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MEETING REPORT

Biodistribution studies: understanding international expectations

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On 15 May 2015 during the 18th Annual American Society of Gene and Cell Therapy (ASGCT) Meeting[1] regulators from the International Pharmaceutical Regulators Forum Gene Therapy Working Group presented current expectations of various international regulatory authorities for preclinical/nonclinical biodistribution (BD) studies. This session began with a presentation by an industry representative that summarized the discussion of BD studies during the ASGCT 2014 Standard Pathways Conference[2] in February 2014. The 2014 Conference identified the BD topic as an area in which existing preclinical data and clinical trial experiences for various gene therapy (GT) products could potentially be leveraged to establish a standardized regulatory approach worldwide for industry and investigators developing GT products. The 2014 meeting participants recognized that in order to accomplish this goal, participation of international regulatory authorities, in addition to the US Food and Drug Administration (FDA), would be required. Realizing the importance of this effort, the ASGCT decided to host this session entitled "Biodistribution studies: Understanding International Expectations."

The session was chaired by the US FDA and HSA Singapore, and included presentations from representatives of industry, European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency—Japan (PMDA), and Health Canada (HC). These presentations conveyed similar perspectives on the definition of BD and the importance of collecting BD data. The presentations were followed by a panel discussion that included session co-chairs, presenters, additional regulators from Taiwan Food and Drug Administration (Chinese Taipei), Swissmedic, National Health Surveillance Agency Brazil, Thailand Center of Excellence for Life Sciences, South Korea Ministry of Food and Drug Safety, and audience members.

The EMA presentation emphasized the importance of collecting BD information early in product development to guide design of preclinical toxicology studies and inform decisions on the need for additional preclinical studies (if any). The presentation summarized EMA requirements for BD study design, which include a dosing protocol that mimics the proposed clinical protocol with appropriate safety margins (usually highest dose), assessing all relevant organs, and extension of the analysis interval until the GT product is not detected or until a plateau phase is reached. Furthermore, the EMA noted that a study design may be adapted to different GT products and is not one-size-fits-all.

The PMDA presentation provided an overview of different BD studies for adenovirus and adeno-associated virus vectors. The presentation introduced the idea of inclusion of a relevant animal species and the use of different detection methodologies, including quantitative polymerase chain reaction, immunohistochemistry, fluorescent protein expression, and *in vivo* imaging.[3–5]

The HC presentation provided an overview of recommendations for BD assessment and noted that HC expectations are similar to those of the EMA and FDA. HC also elaborated on BD expectations for replication competent vectors, emphasizing that target tissue selectivity is a particularly important aspect of BD studies for product development.

In general, the presentations from the international regulatory agencies relayed a similar position on the utility of BD data in understanding the biological activity of a GT product, and the importance of collecting BD data for new GT vectors.[6–8] Some regulators suggested that there may be situations in which collecting new or additional BD data is not always necessary. Considerations for reducing redundant BD studies for GT products within the same vector class were discussed; however, a number of caveats exist (*e.g.*, vector design, dose, route of administration, disease).

The panel discussion that followed the presentations deliberated on the limitations associated with preclinical BD studies, such as the inherent differences between animals and humans (*e.g.*, differences in organ size, receptor distribution, and physiology/pathophysiology). The stated position of the panelists was that BD studies are currently designed on a case-by-case basis. There was general acknowledgement among the panel members that a rationale should be developed for each BD study for a particular GT product to support the choice of animal species or model system, and this rationale should address any differences compared to humans.

The need for regulatory harmonization of BD studies across the different regions to address international differences in approaches to design and assessment of integration and germline transmission studies was suggested. In addition, guidance for developing technologies (*e.g.*, gene editing), in which low copy numbers may limit usefulness of even quantitative polymerase chain reaction in BD studies, was proposed. Moreover, panel members recognized that the appropriate use of existing data or sharing BD data would facilitate GT product development.

In conclusion, the session held jointly by the ASGCT and International Pharmaceutical Regulators Forum/Gene Therapy Working Group on the topic of BD studies highlighted: (i) the importance of collecting BD data for new GT products, (ii) understanding the limitations of available model systems and analysis methods, (iii) application of a flexible, scientific approach to assessment of BD, and (iv) consideration of various paradigms for reducing redundant BD studies for GT products within the same vector class. This ASGCT session provided a first-time opportunity for scientists from regulatory bodies across the globe and developers of GT products to dialog together on this important issue.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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