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S12 : Nonclinical Biodistribution Considerations for Gene Therapy Products

Step 2

Step 2 document – to be released for comments

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International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Legal Notice

Background

- **This document has been signed off as a *Step 2* document (3 June 2021) to be issued by the ICH Regulatory Members for public consultation**
- **This document was developed based on a Concept Paper (18 November 2019) and a Business Plan (18 November 2019)**
- **Anticipating finalization as a *Step 4* document to be implemented in the local regional regulatory system: June / 2023**

Key Principles

- Biodistribution (BD): the *in vivo* distribution, persistence, and clearance profile of the administered gene therapy (GT) product
- Nonclinical BD data contribute to interpretation and design of nonclinical pharmacology and safety studies intended to support administration of investigational GT products in early-phase clinical trials
- Recommendations provided for the design elements of a nonclinical BD study for a GT products
- To help reduce the use of animals, in accordance with the 3Rs (reduce/refine/replace) principles

Guideline Objectives

- To provide harmonised recommendations for the BD component of a nonclinical development programme of GT products which facilitates clinical trial design, and helps reduce the use of animals, in accordance with the 3Rs (reduce/refine/replace) principles
- Achieve consensus that supports optimal design of nonclinical BD studies, and promotes development of safe and effective GT products

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Section 1 : Introduction

- Objective of S12 is to provide harmonised recommendations for the nonclinical BD assessment of GT products while following the 3Rs principles
- Nonclinical BD data contribute to the interpretation and design of nonclinical pharmacology and toxicology studies conducted to support early-phase clinical trials in the target population
- Describes the types of GT products within the scope of S12
- Evaluation of shedding and genomic/germline integration is not within the scope of S12

Section 2 : Definition of Nonclinical BD

- **Nonclinical BD is 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 (e.g., blood, cerebrospinal fluid, vitreous fluid), in a biologically relevant animal model**

Section 3 : Timing of Nonclinical BD Assessment

- **Nonclinical BD assessments should be completed prior to initiation of the first-in-human clinical trial**
- **Preliminary BD data at an early stage of product development aids animal species selection**
- **BD data should be available for interpretation of pharmacological or toxicological findings**

Section 4 : Design of Nonclinical BD Studies

- **4.1. General Considerations**
  - BD studies can be conducted as stand-alone BD studies or in conjunction with nonclinical pharmacology and toxicology studies
- **4.2. Test Article**
  - The test article should be representative of the intended clinical GT product
- **4.3. Animal Species or Model**
  - BD assessment should be conducted in a biologically relevant animal species or model that is permissive for transfer and expression of the genetic material

Section 4 : Design of Nonclinical BD Studies Cont'd

- **4.4. Group Size and Sex of Animals**
  - An appropriate number of animals per sex (as applicable) should be evaluated at predetermined sampling time points to generate sufficient data
- **4.5. Route of Administration and Dose Level Selection**
  - GT product should be administered using the intended clinical route of administration (ROA), as feasible
- **4.6. Sample Collection**
  - Time points should cover anticipated time to reach peak, steady-state (i.e., plateau), and declining (if feasible) levels following GT product administration
  - Core panel of tissues/biofluids: blood, injection site(s), gonads, adrenal gland, brain, spinal cord (cervical, thoracic, and lumbar), liver, kidney, lung, heart, and spleen

Section 5 : Specific Considerations

- **5.1. Assay Methodologies**
  - BD determined by quantitating the amount of genetic material (DNA/RNA) of the GT product in tissues/biofluids and, if appropriate, expression products
  - The limit of sensitivity and reproducibility of the quantification method should be established and documented
- **5.2. Measurement of Expression Products**
  - Expression product assessments can contribute to the characterisation of the safety and activity profiles of a GT product
- **5.3. Nonclinical BD Assessment as a Component of Pharmacology and Toxicology Studies**
  - In addition to stand-alone studies, BD assessment can also be performed as part of nonclinical pharmacology and toxicology studies

Section 5 : Specific Considerations Continued

- **5.4. Immunogenicity**
  - Pre-existing immunity in animals against a GT vector could affect the BD profile
  - Immune response triggered in other species which may result in a BD profile that is not informative
- **5.5. *Ex vivo* Genetically Modified Cells**
  - Considerations for BD assessment of GT products that consist of *ex vivo* genetically modified cells
- **5.6. BD Assessment in Gonadal Tissues**
  - Conduct BD assessment of the administered GT product in the gonads for both sexes unless justified
  - Persistent presence of GT product in gonads can lead to additional studies to determine GT product levels in specific type of cells in the gonad (e.g., oocytes, sperm, Sertoli cells, Leydig cells)

Section 5 : Specific Considerations Continued

- **5.7. Triggers for Additional Nonclinical BD Studies**
  - Examples that necessitate additional nonclinical BD assessment are provided
- **5.8. Circumstances when Nonclinical BD Studies may not be Needed or are not Feasible**
  - Consider factors such as dose levels, regimen, ROA, etc., to decide whether existing BD data obtained from nonclinical studies conducted with the same GT product support a different clinical indication for a new clinical population
  - Nonclinical BD study may not be feasible when biologically relevant animal species that can inform the BD profile in the clinical population does not exist

Section 6 : Application of Nonclinical BD Studies

- **Nonclinical BD data contribute to the overall interpretation of the animal study to enable a better understanding of the potential correlation of the various findings (desired and undesired) to the administered GT product**
- **Attribution of findings observed in the dosed animals to the genetic material (DNA/RNA) and/or to the expression product help establish a benefit:risk profile of the GT product before administration in humans**
- **The relevancy of the BD data to the clinical population is influenced by factors such as the ROA, dose level(s), dosing regimen, and animal immune response to the GT product**
- **BD data can also inform elements of a first-in-human trial and subsequent clinical trials**

Conclusions

- **S12 is the first ICH guideline that specifically addresses an important nonclinical development component of GT products**
- **The S12 guideline provides consideration points for optimal design of the BD component of nonclinical studies**
- **The S12 guideline facilitates nonclinical and clinical development programmes for GT products, while observing the 3Rs principles**

Contact

- **For any questions please contact the ICH Secretariat:**

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