Magnolia Kobus

PMDA Updates

March, 2015

News

1. JICA FY2014 Training on "Regulatory Systems for EPP Medical Devices" for Malaysian regulators (February 10 and 23)

On February 10, staff members of related offices of PMDA gave lectures and held Q & A sessions for the 5 visiting officials from the Medical Device Agency (MDA) of Malaysia, on the outlines of approval review of medical devices, post-marketing safety measures, Quality Management System (QMS) inspection and Good Clinical Practice (GCP) inspection. In addition, on February 23, a staff member of the Office of International Programs attended the presentation of the training results by the trainees, which was held at the Japan International Cooperation Agency (JICA) Tokyo Main Building, and gave additional explanations and further exchanged opinions.

This training was provided upon the request from the Japan International Cooperation of Welfare Services (JICWELS), as a part of the training program on the regulatory systems for EPP [1)] medical devices, specifically arranged for Malaysia by the JICA. This is the third time that PMDA provided the training to the MDA officials, following the 1st PMDA Medical Devices Training Seminar in March and another lecture on Good Laboratory Practice (GLP)/GCP/ Good Post-marketing Study Practice (GPSP) assessment In October last year.

1) Economic Partnership Program; EPP

2. International Regulatory Endeavor towards Sound Development of Human Cell Therapy Products (February 18 to 19)

Left: Dr. Kondo,
Right: 1st from right, Dr.Sato

From February 18 to 19, a symposium entitled "International Regulatory Endeavor towards Sound Development of Human Cell Therapy Products" was held co-hosted by PMDA, International Alliance for Biological Standardization (IABS), Japan Science and Technology Agency (JST), and National Institute of Biomedical Innovation (NIBIO) in Tokyo, Japan. Dr. Tatsuya Kondo, Chief Executive, PMDA, Dr. Daisaku Sato, Office Director, Office of Cellular and Tissue-based Products, PMDA, and approximately 180 participants of regulatory authorities, research institutions and industry from both in and out of Japan met together in the symposium. This symposium aims to develop internationally applicable common technical requirements, based on characteristics of human cell therapy products used for regenerative medicine, by sharing recognition of regulatory challenges in the evaluation of the quality, efficacy and safety of the products, as well as by comprehending its scientific principles/concepts and the points to consider. In the symposium, discussions took place on specific challenges for cell therapy products, for example, an approach for setting specification including potency of finished products in terms of quality, an ideal way to evaluate tumorigenicity in terms of safety, and so on.

As the outcome of the symposium, it was confirmed that ICH guidelines (Q5A, Q5D, Q5E, Q6B, S6) are also applicable and useful to various matters in the quality control and safety assurance of cell therapy products. In addition, handling of the specific challenges to which ICH guidelines are hard to apply has been raised as a future issue. A risk-based approach in regulations should be taken to handle the challenges, particularly under the conditions where types of cell therapy products, patients and manufacturing controls widely varies. Finally necessity of international consensus through the activities of WHO and other relevant organizations as ever was confirmed.

Please refer to the following web site for the detailed information.
http://www.pmda.go.jp/review-services/reexamine-reevaluate/symposia/0006.html (Japanese)

3. HBD Town Hall Meeting at CRT 2015 (February 23)

In conjunction with the Cardiovascular Research Technologies (CRT) 2015 conference held in Washington D.C. from February 21 to 24, one-day Harmonization By Doing (HBD) Town Hall Meeting was held, and Dr. Toshiyoshi Tominaga, Associate Executive Director (for International Programs), 3 staff members of the Office of Medical Devices Review I, and a staff member of the Office of International Programs participated in the meeting. In the Town Hall Meeting, there were 5 sessions on the topics of 1) Post-marketing Registry, 2) Mobile Health, 3) Bio-absorbable Stents, 4) Renal Denervation and 5) Peripheral Arterial Calcification, and presentations were given by the speakers from academia, industry and regulators of both the U.S.A. and Japan, many of whom were members of HBD. The members of PMDA presented the current situations of Japan and the regulatory view on the 4 topics other than Post-marketing Registry, and Dr. Tominaga concluded the meeting with thanks. There were total of about 80 participants throughout the sessions, notably physicians, as well as stakeholders from industry and regulators, engaging in active Q & A and intensive opinion exchange.

