Development and Practical Use of Cell and Gene Therapy Products

4th DIA Cell and Gene Therapy Products Symposium in Japan

Akiko Ikeda
Jansen Pharmaceutical K.K

The development of regenerative medicines such as cell and gene therapy products was accelerated in Japan by new regulatory and legal systems that came into effect in 2013 and it continues to attract considerable international attention in not only scientific journals but in more general publications. Reports on these development advancements have revealed numerous challenges in the development, distribution, and post-market management of these products.

Since 2016, DIA Japan has convened an annual symposium to help local and global product developers address these challenges. Its agenda has been updated each year to reflect scientific progress in each stage of development, and to articulate global development strategies for these novel therapeutics, culminating in the recent *4th DIA Cell and Gene Therapy Products Symposium* held in December 2019 in Tokyo.

Genome Editing

Genome editing technology, which modifies a target gene by "editing," continues to be studied in many clinical trials worldwide. These trials have already identified such risks as chromosome translocation or deletion, and off-target effects. Teruhide Yamaguchi (Kanazawa-Institute of Technology) and Keynote Speaker Kohnosuke Mitani (Research Center for Genomic Medicine, Saitama Medical University) led discussions in this area through a series of questions, such as: How do we detect functionally important DNA mutations? How do we evaluate the functional genotoxicity of off-target mutations? It seems reasonable to expect that further activities in the development of these innovative products will incorporate more benefit-risk discussions.

Concept of Comparability in Cell and Gene Products

Manufacturers of regenerative medicines sometimes make changes during product development and after product approval for the purposes of improving processes, facilitating product manufacturing scale-up, and other constructive reasons. The delicate nature of these products can make demonstrating comparability after implementing such improvements essential. Comparability has emerged as an important topic in cell and gene therapy product development, and these discussions will continue.

Conformity with Cartagena Act

Development and commercialization of gene therapy products in Japan must conform to the principles of the Cartagena Act through the Japanese unique law, Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. For products developed without the containment measures defined in this Act, developers must receive approval from the Ministry of Health, Labour and Welfare (MHLW) to establish operational conditions aligned with the MHLW Type 1 Use Regulation before beginning any clinical study of these products. Academic and industry researchers joined regulatory representatives from the PMDA to share experiences with problems and solutions in these

situations in a panel discussion forum. While issues remain with conducting clinical trials under the Cartagena Act, each presentation provided clarity on specific aspects of these challenges.

Japan, EMA and US Regulatory Panel Discussion

As development of gene therapy products continues to progress all over the world, monitoring their efficacy and safety profiles after treatment, compared with more conventional therapies, is extremely important. It is essential to consider risk management planning and risk assessment as part of the development of these innovative new products. Expert representatives from Japan PMDA and US FDA were remotely joined by regulatory speakers from the EU through the WebEx platform to discuss the relative states of regulatory and related frameworks for gene and cell therapy products across Japan, the EU, and the US. We found that the basic concept of follow-up treatment using genetically modified organism (GMO) products is almost identical between these three parties, and that we can expect their shared experiences to facilitate product development in this area.

Keynote Speakers and Program Chair

The Program Team wishes to thank the key opinion leaders who delivered Keynote Addresses on their cutting-edge research: Kohnosuke Mitani (Saitama Medical University) on genome editing; Koji Eto (Center for iPS Cell Research & Application, Kyoto University) on platelet production from iPS cells; and Hiroshi Shiku (Mie University Graduate School of Medicine) on CAR-T research. Special thanks to Program Chair Daisaku Sato of PMDA, who is also one of the founders of this annual symposium.