PMDA 5th International Symposium on Biologics

Quality and non-clinical evaluation of cell/tissue-based products

26th August, 2010
Nadao Hall, Tokyo, Japan

Pharmaceuticals and Medical Devices Agency (PMDA)

AGENDA

Opening Remarks

13:30-13:35 Opening Remarks
内海英雄 独立行政法人医薬品医療機器総合機構 審査センター長
Dr. Hideo Utsumi, Executive Director and Director, Center for Product Evaluation, PMDA

Session I Chair: Dr. Shikano, PMDA & Prof. Aoi, Kyoto Univ.

13:35-14:05 European perspectives on quality and non-clinical evaluation of cell based medicinal products
Dr. Bettina Klug, Advanced Therapy Medicinal Products, Tissue Preparations, Paul-Ehrlich-Institute PEI

14:05-14:35 France legal & regulatory framework for cell/tissue-based products and its relationship with the European system
Dr. Pierrette Zorzi, Head, Biological Products Department, AFSSAPS

14:35-14:50 Break

Session II Chair: Dr. Tominaga, PMDA & Mr. Takayama, PMDA

14:50-15:20 PMDA's perspective on quality and non-clinical evaluation of cell/tissue-based products
鹿野真弓 独立行政法人医薬品医療機器総合機構 生物系審査第2部 部長
Dr. Mayumi Shikano, Office Director, Office of Biologics II, PMDA

15:20-15:50 Researcher's perspective on quality and non-clinical evaluation of cell/tissue-based products
青井貴之 京都大学 iPS細胞研究所 規制科学部門 教授
Prof. Takashi Aoi, Department of Regulatory Science, Center for iPS Cell Research and Application (CiRA) Kyoto University

15:50-16:20 FDA's perspective on quality and non-clinical evaluation of cell/tissue-based products
Dr. Raj K. Puri, Director, Division of Cellular and Gene Therapies, Office of Cellular, Tissue and Gene Therapies, CBER/ FDA

16:20-16:40 Break

Panel Discussions Chair: Dr. Miyake, PMDA

16:40-17:30 Dr. Raj K. Puri, Dr. Bettina Klug, Dr. Pierrette Zorzi, Dr. Mayumi Shikano, Prof. Takashi Aoi

Closing Remarks

17:30-17:35 Closing Remarks
近藤達也 独立行政法人医薬品医療機器総合機構 理事長
Dr. Tatsuya Kondo, Chief Executive, PMDA

Overall Chair: Dr. Tadano, PMDA

Speakers

(Abstract, Curriculum Vitae & Slides)

Opening Remarks

内海英雄　独立行政法人医薬品医療機器総合機構　理事・審査センター長
Dr. Hideo Utsumi, Executive Director and Director, Center for Product Evaluation, PMDA

Curriculum Vitae

Dr. Hideo Utsumi is currently Executive Director, Director of Center for Product Evaluation at the Pharmaceuticals and Medical Devices Agency (PMDA). He is responsible for the review and evaluation of NDA, Biologics, OTC/Generic Drugs, Medical Devices and Conformity Audit.

He graduated from the Faculty of Pharmaceutical Science, the University of Tokyo on 1971. He received a PhD degree from the Graduate School of Pharmaceutical Science, the University of Tokyo on 1976.

He served as an assistant professor of the School of Pharmaceutical Science of the Showa University (1982-1994) and the Kyushu University (1994-2000). Then, he served as a professor of the Graduate School of Pharmaceutical Science, the Kyushu University (2000-2008). He is an associate member of the Science Council of Japan from 2006. He was the head of the Pharmaceutical Society of Japan at 2007. He served as a Vice President and head of the Office for Strategic Research Planning of Kyushu University (2008-2010) before joining the PMDA.

Session I

European perspectives on quality and non-clinical evaluation of cell based medicinal products

Dr. Bettina Klug, Paul-Ehrlich-Institut, Langen Germany

Abstract

Cell based medicinal products (CBMP) as all other biotechnology medicinal products, are subject to a centralised authorisation procedure, involving one single scientific evaluation of the quality, safety and efficacy of the product, carried out by the European Medicines Agency (EMA). Overall, the same regulatory principles apply as for all other types of biotechnology medicinal products.

