Managed through pharmaceutical quality system
GMP for ATMP CHANGE MANAGEMENT

CRITICAL - might require COMPARABILITY
Impact on the manufacturing step/ whole process and product
OUT PUTS – material attributes

Process changes

• Optimisation
• Upscaling
• Tech transfer

Before clinical exposure - comparability not needed

Process performance
Impact on product attributes

Stringency according to stage of development
Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products

- genotypic and phenotypic identity,
- purity - ratio of infectious to non-infectious particles
- Empty particle number / empty to full ratio
- Particle size / aggregates
- biological potency/therapeutic sequence activity,
- infectivity/transduction efficiency
- replication capacity
- ...

Extended characterisation – gene therapy
• same process – same AAV – same capsid
• Impact expected mostly on potency – transgene expression
• Consider also impact on:
  • Genomic integrity
  • virus titre / infectious titre - ratio
  • empy/full capsid ratio
  • agreggation
  • stability
• Additional pharmacotox on AAV for increased expression
• **Process:**
Sequence integrity, copy number of gag / pol / env and genetic stability of packaging / producer cells + Vector titer

• **Viral vector:**
  • Full sequence (therapeutic gene + genetic elements for selectivity/regulation/control - *no oncogenic/tumourigenic*
  • genome or plasmid integrity, homogeneity and genetic stability of the vector and therapeutic gene.
  • Expression of the therapeutic sequences and selectivity/regulatory elements delivered
  • the tissue tropism, infectivity (in a variety of cell cultures), virulence, replication capacity, ratio of infectious to non-infectious particles, insertion sites
  • Mean particle size and aggregates

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**Strimvelis EPAR on vector comparability**:
potency, identity, genetic stability, aggregates and safety.
Comparability of GM-CELLS

<table>
<thead>
<tr>
<th>Viral vector changes</th>
<th>Transduced cells</th>
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<tbody>
<tr>
<td>• Critical process steps – CPP</td>
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<tr>
<td>• Consistency of the cell bank</td>
<td>• Immunophenotypic profile</td>
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<tr>
<td>• Infectious viral titre / total particules</td>
<td>• Differentiation / scnescent</td>
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<tr>
<td>• Infectivity</td>
<td>• Cell number, viability</td>
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<tr>
<td>• Transgene sequence</td>
<td>• Transduction efficiency</td>
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<tr>
<td>• Transgene expression</td>
<td>• Vector copy number</td>
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<tr>
<td>• Stability</td>
<td>• Transgene sequence</td>
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<tr>
<td>• Confirmation of transgene expression in permissive cell</td>
<td>• Biological characterisation</td>
</tr>
<tr>
<td>+ Comparability of transduced cells (DS/DP)</td>
<td>• Potency</td>
</tr>
<tr>
<td></td>
<td>• Stability (accelerated)</td>
</tr>
<tr>
<td></td>
<td>• Confirmation with patient cells</td>
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**Safety** not part of comparability:
process related impurities, microbiological / viral safety required to be kept to the minimum / absent as considered safe
Additional considerations for autologous donor variability

- process characterisation / validation with healthy donor cells
- Phenotypic profile can be defined with wide ranges to accommodate variability
- Potency very relevant to integrate variability (*in vitro* and/or *in vivo* assay)
- Comparability between healthy and patient starting material necessary
- Substantial manipulation e.g. viral transduction might have different consequences for cell viability / apoptotic state / differentiation
- Accelerated stability studies could be relevant to identify differences
- Acceptability of concurrent validation with patient materials to be agreed upfront

Risk evaluation to assess impact on safety and efficacy
Additional considerations for technology transfer
Multiple sites with same manufacturing process

- Enhanced focus on critical manufacturing steps IPC‘s, intermediates quality attributes and stability
- Manufacturing process validated for multiple sites with comparable outcome
- Side by side comparability exercise of statistically significant number of batches
- Comparability of analytical methods
- Split samples when possible
Considerations on statistical methodologies for comparability

- Small/uneven number of batches from pre and post-change process / non-random sampling – questions representativeness
- Two unknown distributions pre and post-change to be compared
- Comparability of statistically significant number of batches taken in consideration the variability of the method (min-max suitable for specs – adequate for low numbers in comparability?)
- Appropriate statistical method to be defined – non-inferiority, data distribution, metrics for the difference measurement (difference of means) and distribution of the metric itself (normal?) – statistical interval (tolerance interval) possible?
- Comparison of single post-change values with min-max ranges for pre-change or side-by-side comparability in the same assay run generally considered adequate for low number as in earlier development phases
- Inferential statistics possible for later development – higher number of batches

Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development Draft
EMA/CHMP/138502/2017
Change management - Comparability

- Change in raw materials
- Change in starting materials - viral vector - cells
- Process improvement
- Tech transfer
- Multiple sites
- ...

Consult authorities how to approach comparability requirements

Changes before clinical trials require data filiation – improvement welcome

Changes during clinical trials require prior approval (substantial amendment)

Improvement expected - Comparability to ensure safety

Changes after Market Authorization require prior approval (Variation)

Improvement acceptable based on Comparability to ensure safety and efficacy

Consult Variation Regulation

COMMISSION REGULATION (EC) No 1234/2008
of 24 November 2008

Revised 2012

concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
Thank You!

Questions?