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ICH S12 Nonclinical Biodistribution Considerations for Gene Therapy Products

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Timeline

- Concept Paper and Business Plan endorsed - November 2019
- Step 1 technical document signed by EWG experts - May 2021
- Step 2 draft guideline endorsed - June 2021
- Currently in Step 3 – EWG sign-off
- Step 4 guideline adoption - May 2023

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Table of Contents

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Introduction – Objectives

- To provide harmonised recommendations for nonclinical biodistribution (BD) studies for gene therapy (GT) products
- To provide recommendations for the overall design of nonclinical biodistribution studies
- To provide considerations for the interpretation and application of biodistribution data

Introduction - Definition of Gene Therapy Products

- "Therapeutic products that mediate their effect by the expression (transcription/translation) of transferred genetic materials, or by specifically altering the target genome of human cells."
  - Examples:
    - purified nucleic acids
    - microorganisms genetically modified to express transgenes
    - *ex vivo* genetically modified human cells
  - Excluded from scope:
    - prophylactic vaccines
    - chemically synthesized oligonucleotides

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Definition of Nonclinical Biodistribution

- "…the *in vivo* distribution, persistence, and clearance of a GT product at the site of administration and in target and non-target tissues, including biofluids"

  - Excluded from scope:
    - shedding
    - genomic/germline integration

Timing of Nonclinical Biodistribution Assessment

- Data should be available for interpretation of pharmacological and toxicological findings

- Biodistribution assessment should be completed prior to the first-in-human trial

Design of Nonclinical Biodistribution Studies

Study Element	Guideline Recommendations
Study type	Stand alone or combined with pharmacology or toxicology study
GLP status	GLP-compliant or non-GLP-compliant
Test article	Representative of the intended clinical product
ROA	Intended clinical route of administration (ROA)
Dose levels	Equal to or greater than anticipated maximum clinical dose High-dose should be the expected high-dose in toxicology studies

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Design of Nonclinical Biodistribution Studies – cont'd

Study Element	Guideline Recommendations
Species/Model	Biologically relevant species Model that supports transfer and expression of the genetic material
Sex	Males and females, unless otherwise justified (clinical use in 1 sex)
Animal numbers	Appropriate number/sex/group/time point (see also Note 2)
Sample collection	Select time points to cover time-related changes in levels Blood, injection sites, gonads, adrenal gland, brain, spinal cord, liver, kidney, lung, heart, spleen, and any other relevant tissues

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Specific Considerations

Considerations	
Assay Methodologies	Quantitates amount of the genetic material in tissues/biofluids
Measurement of Expression Products	Contributes to the characterisation of safety and activity profiles
Immunological Considerations	Pre-existing immunity: screen animals Immune response to gene therapy: immunogenicity analysis Immune response to expression product: orthologous transgene
Ex vivo Genetically Modified Cells	Consider factors such as: - cell type - ROA - potential for the expression product or gene modification event to affect the expected distribution of the cells

Specific Considerations cont'd

Considerations	
BD Assessment in Gonadal Tissues	Include both male and female gonadal tissues Persistent presence in gonads can lead to additional studies to determine levels in specific cell types in the gonad (refer to ICH considerations paper)
Triggers for Additional Nonclinical BD Studies	Significant changes in: - ROA, dose (increase), and/or dosing regimen - vector structure or serotype - changes in final formulation and properties
Considerations for Alternative Approaches	Existing BD data can support additional indications/populations for the same product, but consider changes in ROA, dose/dosing regimen, promoter, etc. Study may not be feasible when a biologically relevant species does not exist: use an alternative approach

Application of Nonclinical Biodistribution Studies

Nonclinical biodistribution data:

- Contribute to the interpretation and design of nonclinical pharmacology and toxicology studies

- Inform elements of a first-in-human trial and subsequent clinical trials
  - E.g., dosing procedure and monitoring and long-term follow-up plans

Summary

ICH S12 is the first nonclinical ICH guideline on gene therapy products and provides for :

- A harmonised definition for gene therapy products
- Recommendations on the timing and optimal design of biodistribution studies
- Factors and potential effects to consider when designing biodistribution studies
- Factors to consider when determining the need for biodistribution studies

Thank You