A multidisciplinary guideline addressing manufacturing and quality control as well as non-clinical and clinical development of cell-based medicinal products lays down the requirements for CBMPs entering the Marketing Authorisation (MA) procedure. However, the principles laid down in the guideline should already be considered by applicants entering into clinical trials.

The guideline covers CBMPs of human origin as defined in Directive 2001/83/EC, Part IV, Annex I and tissue engineered products as defined in Regulation 1394/2007/EC.

A comprehensive risk analysis should be used to justify the product development

Donation, procurement and testing of cells from human origin must comply with the overarching Directive 2004/23/EC4 and the subsequent technical Directives 2006/17/EC5 and 2006/86/EC. A system allowing complete traceability of the patient as well as the product and its starting materials is essential to monitor the safety and efficacy of cell-based medicinal products.

The risk posed by the administration of a cell-based medicinal product is highly dependent on the origin of the cells, the manufacturing process, non-cellular components and on the specific therapeutic use. As required by the legislation a risk analysis has to be performed. At the beginning of the product development, an initial risk analysis may be performed based on existing knowledge of the type of product and its intended use. This should be updated by the applicant throughout the product life cycle as data are collected to further characterise the risk.

With regard to the quality requirements guidance is provided control of the starting material, design and validation of the manufacturing process, characterisation of the CBMP, and products, quality control aspects.

The guideline acknowledges that conventional non-clinical pharmacology and toxicology studies may not be appropriate for cell-based medicinal products. Therefore the guideline addresses which non-clinical studies are necessary to demonstrate proof-of-principle and to define the pharmacological and toxicological effects predictive of the human response.

With regard to the clinical development of a CBMP the same requirements as for other medicinal products apply. However due to specific biologic characteristics of CBMP, it is acknowledged that alternative approaches to Phase I to Phase III clinical trials might be required. However alternative approaches need to be justified and supported by scientific data.

As required in the legislation, CBMP are subject to long-term follow up studies to monitor specific safety issues, including loss of efficacy.

Curriculum Vitae

Bettina Klug graduated in Medicine at the Johannes Gutenberg University, Mainz (Germany). After completion of her thesis she joined the Institute Pasteur as a research fellow.

In 1989 Bettina Klug started in the Department of Bacteriology at the Paul-Ehrlich-Institute as a deputy Head of sector section “toxoid vaccines. Her research focused on Hapten-carrier vaccines.

In 1996 she joined the newly established department of Haematology and Transfusion Medicines as deputy head of sector “coagulation factor II”. Amongst others her responsibilities included clinical assessment of blood and plasma derived products.

After holding for 5 years a position as scientific administrator at the EMA, London, she recently joined the

department of medical biotechnology at the Paul-Ehrlich-Institute.

Bettina Klug holds a degree in Immunology from the Pasteur Institute and a Master Degree in Infectious diseases from the University of London. Her major interests are infectious diseases, with special emphasis to vaccine development.

Session I

France legal & regulatory framework for cell/tissue-based products and its relationship with the European system

Dr. Pierrette Zorzi, Head, Biological Products Department, AFSSAPS

Abstract

The European framework for cell/tissue-based products is based on 3 sets of legal texts:

- The first one is the community code for medicinal products set up in 2001 which integrates the cell therapy and gene therapy products in the field of medicinal products.
- The second one (2004 and 2006) is a set of three directives aimed at setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of « Human Tissues and Cells». As a Directive, it represents the minimal requirements that have to be implemented nationally by each member state.
- The third one is the ATMP regulation governing the use of the cell therapy and gene therapy products also including now a new category named « tissue engineered products ». As this text is a regulation, all the requirements are mandatory for all member states

National and European levels of regulation remain continuously interactive, this make the regulatory frameworks at the European level but also in the 27 member states quite complex.

This presentation will specifically present the French regulatory framework and its relationship with the EU framework.

In France since 1994 several laws have progressively placed these products under the French drug agency responsibility. The French law of 1998 gave the agency (then becoming Afssaps) more responsibilities with regards to Cells, Tissues and Organs. Therefore since 1998, there are the 2 possible status for these products in France, Medicinal Product or non-MP.