4. The first Malaysia-Japan Symposium (March 10 to 11)

From March 10 to 11, the 1st Malaysia-Japan joint Symposium was held in Malaysia, Kuala Lumpur, and Dr. Taisuke Hojo, Senior Executive Director; Dr. Seiko Miyazaki, Director, Office of Standards and Guidelines Development; Dr. Hiroaki Yamada, Director, Office of New Drug II; Mr. Teruyoshi Ehara, Director, Office of International Programs, and 6 staff members from the Offices of International Programs, Standards and Guidelines Development, New Drug III, Cellular and Tissue-based Products, Manufacturing/Quality and Compliance, participated in the symposium.

The objective of the symposium is to cultivate better understanding on the regulatory system of Malaysia and Japan for both the regulators and industry members, and contribute in enhancements in cooperative relationship and innovation, and cohosted by the National Pharmaceutical Control Bureau (NPCB) and PMDA.

From PMDA, Dr. Hojo introduced outline of PMDA, international activities, and recent efforts including MIHARI project in the Keynote lecture, and staff members delivered presentations on new drug review, Japanese pharmacopoeia, Good Manufacturing Practice (GMP) inspection, and regulatory control for biotherapeutic products, etc. From NPCB, Mdm. Siti Aida Abdullah, Deputy Commissioner, introduced Malaysia's pharmaceutical regulation system, and staff members delivered presentations on Halal regulation, the MS 2424 guideline for Halal pharmaceuticals, and regulatory control for herbal/traditional medicines, etc. There were approximately 150 participants in the symposium and had lively discussions.

The details of the symposium are available at following web site.
http://www.pmda.go.jp/english/symposia/0025.html

5. The 20th Anniversary Event of EMA (March 16 to 19)

The 20th Anniversary of EMA was held in London, United Kingdom, from March 17 to 18. Dr. Tatsuya Kondo, Chief Executive, Dr. Toshiyoshi Tominaga, Associate Executive Director (for International Programs), two staff members from Office of International Programs including a liaison officer staioned at EMA, and Dr. Nobumasa Nakashima, International Planning Director, Ministry of Health, Labour and Welfare (MHLW), participated in the event. Pannel discussions were held under the theme of "What is expected for EMA's activities in the next five years" by regulatory authorities, academia, and representatives from the organization of the patients, etc. There were approximately 300 participants including EMA staff members and regulaters from other EU organizations and EU member states.

6. English translation of review reports

PMDA released 9 review reports (7 pharmaceuticals and 2 medical devices) in English in the fiscal year 2014.

Pharmaceuticals http://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0001.html

Brand Name	Generic Name	Posting date
Topiloric/ Uriadec	Topiroxostat	June 16
Sovriad	Simeprevir Sodium	August 4
Alabel/ Alaglio	Aminolevulinic Acid Hydrochloride	September 12
Kadcyla	Trastuzumab Emtansine(genetical recombination)	September 15
Stelara	Ustekinumab (genetical recombination)	November 17
Romiplate	Romiplostim (genetical Recombination)	March 31
NovoEight	Turoctocog Alfa (genetical recombination)	March 31

Medical devices http://www.pmda.go.jp/english/review-services/reviews/approved-information/devices/0003.html

Brand Name	Generic Name	Posting date
Fetal Shunt	Shunt for fetal pleural effusion	March 3
Adacolum	Leukocytapheresis device	March 31

Safety Information

Blue Letter

1. Serious skin disorders suggestively caused by Lamictal (February 4)
   http://www.pmda.go.jp/files/000198527.pdf

English translations of review reports

The followings are current information about English version of review reports on PMDA web site.

