

**Concept Paper**  
**S12: Nonclinical Biodistribution Considerations for Gene Therapy Products**  
**Dated 18 November 2019**  
*Endorsed by the Management Committee on 18 November 2019*

**Type of Harmonisation Action Proposed**

The field of gene therapy (GT) is progressing at an exponential pace. There are many investigational GT products in the development pipeline, starting with the research/discovery stage and extending to all phases of clinical trials. Several GT products are now approved in various global regions for the treatment of oncology and non-oncology medical conditions. As such, the field (industry and regulators) recognises that international harmonisation regarding aspects of the nonclinical development programme for GT products is needed. Therefore, a Safety Guideline discussing the biodistribution (BD) considerations in nonclinical studies to support the development of GT products is proposed. The conduct of BD studies is considered an important component of the nonclinical programme for a GT product. The BD data are considered informative and necessary to support GT product administration and safety monitoring in early clinical trials. This guideline will provide recommendations on the elements of nonclinical studies performed that include BD assessment, and will contribute to the streamlined development of the GT products, while maintaining scientific rigor and minimising the unnecessary use of animals.

**Statement of the Perceived Problem**

Existing regulatory guidance documents released by various regulatory authorities contain different expectations on the BD assessment of GT products. This creates a challenge for both regulators and industry when developing a GT product. Examples of areas in which harmonisation is currently lacking, but is needed, include:

1. GT products that will be covered under this guideline;
2. The definition of BD;
3. The need for and timing of the conduct of BD studies;
4. BD study design components;
5. Assay methodologies for assessing BD;
6. BD data required to justify the selection of most relevant species for nonclinical pharmacology and safety studies; and
7. Interpretation of BD data to help inform aspects of clinical trial design.

Lack of harmonisation in the above areas may lead to divergent nonclinical BD study designs, unnecessary use of animals, and the delay of the overall nonclinical development programme and subsequent administration of an investigational GT product in clinical trials.

## Issues to be Resolved

The guideline will address the areas in which harmonisation is needed as identified above. It will provide a transparent, consistent, and harmonised approach across regulatory regions.

1. The scope of this guideline will specify the GT product types and the objective and definition of BD, as these factors are critical to effective implementation of the guideline.
2. The guideline intends to address the timepoint in a product development programme when BD studies should be performed, as well as any circumstance where a BD study would not be required.
3. The guideline will provide recommendations for the overall design of nonclinical BD studies, such as test article identification, animal species selection, dose levels, sample collection time intervals, and types of samples to be collected.
4. The guideline will provide considerations for when a BD study is incorporated into nonclinical pharmacology and safety studies or conducted as an independent study.
5. The guideline will discuss considerations in assay methodologies.
6. The guideline will discuss considerations for investigational GT products that are modified during product development and the potential need to conduct additional BD studies.
7. The guideline will discuss application of the nonclinical BD data to inform the clinical trial design (e.g., monitoring, long-term follow-up).

## Background to the Proposal

Existing nonclinical regional guidances for GT products differ in scope and their descriptions for BD study considerations. This topic has been discussed by regulatory authorities within the framework of the International Pharmaceutical Regulators Programme (formerly International Pharmaceuticals Regulators Forum) Gene Therapy Working Group (GTWG), which formed in 2013. This WG released a Reflection Paper in 2018 titled, "Expectations for Biodistribution (BD) Assessments for Gene Therapy (GT) Products" (<http://www.iprp.global/working-group/gene-therapy>). This paper also reflects a public discussion that occurred in a dedicated session at the annual American Society of Gene and Cell Therapy meeting in 2015. The interactive discussion that occurred in this session was also summarised in a publication titled, "Biodistribution studies: understanding international expectations" (Huang et al. *Molecular Therapy Methods and Clinical Development* Volume 3, 16022, 2016; <https://doi.org/10.1038/mtm.2016.22>). These documents provide a starting point for the proposed S12 guideline.

## Type of Expert Working Group (EWG) and Resources

The EWG should be composed of nonclinical experts in the fields of toxicology, pharmacology, and biology of GT products, nominated by ANVISA, Brazil; BIO; EFPIA; EC, Europe; FDA, United States; Health Canada, Canada; JPMA; MFDS, Republic of Korea; MHLW/PMDA, Japan; NMPA, China; PhRMA; Swissmedic, Switzerland; TFDA, Chinese Taipei, as well as other regulatory members if requested. Additional observer members can be nominated by WHO, as well as other observer organisations, if requested.

## Timing

After the Concept Paper and Business Plan are endorsed by the Assembly, the EWG will be formally established in early 2020. It is expected that this project could be completed in 3 years (*Step 4* in 2Q 2023), which includes the public consultation period.