



Nemophila

PMDA Updates

May, 2015

News

1. PMDA Expert Dispatched to CDRH, U.S.FDA (April 16)

On April 16, PMDA sent Ms. Rie Fukaya, the review officer at Office of Medical Devices I and Mr. Takehiro Ichikawa, the review officer at Office of Medical Devices II to the Center for Devices and Radiological Health (CDRH), U.S.FDA. Ms. Fukaya has been engaging in discussions and information sharing on clinical trials/studies for Investigational Device Exemption (IDE) approvals and marketing applications for 510(k) clearances and Premarket Approval Application (PMA) approvals in cardiovascular devices area. Mr. Ichikawa has been engaging in discussions and information sharing on processes and review disciplines for ophthalmic and Ear, Nose and Throat (ENT) medical devices. The term of the dispatch is for three months.

2. 9th DIA Annual Conference in Japan for Asian New Drug Development (April 20 to 21)

From April 20 to 21, the 9th DIA Conference for Asian New Drug Development was held in Tokyo under the theme of "Accomplishments and future perspective to be acquired through collaboration among Asian countries." Three PMDA staff, Dr. Takao Yamori, Director of Center for Product Evaluation as a program chair, Dr. Yoshiaki Uyama, Director, Office of Medical Informatics and Epidemiology as a program advisor, and a staff member as a program committee member contributed to the conference planning. In the keynote session on the first day, Dr. Yamori delivered a keynote lecture entitled "Current Challenges of PMDA in Japan and in Asia". In addition, staff members of Office of New Drug II, Office of New Drug III, Office of Cellular and Tissue-based Products, and Office of Standards and Guidelines Development contributed to the sessions of "East-Asian Regulatory Update on Global Clinical Trials", "NDA Review of Drugs Developed by Multi-Regional Clinical Trials" and "Activities by Academia" as speakers and/or chairs. A total of 8 participants attended this conference from PMDA including the above contributors.



Dr. Yamori

At the PMDA exhibition booth in the exhibition hall, staff members of the Office of International Programs communicated with visitors handing out informational brochures, and answering their questions.

The next conference will be held in Tokyo in the spring of 2016.

3. 5th International Meeting of World Pharmacopoeias (April 20 to 22)

From April 20 to 22, the 5th International Meeting of World Pharmacopoeias was held in Rockville, Maryland and Washington D.C., U.S.A. in which Dr. Toru Kawanishi, Director General, National Institute of Health Sciences (NIHS), and Mr. Nobuo Uemura, Senior Coordinator for Information and Analysis, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (MHLW) and 2 staff members from Office of Standards and Guidelines Development, PMDA participated as the representatives of Japanese Pharmacopoeia (JP). The representatives of JP expressed opinions as the member of working group for drafting Good Pharmacopoeial Practices (GPhP) to review and address public comments on the proposed draft on GPhP and consequently edit the GPhP document. On April 22, a meeting with stakeholders including pharmaceutical industry representatives was held where WHO provided updates on the progress of GPhP and the participants exchanged opinions.

The upcoming meetings are to be held in China in September, 2015 co-hosted by Chinese Pharmacopoeia Commission (ChP) and WHO, and in Tokyo in the fall of 2016 co-hosted by JP and WHO.

4. USP Convention 2015 (April 22 to 25)

From April 22 to 25, the USP Convention 2015 was held in Washington D.C., U.S.A. where Dr. Toru Kawanishi, Director General, National Institute of Health Sciences (NIHS), Mr. Nobuo Uemura, Senior Coordinator for Information and Analysis, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (MHLW), and 2 staff members from Office of Standards and Guidelines Development, PMDA attended as the representatives of Japanese Pharmacopoeia (JP). The USP holds these conventions every 5 years inviting many delegates from industry, government and academia. In this convention, the USP's activity policy for the next five-year period (2015-2020 cycle) was determined and Expert Committee chairs were elected. MHLW and PMDA are voting delegates of JP, and contributed to the resolution by voting for the proposals of the next five-year work policy, amendments to the USP Bylaws and Expert Committee chairs to implement the policy. The next convention is to be held in Washington D.C. in April, 2020 which corresponds to the 200th anniversary of the founding of USP.