Pharmaceuticals http://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0001.html

Brand Name	Generic Name	Posting date
Romiplate	Romiplostim (genetical Recombination)	March 31
NovoEight	Turoctocog Alfa (genetical recombination)	March 31

Medical devices http://www.pmda.go.jp/english/review-services/reviews/approved-information/devices/0003.html

Brand Name	Generic Name	Posting date
Fetal Shunt	Shunt for fetal pleural effusion	March 3
Adacolum	Leukocytapheresis device	March 31

Events

Conferences/Meetings PMDA hosts or participates in:

Date	Title	Location
April 9-10	The 4th Asia Partnership Conference of Pharmaceutical Association (APAC)	Tokyo
April 13-15	The 27th DIA Annual EuroMeeting	Paris
April 20-21	The 9th DIA Annual Conference in Japan for Asian New Drug Development	Tokyo
June 7-11	ICH Week	Fukuoka
June 14-18	The 51th DIA Annual Meeting	Washington D.C.

Reports from overseas

Our officers deliver lively reports of their activities at their stationed overseas authorities.

Joint meeting of Working Parties with Patients' and Consumers' Organisations and Healthcare Professionals' Organisations

On 4th March, more than 70 participants from Working Parties with Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP), European Commission (EC) and EMA officers got together in EMA to hold a meeting to share information and discuss on biosimilar products, "EMA Human Scientific Committee's Working Parties with Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP) joint meeting: Information session on Biosimilars". This meeting aims for providing both working parties with comprehensive scientific knowledge and information of regulators' evaluation with regard to biosimilars, bridging clinical reality and public acceptability of biosimilars, and promoting further understanding of biosimilars. At the outset of the meeting, regulators made explanations such as review process and approval situation of biosimilar products (e.g. 21 products approved as of February 2015). Subsequently, both working parties of healthcare professionals and patients raised interests and concerns on biosimilar products, then discuss topics such as bioequivalency, immunogenicity, interchangeability, and post-authorisation activities. The points that intrigued me in the meeting are: from healthcare professionals, who should be responsible to change medicines from an original to its biosimilar drug (medical doctors or pharmacists?) and necessity of enhancement of information provision and awareness on biosimilar products; and from patients, financial aspects to reduce health expenditures of medicines should be taken into consideration for evaluation of biosimilars, and importance of patients' monitoring and support after consent of change to a biosimilar product. Among these points some are difficult to provide answers themselves and others have no answers at this stage and need to study and take measures further. This meeting seems very interesting to deepen mutual understandings through active discussions, and also useful for both stakeholders to have this type of meetings in continuous collaboration with EMA further on.

EMA has emphasized dialogues between working parties of healthcare professionals and patients and held joint meetings to explain EMA's recent activities in various themes such as benefit-risk communication, patients' voice in the evaluation of medicines, and adaptive licensing pilot project. In addition, another joint meeting on risk minimisation plan is also planned in September this year. As a liaison officer stationed at EMA, I would like to continue to pay attention to these joint meetings and to report them later on.

EMA Human Scientific Committee's Working Parties with Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP) joint meeting: Information session on Biosimilars
http://www.ema.europa.eu/docs/en_GB/document_library/Agenda/2015/02/WC500183088.pdf

Mr. Yoshihiko Sano
PMDA's International Liaison Officer stationed at EMA in the United Kingdom

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Dispatch to the USP

I am Chie Mizumaru, Office of Standards and Guidelines Development, PMDA. I was dispatched to the United States Pharmacopeial Convention (USP) as a liaison from March 2, 2015. The dispatch period will be one year. The USP is a scientific nonprofit organization that sets quality standards for medicines, food ingredients, and dietary supplements manufactured, distributed and consumed worldwide. The USP mission is to improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.

