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Comparability Is Not a Nightmare, Just Think Ahead!

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COMPARABILITY

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

Gene Therapy Medicinal Products

Gene Therapy

Genetically Modified Cells

ICHQ5E – general principles apply to ATMP

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.**

ICHQ5E – general methodology apply to ATMP

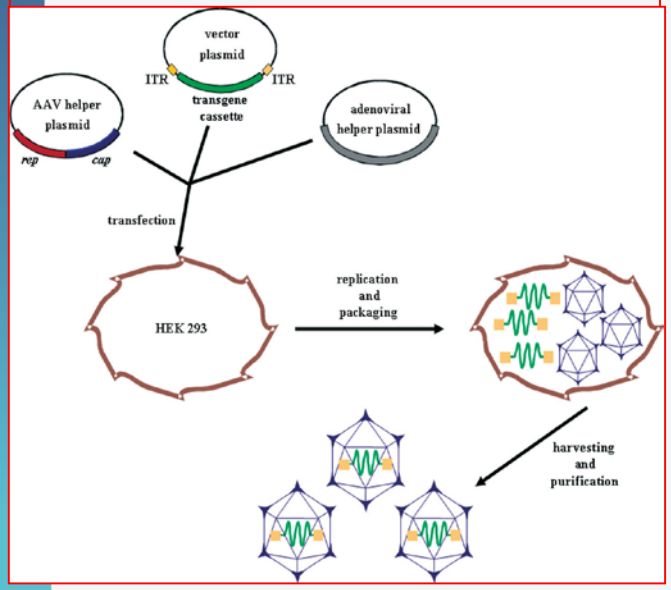
Comparability exercise include:

- **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**

CMC – gene therapy

Adeno Associated Virus - AAV



plasmid

viral seed bank

packaging / producer cell bank

PROPAGATION AND HARVEST

PURIFICATION

VIRAL VECTOR → cells

GENETICALLY MODIFIED CELLS

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28 April 2016
EMA/CHMP/BWP/187338/2014

Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission

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

Raw material - Supplier qualification

Start early from development to validation
Small scale studies – enable acceptance criteria

Non critical - Managed through pharmaceutical quality system

GMP for ATMP CHANGE MANAGEMENT

CRITICAL - might require COMPARABILITY

INPUTS – material attributes

Starting materials - changes

Plasmid – ex. AAV redesign – new promotor

cell substrate – cell factory change

viral vector - retroviral vector safety improvement

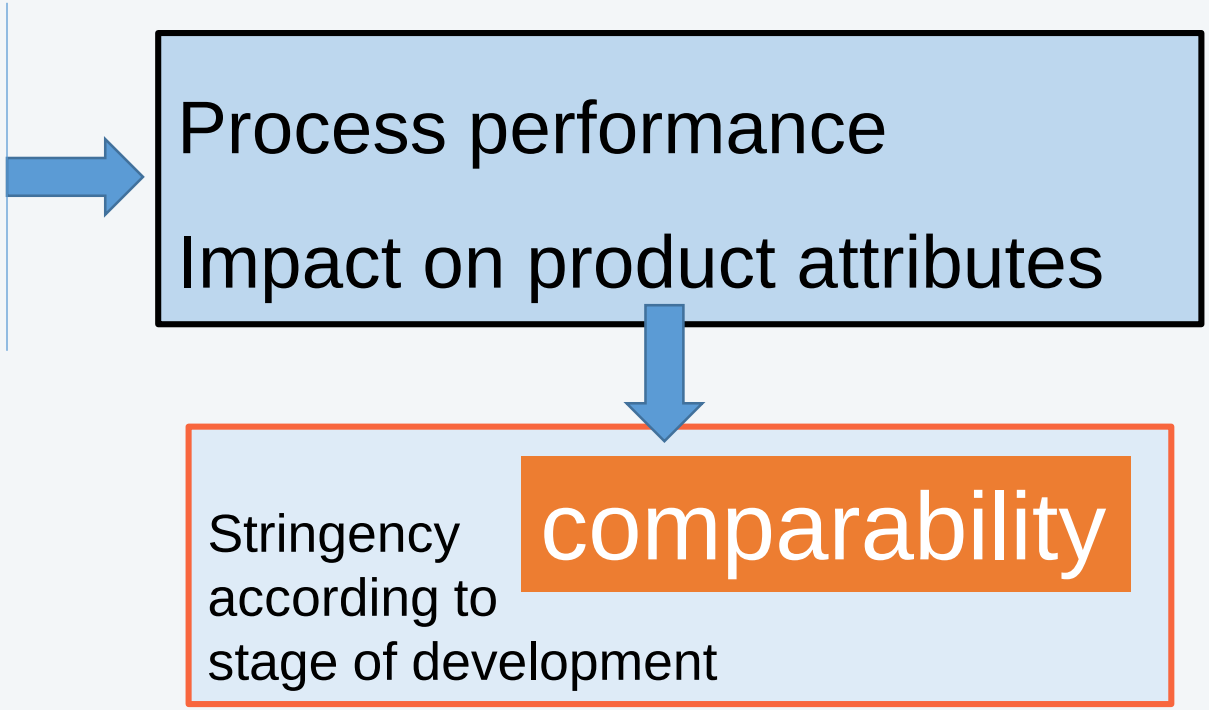
Human cells – expected for autologous gene therapy

