The Drug Information Association (DIA) of Japan hosted its 11th Annual Meeting from November 16-18 in the Tokyo Bay Area, where the futuristic culture is flowing. Over 800 attendees from worldwide regulatory agencies, pharmaceutical industries, and Japanese healthcare and academic organizations gathered for 3 days of presentations and discussions. Having succeeded to last year’s theme, “Revolutionary Drug Development,” this year the annual meeting focused on “Medical Innovation that Transcends Boundaries for Drug Development.” Among the 6-track sessions, 2 sessions discussed on regenerative medicines.

Since Dr. Shinya Yamanaka (Center for iPS Cell Research and Application [CiRA], Kyoto University) discovered how to reprogram mature cells to become induced pluripotent stem cells (iPS) capable of developing into tissues of the body, work for which he received the Nobel Prize in 2013, the research and utilisation of iPS cells has drawn nationwide as well as global attention for exploring the meaningful medical innovation. However, there was no legal basis for assuring the safety of stem cell therapies, and the regulatory framework under the Pharmaceutical Affairs Law (PAL) was not suited to address the characteristics of regenerative and cellular therapeutic products. New regulations were urgently required to fulfill the needs of clinical development and marketing.

REGULATORY FRAMEWORK BROUGHT BY THE REVISION OF THE JAPANESE PHARMACEUTICAL AFFAIRS LAW

The Japanese government promulgated 2 acts in November 2013 in order to define a regulatory framework for regenerative medicines in Japan: the “Act to Revise Pharmaceutical Affairs Law (PAL) (Law No. 84/2013)” and the “Act concerning Safety Assurance of Regenerative Medicine, etc. (Law No. 85/2013).” Both acts were enforced on November 25th.

Under the new regulations, “regenerative medicine” is defined as processed human cells that are intended to be used for: A) either (1) the reconstruction, repair, or formation of structures or functions of the human body or (2) the treatment or prevention of human diseases; or B) for gene therapy that is equivalent to cellular and tissue-based products and gene therapy products as per the US definition, or advanced-therapy medicinal products (ATMPs) as per the EU definition. The 2 acts regulate the matters concerning non-commercialization and commercialization separately, whereas the US regulations on regenerative medicines are applied to both. Law No. 84/2013 regulates production and marketing of regenerative and cellular therapeutic products by companies, and Law No. 85/2013 provisions the matters of non-commercialization, securing safety of stem cell therapies.

The 2 acts make a turning point for developing and marketing regenerative medicines in Japan. Some significant points include:

**Law No. 84/2013:**
- Product approval based on the laws is required from now on.
- Expedited approval system is introduced for regenerative medical products.

**Law No. 85/2013:**
- It became mandatory for medical institutions to submit plans of research and treatment.
- It became possible to provide the products from other than medical institutes. In other words, cell culture can be contracted to a cell culture factory, for example.
- A license system for a cell processing center (CPC) is introduced that should comply with GCTP (Good gene, Cell & Tissue Practice) regulating quality risk management; manufacturing control; quality control; and facility requirements of gene, cell, and tissue products.
Huge impact on R&D and marketing is expected from this new regulatory framework. Both academia and industry were excited about exploring the new opportunities in research and business.

RESEARCH INITIATED BY ACADEMIA

Japanese academia shows great initiative to conduct research on regenerative medicines. The Institute of Advanced Biomedical Engineering and Science at Tokyo Women’s University has conducted clinical and pre-clinical studies for treatment applications using cell sheets in cornea, esophagus, periodontium, heart, ear, cartilage, and lung. Toshiyuki Owaki presented 2 examples of esophageal mucosa regeneration and periodontal tissue reconstruction to provide an overview of the points to be evaluated before clinical study and quality control during studies, and to give a summary of the results. He believes that the new regulations would accelerate research and supply of cell sheets. An example can be seen that the manufacturing cell process in CPCs is shifting from manual to automated manufacturing systems. This shift will reduce the risk of contamination, human error, and high cost of CPC maintenance although anticipation remains concerning issues relating to the transportation of the materials.

Osaka University achieved the first successful clinical result for regeneration therapy using myoblast sheet for the treatment of severe cardiomyopathy. This research highlighted the characteristics of regenerative medicines that were inherited from both drugs and medical devices. For example, manufacturing process is required for sterility and other attributes, as is the case for drugs, but it is not easy to sustain homogenization as it is for drugs. Also, efficacy sometimes depends on the technique of the operator, as is the case for medical devices. Kiyoshi Okada shared his perspective by addressing that these special characteristics should be taken into account carefully in quality control and product evaluation. Osaka University also operates the iPS Cell Clinical Research Network, which conducts the iPS cell research collaborating with CiRA. The network connects industry and universities to realize the production of regenerative medicines. The goals for the next 7 years are set up for applying new drugs developed by iPS cell technology to clinical trials, increasing the number of approved cellular therapeutic products, expanding the target diseases in clinical trials, and developing equipment or devices related to regenerative medicine.

COMMERCIALIZATION AND BUSINESS OF REGENERATIVE MEDICINES

Kenichiro Hata (Japan Tissue Engineering) presented business experience, since 2008 under the PAL prior to its revision, regarding tissue-engineered cartilage and epidermis. Regenerative medicine business covers various segments including establishment of cell banks for R&D; standardization of the production cycle of cell culture from donor, culture, and transplant; evaluation of product characterization; development of product packages and delivery systems; and construction of GMP. He described that the business structure is quite delicate without a solid legal framework. The 2 acts cast a light on the pathway for commercialization of regenerative medicines. Law No. 84/2013 introduced an expedited approval system for marketing regenerative medicines. A conditional and term-limited authorization is granted after the safety is confirmed and the results predict likely efficacy. Re-application within a certain period (to a maximum 7 years) is made after further confirmation of safety and efficacy is collected during the primary marketing period. In addition, Law No. 85/2013 permits the contracting of cell processing to licensed enterprises. This regulation opens a business opportunity of cell processing for the medical institutions.

The Japanese authorities are also taking key measures to promote commercialization. The Pharmaceutical and Medical Device Agency (PMDA) is planning to facilitate R&D to provide sponsors with strategic consultation that will encourage R&D and put products in market. The Ministry of Health, Labour and Welfare (MHLW) has been busy to issue guidelines and guidance documents on manufacturing and quality control, marketing, and post-marketing surveillance; by year end, there will be an estimated 40 notifications.
CONTINUING CHALLENGES

So does the new regulatory framework fulfil the needs for revolutionary drug development? Although the legal basis is established and guidelines and guidance documents would help with facilitating the regulations on process and quality control of regenerative medicines, it may take some time to strengthen the foundation. Both academia and industry do not hide their anticipation particularly of characterization and understanding of the specific profiles of the cells at critical steps. A few factors on quality control of final products and delivery remain to be resolved in order to bring the products to the real world. Furthermore, the market is not yet set up clearly and global competition is immeasurable at this stage. Nevertheless, the regulatory pathway for regenerative medicines just opened a new chapter. A couple of sessions were closed by showing that the Japanese authorities, industry, and academia have strong motivation for achieving the common goal: accomplishing medical innovation to provide medical care that truly meets the needs of patients.