The most important work in the USP is to publish a compendium named the United States Pharmacopeia–National Formulary (USP–NF). I belong to USP excipients team as a visiting scientist, which is in charge of development and revision of monographs for excipients. PMDA, as the secretariat to the Japanese Pharmacopoeia (JP) committees, has expedited international harmonization and implementation thereof among the JP, USP-NF and European Pharmacopoeia (EP) through the Pharmacopoeial Discussion Group meeting (PDG). Harmonization of the monographs for excipients is one of the most important

activities in the PDG, and excipients team I belong to is involved in such activities. Furthermore, Office of Standards and Guidelines Development, PMDA, is operationalizing the bilateral project regarding pharmaceutical excipients proposed by the former PMDA liaison, Dr. Eriko Fukuda. During my stay in the USP, I will make efforts to strengthen the partnership between PMDA and USP including collaboration in this project. I will write this column on topics that I learn during this dispatch. I hope this information will be of use to you.

Dr. Chie Mizumaru
PMDA's International Liaison Officer stationed at USP in the U.S.A.

How to obtain drug safety-related information from the U.S. FDA

What would you do when you want to get information about drug safety in the U.S.? You might search the internet and may reach this website (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm). The website "Postmarket Drug Safety Information for Patients and Providers" is the U.S. FDA's main page for drug safety, which was developed to improve the transparency of drug safety information and allow patients and healthcare providers better access to information about drugs. The Food and Drug Administration Amendments Act (FDAAA) required the U.S. FDA to develop maintaining of this webpage. Although you can get detailed postmarket drug safety information from this site, it might be overwhelming for people who are unfamiliar with this area and are seeking information about a particular drug. If this is the case for you, you could use a website made by the Division of Drug Information (DDI) in CDER at the U.S. FDA (http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm082585.htm). DDI is CDER's focal point for public inquiries regarding drugs. Working together with other offices in CDER, they offer a wide range of information for patients and consumers as well as for healthcare professionals. For example, healthcare professionals who want to know emerging information about drugs may find the Drug Safety Podcasts useful. DDI's student webinars for students may be a good resource for those who want to understand basic pharmacovigilance in the U.S. In addition to these resources, you may be interested in visiting a webpage that explains the past, present and future of drug safety at the U.S. FDA. This page, which was created cooperatively by DDI and the Office of Surveillance and Epidemiology (OSE) a few years ago, provides a good overview of OSE's work (http://www.fda.gov/Drugs/NewsEvents/ucm343275.htm). Multiple methods of communication, each directed to a specific audience, allows the U.S. FDA to provide information to many stakeholders. I plan to continue thinking about better ways to communicate with the public.

Ms. Shohko Sekine
PMDA's Officer at CDER, U.S. FDA in the U.S.A.

Medical Device Single Audit Program (MDSAP) and international initiatives

This report about my dispatch will be my last. In this report, I will consider the relationship between the MDSAP Pilot and Japan. This program, as I introduced in the previous report, is a program for conducting efficient Quality Management System (QMS) audits utilizing certification bodies. This program includes standardized assessments of certification bodies conducted by regulatory authority assessors; and standardized audits of manufacturers by certification body auditors. How the results of audits conducted by certification bodies will be used will vary amongst the participating countries.

The U.S. FDA will accept MDSAP Audit reports as a substitute for U.S. FDA's routine inspections. Upon successful completion of the MDSAP Pilot, Health Canada intends to implement MDSAP as the mechanism to achieve regulatory compliance for QMS requirements. Australia's Therapeutic Goods Administration (TGA) will take into account MDSAP Pilot audit reports as a way of confirming product or QMS requirements. Brazil's ANVISA may use MDSAP Pilot audits in lieu of an inspection by ANVISA to grant ANVISA's Good Manufacturing Practice (GMP) Certificate which is required before and after marketing.

For more information, please refer to the following web site.
http://www.fda.gov/downloads/MedicalDevices/InternationalPrograms/MDSAPPilot/UCM429958.pdf

In the case of Japan, QMS audits are required before marketing approval and every five years after marketing approval. The result of MDSAP audits could also be utilized effectively in Japan, when the result of the QMS audit by MDSAP is successful.