OUT PUTS – material attributes

Process changes

- Optimisation
- Upscaling
- Tech transfer

NOT necessarily EQUAL prior to clinical development



16 February 2018
EMA/CAT/143641/2017
Committee for Advanced Therapies (CAT)

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Appropriate comparability studies according to the principles outlined in **ICH Q5E** for biotechnological/biological products should be conducted in order to demonstrate comparability of the pre- and post-change product. The criteria for determining comparability of GTMP medicinal products after manufacturing changes should be justified.

Safety attributes not part of comparability :
process related impurities, microbiological / viral safety required to be kept to the minimum / absent as considered safe

BIOLOGICAL / BIOTECHNOLOGY DERIVED MEDICINAL PRODUCTS – GUIDELINES ON QUALITY - ICH

Applicable to Gene Therapy

- **Expression Construct**

  (ICH Q5B - Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines used for Production of r-DNA derived Protein Products)

- **Cell Substrates**

  (identity, purity, stability of the expression system)

  (ICH Q5D - Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates used for Production of Biotechnological/Biological Products)

- **Viral safety**

  (ICH Q5A - Quality of Biotechnological Products: Viral safety Evaluation of Biotechnology Products derived from Cell Lines of Human or Animal Origin

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Extended characterisation – gene therapy

Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products

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- 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
- …

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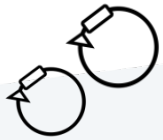
5.14. GENE TRANSFER MEDICINAL PRODUCTS FOR HUMAN USE

This general chapter is published for information.

- Recombinant vector production
- Genetically modified cells
- Plasmids
- Bacterial cell for plasmid production
- Adenovirus vectors
- Poxvirus vectors
- Retrovirus vectors
- Adeno-associated virus vectors



Plasmids as products

Plasmid DNA concentration – sequence
form: Supercoiled, multimeric, monomer or linear
ratio of circular to linear forms,

transfection efficiency and copy number should be demonstrated in relevant cell type(s)
Functional assay following transfection

AAV vector product

Plasmid DNA integrity - rep / cap / ITR + transgene – sequence

Viral genome sequence - genetic stability
Virus particle titre
Infectious titre
Ratio particle to infectious particle ratio
Empty to full capsid ratio
Aggregates

AAV redesign …. Plasmid as starting material – new more efficient promotor and refined construct.

- 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

Retroviral vector for transduction of patient cells

- 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

Strimvelis EPAR on vector comparability :
potency, identity, genetic stability, aggregates and safety.

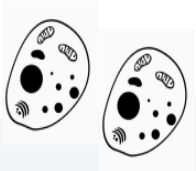
Reflection paper on design modifications of gene therapy medicinal products during development

Adoption by CAT	14 December 2011

Mostly Q few NC considerations – NOT COMPARABILITY GUIDANCE

- Change in vector design
- Change in packaging cell line
- Retroviral transduced cell product
- Adenoviral vector humanised
- Plasmid selection marker change
- Encapsulated cells promotor change
- AAV serotype change
- RV to RV-SIN

Finally, it is desirable to demonstrate that the characteristics and quality attributes of the re-designed RV product are comparable to the parental RV product in terms of vector titre, vector impurity profile, transduction efficiency and copy number per cell and potency of the redesigned RV particles in the transduced cells, in agreement with the general principles laid down in ICH Q5E.



Comparability of GM-CELLS

Viral vector changes

- Critical process steps – CPP
- Consistency of the cell bank
- Infectious viral titre / total particules
- Infectivity
- Transgene sequence
- Transgene expression
- Stability
- Confirmation of transgene expression in permissive cell

\+ Comparability of transduced cells (DS/DP)

Transduced cells

- Critical process steps - CPP
- Immunophenotypic profile
- Cell number, viability
- Transduction efficiency
- Vector copy number
- Transgene sequence
- Biological characterisation
- Potency
- Stability
- Confirmation with patient cells

Additional considerations for technology transfer
Multiple sites with same manufacturing process

- ✓ Enhanced focus on critical manufacturing steps IPC‘s, intermediates quality atributes 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

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 filiations – 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

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

Revised 2012


Thank You !
Questions?