The activities conducted by Afssaps for these products will be described particularly the marketing authorization procedures and clinical trial evaluation.

Curriculum Vitae

Pierrette Zorzi is head of the Department for Evaluation of Biological Products at Afssaps (French Agency for the Safety of Health Products), and member of the CHMP Biology Working Party at the European Medicines Agency (EMA). Products evaluated by the department are recombinant products, vaccines, plasma derived medicinal products, other extractives products, blood products, cell and gene therapy products, tissues, organs and ancillary products. Activities cover marketing authorizations, post approval variations, clinical trials, scientific advices, contribution to national and European legal frameworks and technical guidances. The department is also in charge of the haemovigilance and biovigilance.

Before joining Afssaps in 1999, P. Zorzi was in the pharmaceutical industry, most part of it in the biotechnology sector. She has been involved since 1992 in the ICH process. She is now participating as EU representative for the development of ICH guidelines on biotech products (Q11).

Session II

PMDA's perspective on quality and non-clinical evaluation of cell/tissue-based products

鹿野 真弓　独立行政法人医薬品医療機器総合機構 生物系審査第 2 部 部長
Dr. Mayumi Shikano, Office Director, Office of Biologics II, PMDA

Curriculum Vitae

Dr. Mayumi Shikano is currently Director of Office of Biologics II at Pharmaceuticals and Medical Devices Agency (PMDA). She has worked on review of biologics including vaccines, blood products, biotech products and cell/tissue-based products for 12 years. She also participated in ICH as a quality expert. She studied in CBER/FDA in US from April 2000 to Mar 2001.

Dr. Shikano graduated from the University of Tokyo, Faculty of Pharmaceutical Sciences in 1981. She received her Ph.D. from the University of Tokyo in 1992. Her career includes Researcher in Sagami Chemical Research Center and National Institute of Infectious Diseases before joining Pharmaceuticals and Medical Devices Evaluation Center, the predecessor of PMDA in 1998 as a reviewer.

Session II

Researcher's perspective on quality and non-clinical evaluation of cell/tissue-based products

青井貴之　京都大学　iPS 細胞研究所　規制科学部門　教授
Prof. Takashi Aoi, Department of Regulatory Science, Center for iPS Cell Research and Application (CiRA)
Kyoto University

Abstract

Induced pluripotent stem (iPS) cells are generated from somatic cell by introducing small sets of transcription factors. Like Embryonic stem (ES) cells, iPS cells can proliferate infinitely and differentiate into various kinds of somatic cells. In addition, unlike ES cells, iPS cells are generated from cells of various characterized donors without destruction of an embryo accompanied by ethical issues. Therefore iPS cells are expected to apply to studies on pathogenesis, drug discovery and cell therapy.

To realize cell therapy using iPS cells, the issues on safeness are the most important. We should control the risks of infection and tumorigenesity, and stability of the quality of the product. For that purpose, we must take heed of several points unique to cell therapy using iPS cells.

The first, cell therapy using iPS cells consist of a lot of processes and spend long time. Processes for cells and organ transplantation therapy are generally divided into harvesting, processing and transplantation. In iPS-cell therapy, cell processing is very complex and has heavy weight: primary culture of donor cells, generation and expansion of iPS cells, evaluation of undifferentiated iPS cells, differentiation and evaluation of terminal products. It takes more than a half year for these sequential processes using many kinds of materials. Then, fears of pathogen contamination in the cell processing should be relatively higher. On the other hand, risks of infection from the donor could be relatively lower because long period between harvest and transplantation allows us to do repeated test, e.g. paired serum, for avoiding pseudo-negative results. The risk of genetic or epigenetic abnormality given rise to in the processing should be noted rather than those carried by the donor.

The second, in contrast to embryonic stem cells, which are generated fundamentally one method, there are variations in technologies for generating iPS cells. iPS cells are generated from various origins, by introducing several sets of programming factors with various gene transduction methods. These variations affect quality of iPS cells, so we must establish appropriate method to generate iPS cells for clinical use.

The third, at least so far, there is diversity of qualities even among iPS cells generated with the same methods. Although we someday might establish the method to generate iPS cells with uniform quality, we must establish the strategy for selection of good iPS cell lines at the present time.