It is described in "Establishment of guideline for QMS audit" (PFSB/CND Notification No. 0330001 dated October 24, 2014) that the Japanese Auditing organization can conduct document-based audits instead of on-site audits by accepting the audit results of certification bodies accredited by the United States, Australia, or Canada. I think we can expect that the MDSAP audit results can also be utilized effectively in Japan.

It is almost three months since I was appointed and it is already time for me to prepare for my return home. I have been here since January 2015, and every day has been fulfilling and a productive learning experience. I am very grateful to the people of the U.S. FDA who took care of me during this time. This time of dispatch was short, but it was rare opportunity to actually experience the most advanced international activities in the medical device field. As globalization progresses, I think it would become more frequent that cooperation and harmonization between Regulatory Authorities become the key to problem solving. Taking advantage of what I have learned during this dispatch, I would like to continue contributing to international cooperation activities of Japan.

Mr. Kenichi Ishibashi
PMDA's Officer at CDRH, U.S. FDA in the U.S.A.

Utilization of physiologically based pharmacokinetics modeling in regulatory review in U.S. FDA

I would like to introduce the utilization of physiologically based pharmacokinetics (PBPK) modeling, which is one of the modeling and simulation techniques conducted in division of pharmacometrics in CDER U.S. FDA during new drug review.

In base PBPK models, individual organs relevant to pharmacokinetic, pharmacological and toxicological process are interconnected by systemic circulation, considering physiological and biochemical information. PBPK modeling and simulation can describe the concentration-time profile and exposure in blood and other tissues. Over the past several decades, the understanding of physiological and biological process including drug metabolizing enzyme and drug transporters, the knowledge accumulation about the prediction from human biomaterial experiments, and the advancement of computer science and software supported the development of PBPK modeling. PBPK modeling recently has been applied in drug development and regulatory review. The application and utilization of PBPK modeling during drug development and review have been reported from U.S. FDA through many scientific journals and draft guidance for industry.

PBPK modeling is primarily used to assess effects of intrinsic or extrinsic factors on drug pharmacokinetics under the current drug development and review. The number of the application of PBPK modeling towards assessing the potential drug-drug interaction (DDI) in clinically relevant scenarios has increased in new drug application in U.S. FDA over the years. Because DDI may cause serious adverse effects or attenuation of therapeutic effects, magnitude of potential DDI should be evaluated during drug development. However, it is realistically difficult to assess the magnitude of all potential DDI by conducting clinical studies. Therefore, it is necessary to appropriately predict the characteristics and severities of possible DDI, and PBPK modeling and simulation is useful to achieve this purpose.

Recently, U.S. FDA evaluated the predictive performance of PBPK modeling in predicting cytochrome P450 (CYP)-mediated DDI (Wagner C et al., Clin Pharmacokinet, 54: 117-127, 2015). This evaluation was based on 15 substrate PBPK models and 26 DDI studies with various CYP inhibitors. As the results, a total of 21 of 26 DDI studies (81%) were predicted within 1.25 fold change and all studies were predicted within 2 fold change for ratio in AUC. These results suggest a higher degree of confidence in using PBPK modeling to predict the effect of CYP inhibition. Further experience and knowledge accumulation about the predictive performance for induction effects and transporter-related DDI in addition to CYP-inhibition can be useful to clarify the utility of prediction of potential DDI based on PBPK modeling.

Over the years, the number of application of PBPK modeling and simulation has increased in pharmacokinetics and clinical pharmacology area. This may result in increased submissions on PBPK modeling and simulations to PMDA for review and consultation. To prepare for this, I am going to learn how to utilize the PBPK modeling technique in CDER, U.S. FDA, during my training program.

Dr. Masanobu Sato
PMDA's Officer at CDER, U.S. FDA in the U.S.A.