5. IMDRF Registry Working Group Meeting (April 20-23)

From April 20 to 23, a meeting of International Medical Device Regulators Forum (IMDRF) Patient Registry Working Group was held at PMDA and National Center for Global Health and Medicine, and 4 members collectively from Office of Medical Devices I, Office of Safety I and Office of International Programs attended. In addition, Dr. Tatsuya Kondo, the Chief Executive, gave a welcome speech on the first day of the meeting. This was the first face-to-face meeting of the given working group, whose establishment was approved at the IMDRF Management Committee Meeting held in Washington D.C. in September last year. This working group is chaired by Dr. Danica Marinac-Dabic from US FDA, aiming at development of a guidance document on essential principles for global harmonization of medical device registries.



Dr. Kondo at the 6th from the right

Safety Information

Pharmaceuticals and Medical Devices Safety Information No. 322, April 28, 2015

1. Adherence to the Cleaning and Disinfection Method to Prevent Transmission of Multidrug-resistant Bacteria by Duodenoscope
2. Important Safety Information
 - (1)cyclophosphamide hydrate
 - (2)sitagliptin phosphate hydrate
 - (3)triamcinolone acetonide (intramuscular, intra-articular, and intradermal)
 - (4)pazopanib hydrochloride
 - (5)panitumumab (genetical recombination)
3. Revision of Precautions (No. 264)
 - Rebamipide (ophthalmic suspension) (and 2 others)
4. List of Products Subject to Early Post-marketing Phase Vigilance (as of April 2015) (Reference)

Precautions Concerning Recurrence and Similar Incidents of Medical Accidents

<http://www.pmda.go.jp/english/safety/info-services/drugs/medical-safety-information/0013.html>

Events

Conferences/Meetings PMDA hosts or participates in:

Date	Title	Location
June 6-11	ICH Week	Fukuoka
June 14-18	DIA 2015 51st Annual Meeting	Washington D.C.
June 22-26	MDSAP RAC, MDSAP Forum 2015	Washington D.C.
June 30-July 1	Pharmacopoeial Discussion Group Meeting	Tokyo
July 20-Aug 1	CVIT2015 HBD Session	Tokyo

Reports from overseas

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

Giving presentations about Japan's recent activities in European Medicine Agency and European Commission

On April 22, I was invited to the Management Meeting at EMA to give a presentation about Japan's recent activities. This meeting was internal and composed of high level officers including Mr. Andreas Pott, Deputy Executive Director, and Professor Guido Rasi, Principal Adviser in Charge of Strategy.

At the meeting, my presentation followed the opening greetings and brief introduction about PMDA liaison stationed at EMA by Mr. Pott. As I had heard that some officers were not familiar with Japan's situation, I explained the functions of two Japanese regulatory authorities (MHLW and PMDA), then introduced PMDA's third mid-term plan, PMDA's International Vision, interactions between EMA and MHLW/PMDA, The Pharmaceuticals and Medical Devices Act (PMD Act), and the Strategy of Sakigake as a Package. After the meeting, I received some positive comments from EMA colleagues who told me it was informative and a good opportunity to know Japan's current situation. The topics such as PMD Act and Sakigake Strategy in particular were of high interest, and I was asked for in-depth information.

There was another opportunity to introduce the two recent activities at an expert meeting on Safe and Timely Access to Medicines for Patients (STAMP meeting) held on May 6 in the European Commission in Brussels. The STAMP meeting was to exchange views and information about the experience of Member States, examine national initiatives and identify appropriate ways to use the existing EU regulatory tools more effectively with the aim of further improving safe and timely access and availability of medicines for patients. This was the second closed meeting since the first one was held in January 2015, and the summary was published later (see URL at the end of this article). At the meeting, following other presentations such as EU's activities of Health-Technology-Assessment (HTA), I gave my presentation about Japan's two recent activities and I received questions from the floor about the assumption of efficacy of regenerative medicines for conditional approval under PMD Act and the current situation of the review partner of Sakigake Strategy as a "conciierge".

Such opportunities to give various presentations about the regulatory situation in Japan are of great and unique benefit for the on-site liaison officer.

I will continue to make use of such opportunities to attend meetings actively as a liaison officer stationed at EMA and explain Japan's activities.

