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ICH S12 Nonclinical Biodistribution Considerations for Gene Therapy Products

Step 4 document – to be implemented

6 March 2023

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

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Background

- **This document has been signed off as a *Step 4* document (14 March 2023) to be implemented by the ICH Regulatory Members**
- **This document was developed based on a Concept Paper and a Business Plan (both approved 18 November/2019)**

Key Principles

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

Guideline Objectives

- To provide harmonised recommendations for assessment of BD during nonclinical development of a GT product
- To provide recommendations for the overall design of nonclinical BD studies
- To provide consideration points for the interpretation and application of BD data
- To facilitate nonclinical development of GT products while remaining in accordance with the principles of 3Rs

Table of Contents

Section 1 : Introduction

- The objective of ICH S12 is to provide harmonised recommendations for the nonclinical BD assessment of GT products while following the principles of 3Rs
- 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
- With continued scientific advances in the GT field, incorporation of this topic in early discussions of the nonclinical program for a GT product with the appropriate regulatory authority is encouraged
- Describes the types of GT products within the scope of ICH S12
- Evaluation of shedding and genomic/germline integration are not within the scope of ICH 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)

Section 3 : Timing of Nonclinical BD Assessment

- BD data should be available when evaluating the nonclinical pharmacology and toxicology findings
- Nonclinical BD data can inform design aspects of a first-in-human clinical trial
- It is important that nonclinical BD assessment(s) be completed prior to initiation of the clinical trial

Section 4 : Design of Nonclinical BD Studies

- **4.1. General Considerations**
  - Can be conducted as stand-alone BD studies or in conjunction with nonclinical pharmacology and toxicology studies
  - The GT product administered should be representative of the intended clinical product and use the clinical the route of administration (ROA)
  - While non-GLP (Good Laboratory Practice) BD studies are acceptable, BD evaluation as part of a GLP toxicology study should maintain GLP compliance for in-life procedures and sample collection (analysis of BD samples can be conducted in non-GLP manner)

Section 4 : Design of Nonclinical BD Studies

- **4.2. Test Article**
  - The test article should be representative of the intended clinical GT product, taking into consideration the manufacturing process, important product characteristics (e.g., titre), and the final clinical formulation
  - In some situations, nonclinical BD data generated with a GT product consisting of the same vector intended for clinical use and a different therapeutic transgene or an expression marker can be leveraged

Section 4 : Design of Nonclinical BD Studies continued

- **4.3. Animal Species or Model**
  - Animal species/model should support transfer and expression of the genetic material
  - Selection factors can include species differences in tissue tropism of the GT product, gene transfer efficiency, and transgene expression in target and non-target tissues/cells
  - Replication competent viral vectors should be studied in an animal species or model that is permissive to vector replication
  - The influence of species, sex, age, physiologic condition (e.g., healthy animal vs. animal disease model) on the BD profile can be important

Section 4 : Design of Nonclinical BD Studies continued

- **4.4. Group Size and Sex of Animals**
  - An appropriate number of animals should be evaluated at each sampling time point for comprehensive BD assessment
  - In keeping with the principles of the 3Rs, the total number of animals can be an aggregate from several studies
  - Justification should be provided for:
    - The number of animals evaluated at each time point
    - The use of combined data from multiple studies, as applicable
    - The use of a single sex, as applicable

Section 4 : Design of Nonclinical BD Studies continued

- **4.5. Route of Administration and Dose Level Selection**
  - The GT product should be administered using the intended clinical ROA, as feasible
  - The selected dose levels should provide adequate characterisation of the BD profile to aid in interpretation of the pharmacology and toxicology assessments
  - The highest dose level evaluated should be the expected maximum dose level in the toxicology studies (usually limited by animal size, ROA/anatomic target, or GT product concentration)
  - Dose levels for BD evaluation should equate or exceed the anticipated maximum clinical dose level, but should not exceed the highest dose level administered in the toxicology study

Section 4 : Design of Nonclinical BD Studies continued

- **4.6. Sample Collection**
  - The sample collection procedure for target and non-target tissues and biofluids should be designed to minimise the potential for contamination and include appropriate sample retention and documentation
  - Multiple sample collection time points to characterise the changes in GT product levels over time
  - Replication competent vectors should be evaluated for the second peak due to viral replication
  - Recommended panel of tissues/biofluids: injection site(s), gonads, adrenal gland, brain, spinal cord (cervical, thoracic, and lumbar), liver, kidney, lung, heart, spleen, and blood
  - Collected samples can also be analysed for the presence of the expression product