One of the most important advantages of iPS cells in the quality control of cell-based products is their ability of infinite proliferation. Once we select a good iPS clone, we can expand the clone unlimitedly, providing enough samples for exhaustive tests. And we can manufacture well-investigated "good" cells in large lot.

We must struggle to clarify what iPS clones should be regarded as "good" ones, especially in tumorigenecity and function. Non-clinical evaluations of them are not simple. We should discreetly infer the risk for transplanted iPS-derived cells of developing tumor in human recipients, through both deterministic approaches such as genomics and epigenomics, and stochastic ones such as transplantation assay in animals. Each approach has both advantages and disadvantages. Well-managed comprehensive evaluations should be required.

Curriculum Vitae

Dr. Takashi Aoi is currently professor of department of regulatory science in Center for iPS cell Research and Application (CiRA), Kyoto University. His responsibilities include coping with regulatory issues on iPS cell therapy.

He graduated Kobe University, school of medicine in 1998. He received his PhD from Kyoto University in 2008.

His career includes a junior resident at Tenri Hospital (1998-2000), a clinical fellow of department of internal medicine at St. Luke's International Hospital (2000-2002) and a medical staff of department of gastroenterology and hepatology at Japanese Red Cross Society Wakayama Medical Center (2002-2004), before postgraduate School of Medicine, Kyoto University (2004-2008).

He was a research fellow (2008-2009) and an assistant professor (2009) of department of Stem Cell Biology at Institute for Frontier Medical Sciences, Kyoto University

His major interests are gastroenterology, hepatology, stem cell biology and regulatory science.

Session II

FDA's perspective on quality and non-clinical evaluation of cell/tissue-based products

Dr. Raj K. Puri, Director, Division of Cellular and Gene Therapies, Office of Cellular, Tissue and Gene Therapies, CBER/ FDA

Curriculum Vitae

Raj K. Puri, M.D., Ph.D. is the Director of the Division of Cellular and Gene Therapies (DCGT) in FDA's Center for Biologics Evaluation and Research (CBER). He is also a Chief of Tumor Vaccines and Biotechnology Branch in CBER. Dr. Puri has been a research regulator at CBER for 22 years. Dr. Puri oversees investigational new drug (INDs), investigational device exemptions (IDEs), and biological license applications (BLAs) for tumor vaccines, immunotherapy, cellular and gene therapy, tissue engineering, and xenotransplantation products and development of policies and guidance documents in these cutting edge areas of medical research. Dr. Puri and his staff interacts with stakeholders to bring FDA, industry, patient advocates, scientists, and the public together in a collaboration to promote and develop new therapies for the 21st Century, while protecting human subjects and maximizing biological product safety. In addition, Dr. Puri oversees and manages the Critical Path research performed by principle investigators in DCGT to support medical product development. Dr. Puri also directs translational research program in the field of cancer biology/immunology. His laboratory is engaged in research in the areas of tumor vaccines, cancer immunotherapy, cellular therapy, and gene therapy. A portion of his research program is also focused on identifying and characterizing cancer stem cells in human cancers by molecular profiling of human embryonic stem cells and targeting of cancer stem cells for cancer therapy. Dr. Puri is also involved in the application of genomics technology in policy and guidance documents development, and numerous outreach activities.

Closing Remarks

近藤達也　独立行政法人医薬品医療機器総合機構　理事長
Dr. Tatsuya Kondo, Chief Executive, PMDA

Curriculum Vitae

He has a lot of clinical experiences as a neurosurgeon since he graduated from Medical Department of the University of Tokyo in 1968. He worked for the department of neurosurgery in the 1st national hospital (1972 ~ 1974) and the department of Neurosurgery, Faculty of Medicine, The University of Tokyo (1974 ~ 1978).

He studied the biology of brain tumor as a visiting researcher with Max-Planck scholarship at Max-Planck Institute, West Germany from March to December of 1977.

He served as a neurosurgeon at International Medical Center of Japan from 1978 to 2003 and he contributed to hospital management and clinical discipline as the Director of the hospital, International Medical Center of Japan from April, 2003 to March, 2008.