Final Business Plan
S12: Nonclinical Biodistribution Considerations for Gene Therapy Products
Dated 18 November 2019
Endorsed by the Management Committee on 18 November 2019

Background

Understanding the distribution, persistence, and clearance profiles (biodistribution assessment) of gene therapy (GT) products following *in vivo* administration is an important element of the nonclinical development programme for investigational GT products. These data contribute to the design of safety studies in animals, as well as provide insight and supportive information for pharmacology/proof of concept studies. In addition, the biodistribution (BD) data can inform dose levels, dose-escalation paradigms, dosing schedules, and monitoring plans for clinical trials in the target clinical population. In July 2018, the International Pharmaceutical Regulators Programme (IPRP) Gene Therapy Working Group (GTWG) published a Reflection Paper titled "Expectations for Biodistribution (BD) Assessments for Gene Therapy (GT) Products" (http://www.iprp.global/working-group/gene-therapy). The purpose of this document was to communicate current thinking of global regulators regarding: 1) when BD studies are necessary; 2) the timing for conduct of BD studies; and 3) the design of nonclinical BD studies. While this document is generally informative in content, regulators and sponsors/investigators in this field recognise that existing nonclinical regulatory guidances for GT products authored by various regulatory bodies differ in the classification of a GT product, the scope of the respective guidance, the definition of BD, and overall considerations for BD assessment. Therefore, a harmonised guideline is needed that will address these issues, as well as provide discussion and recommendations regarding the timing, design and analysis tools of BD assessment, and its application to clinical trial design.

1. The issue and its costs

Existing regional guidances address nonclinical BD studies and relevant technical aspects, including the need for, scope, timing and design of BD studies, as well as overall application of resulting BD data in product development. However, there is a lack of consistency between regions. Due to global development of GT products, there is a need for harmonisation.

The consequences of this issue include unnecessary use of animals, repeating studies due to differing regulatory requirements, and inconsistencies in study design and data quality that may affect understanding the product safety profile. This can lead to increases in the cost of development programmes for GT products and delays in clinical trial initiation. Of note, many of the investigational GT products are intended for the treatment of diseases/medical conditions for which no effective therapy exists. Thus, lack of harmonisation can be deleterious for the regulators, the sponsors/investigators, and the patients.

2. Planning

- *What are the main deliverables?*

  A harmonised guideline on nonclinical BD assessment for GT products will provide clarity and transparency for the following critical elements:
  - GT products that will be covered under this guideline;
  - The definition of BD;

- The need for and timing of the conduct of BD studies;
- BD study design components;
- Assay methodologies for assessing BD;
- BD data required to justify the selection of most relevant species for nonclinical pharmacology and safety studies;
- Interpretation of BD data to help inform aspects of clinical trial design; and
- Application of the "3Rs" (Replacement/Reduction/Refinement) principles of animal use.

- *What resources (financial and human) would be required?*

  Formation of an expert working group (EWG) (maximum of two experts 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, and other regulatory members as requested). One member designated as an observer can also be nominated by WHO, as well as other observer organizations, and active/dedicated participation by industry, regulatory, and *ad hoc* advisory members as necessary. The EWG members are expected to have expertise in nonclinical toxicology, pharmacology, and biology of GT products, as well as an understanding of the regulatory process in their respective regions. Technical support for EWG activities that include teleconferences and online information exchange will be necessary.

- *What is the time frame of the project? What will be the key milestones?*

  The Concept Paper and this Business Plan will be submitted to the ICH Management Committee (MC) and placed for endorsement by Assembly on November 18, 2019. Establishment of EWG is to be in early 1Q 2020, with the expectation of the first face-to-face meeting of the EWG in May 2020. It is anticipated that a Step 2b guideline will be completed by 2Q 2021, with Step 4 reached by 2Q 2023.

- *What special actions to advance the topic through ICH, e.g. stakeholder engagement or training, can be anticipated either in the development of the guideline or for its implementation?*

  Training materials, such as a slide presentation, that explain the S12 guideline background and document contents, will be generated as needed, for critical phases of guideline development (*i.e.*, Step 2b and Step 4).

3. The impact of this guideline

- *What are the likely benefits (social, health and financial) to our key stakeholders of the fulfilment of the objective?*

  A harmonised guideline will result in more streamlined and efficient GT product development programmes, minimise animal use, and provide a basis for consistent scientific evaluation of investigational GT products. These factors will also inform elements of clinical study design and contribute to overall development of safe and effective GT products.

- *What are the regulatory implications of the proposed work – is the topic feasible (implementable) from a regulatory standpoint?*

  The guideline will be consistent with current laws and regulations of the ICH regions. A primary objective of the document is to achieve consistent recommendations on BD assessment for GT products that are in keeping with the regional regulations. The guideline will supersede regional guidances and is intended to reduce the burden on resources needed for regulatory authorities responsible for application review.

- *Will the guideline have implications for the submission of content in the CTD/eCTD? If so, how will the working group address submission of content in the dossier? Will a consult be requested with the ICH M8 working group?*

  The guideline should not affect the submission of content in the CTD/eCTD. It is expected that summaries of the BD evaluations will be included in Module 2, and the study reports will be included in Module 4.

4. Post-hoc evaluation

- *How and when will the results of the work be evaluated?*

  Not applicable.