Section 5 : Specific Considerations

- **5.1. Assay Methodologies**
  - BD is determined by quantifying the amount of a GT product's genetic material (DNA/RNA) and expression products in tissues/biofluids
  - Nucleic acid amplification methods (e.g., qPCR, digital PCR, etc.) are commonly used
  - Quantify the amount of genetic material (DNA/RNA) of the GT product in tissues/biofluids relative to the genome DNA content of the input sample
  - When cellular content varies significantly in a sample (e.g., biofluids), DNA/RNA concentration (e.g., copy number/ microL) can be used
  - Spike and recovery experiments should be performed to demonstrate the ability to detect the target nucleic acid sequence in different tissues/biofluids
  - Provide a comprehensive description of the methodology and the justification for the technique used, including the performance parameters (e.g., sensitivity and reproducibility) of the method

Section 5 : Specific Considerations Continued

- **5.2. Measurement of Expression Products**
  - Determination of the level of the expression product in vector genome positive tissues/biofluids can contribute to characterisation of safety and pharmacological activity profiles following GT product administration.
  - The need to measure expression products should be based on a risk-based approach, which can include considerations such as:
    - The GT product levels and persistence in tissues/biofluids
    - The target clinical population
    - Potential safety concerns associated with the vector and/or the expression product

Section 5 : Specific Considerations Continued

- **5.3. Immunological Considerations**
  - Pre-existing immunity in animals against a GT product could affect the BD profile
  - Consider screening animals for pre-existing immunity to the vector prior to inclusion in a nonclinical study and randomisation
  - Collection of samples for immunogenicity analysis may aid interpretation of BD data when immune response to the GT product after administration results in a BD profile that is not informative
  - Immunosuppression of animals for the sole purpose of evaluating BD profile is not recommended
  - A species-specific orthologous transgene can be considered to circumvent the effects of the immune response against the expression product(s)

Section 5 : Specific Considerations Continued

- **5.4. *Ex vivo* Genetically Modified Cells**
  - Considerations should include factors such as the cell type, ROA, and the potential for the expression product or gene modification event to affect the expected distribution of the cells within the body (e.g., new or altered expression of cell adhesion molecules)
  - In general, BD assessment of *ex vivo* genetically modified cells of haematopoietic origin is not critical based on expected widespread distribution following systemic administration
  - If distribution to a target organ(s)/tissue(s) is expected, BD assessment of select tissues should be considered in appropriate animal species/models

Section 5 : Specific Considerations Continued

- **5.5. BD Assessment in Gonadal Tissues**
  - BD of the administered GT product in the gonads should be evaluated for both sexes unless justified (e.g., target clinical population is exclusively either male or female)
  - If long term persistence is detected, additional studies to determine GT product levels in germ cells (e.g., oocytes, sperm) or non-germline cells in the animals to inform the risk of inadvertent germline modification
  - Persistent GT product detection in non-germline cells in gonadal tissues (e.g., leukocytes, Sertoli cells or Leydig cells) can warrant additional consideration of its potential effect on the function of the affected non-germline cells, particularly if the cell type is important to successful reproduction

Section 5 : Specific Considerations Continued

- **5.6. Triggers for Additional Nonclinical BD Studies**
  - A significant change in the clinical development programme, such as: a change in the ROA; an increase in the GT product dose level; changes in the dosing regimen; and inclusion of another clinical indication that includes both sexes
  - A significant change in the vector structure or serotype, or any other modifications that may result in changes in distribution or transgene expression
  - Changes in the manufacturing process that can affect the final GT product formulation (e.g., addition of excipients that could alter vector tissue tropism) or relevant quality attributes of the GT product (e.g., gene transfer activity, product titre)

Section 5 : Specific Considerations Continued

- **5.7. Considerations for Alternative Approaches**
  - Existing BD data from the same GT product for a different clinical indication can potentially suffice with considerations such as the dose level(s), dosing regimen, ROA, and change in promotor factored into this decision
  - BD data obtained with a previously characterised GT product that has the same vector structure and other characteristics that determine its tissue tropism, but a different transgene, can potentially support waiving an additional nonclinical BD study
  - When a biologically relevant animal species that can inform the BD profile in the clinical population does not exist, provide a comprehensive discussion of the issue and justification to support an alternative approach to evaluation of nonclinical BD

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 ascertain a benefit:risk profile of the GT product before administration in humans
- BD data can also inform elements of a first-in-human trial and subsequent clinical trials such as the dosing procedure (i.e., dosing intervals between subjects), the monitoring plan, and long-term follow-up assessment

Conclusions

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

Contact

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