Commission Expert Group on Safe and Timely Access to Medicines for Patients ("STAMP")
2nd Meeting :

http://ec.europa.eu/health/documents/pharmaceutical-committee/stamp/index_en.htm

Mr. Yoshihiko Sano

PMDA's International Liaison Officer stationed at EMA in the United Kingdom

The 5th International Meeting of World Pharmacopoeias and the 2015 USP Convention Meeting

I attended the 5th International Meeting of World Pharmacopoeias facilitated by the World Health Organization (WHO) and hosted by the United States Pharmacopoeial Convention (USP) in Rockville, MD on April 20-22. About 40 delegates from 15 pharmacopoeias around the world attended this meeting and discussed how to address comments, received during the period of public consultation, for the 5th draft of Good Pharmacopoeial Practice (GPhP) drafted by the world pharmacopoeias' drafting group. This meeting was limited to representatives of the pharmacopoeias, and followed by an open meeting hosted by USP in Washington DC where stakeholders attended and discussed subjects to be considered by the pharmacopoeias for future iterations of the GPhP. There seems to be a high expectation for the GPhP to harmonize on pharmacopoeial standards more efficiently. After reviewing of comments from secretariats of pharmacopoeias and stakeholders, the next version of GPhP will be drafted and discussed in the 6th meeting of World Pharmacopoeias to take place in China in September 2015 and hosted by the Chinese Pharmacopoeia commission (ChP).

The 2015 USP Convention Meeting was held on April 22-25 in Washington, DC, following the 5th International Meeting of World Pharmacopoeias. USP Convention Meetings occur once every five years to bring together Delegates from USP Convention Member Organizations to discuss and provide guidance on issues relating to USP's future. The theme of the meeting was "USP and You: Shoulder to Shoulder on the Path to Improve Global Health". The participants of this meeting were the delegates representing more than 450 organizations related to the USP's activities, and they performed the following functions (a) Election of USP's Council of Experts from a pool of nominated candidates; (b) Election of USP's Officers and Trustees, who have fiduciary responsibility for USP between meetings; (c) Adoption of Resolutions that advance the mission and vision of USP; and (d) Confirm USP's structure and operational framework as they review and vote upon amendments to USP's bylaws.

Furthermore, panel discussions on Biologics and on Global Health and invited talk by the guest speakers from the organizations engaged with USP's activities, such as U.S. FDA and Pharmaceutical Research and Manufacturers of America (PhRMA), etc., were held. Throughout the meeting, I was impressed by the emphasis placed on the importance of collaboration and partnership among industry, regulator, academia, and many other organizations in order to carry out USP's mission, i.e., to improve global health. In addition, Resolution 3, Globally Harmonized Standards, was adopted as one of eleven resolutions at the meeting with a focused effort on expanding its commitment to harmonization of compendial standards by working with pharmacopoeias, the WHO, and other stakeholders. Therefore it is considered to be very important for the USP to work with pharmacopoeias around the world. As a PMDA's International Liaison Officer, I will observe USP's activity closely and would like to contribute to the harmonization between the Japanese pharmacopoeia and USP.

Dr. Chie Mizumaru

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

Patient-Focused Drug Development

Have you ever thought that you would like to state your perspective as a patient about your disease to a drug regulatory agency, so that it could incorporate this information into its regulatory decision making? I'd like to introduce you to a U.S.FDA initiative that seeks to understand the viewpoints of patients or their caregivers about those aspects of an illness and its treatments that should be considered in a drug's benefit-risk evaluation.

Under an initiative called "Patient-Focused Drug Development," the U.S. FDA convenes a series of public meetings to discuss with patients disease severity and treatment satisfaction for a specific disease. Over a five-year (Fiscal Years 2013 - 2017), twenty diseases will have been discussed. Patients provide input in two main areas. First, they describe the daily impact of disease symptoms that matter most to them. Second, they provide perspectives on current approaches to treating the disease. I attended a public meeting on Functional Gastrointestinal Disorders held on May 11, 2015.¹ It was really

interesting for me to hear patients describe, in their own words, their experiences and explain how those experiences could better be considered during drug development. For example, some patients noted that currently available pain scales did not adequately assess their pain and that improved pain scales are needed. During the meeting, U.S.FDA staff members from the medical division that reviews drugs for these conditions asked the patients questions. This interaction made the public meeting more valuable.

The direct output of the public meeting is a summary report of the meeting; however, you may wonder how these opinions affect the U.S.FDA decision-making. The U.S.FDA suggests in its FDA's Benefit-Risk Framework brochure that its review process could benefit from a more systematic and expansive approach to obtaining the patient perspective, such as that obtained from the Patient-Focused Drug Development.²⁾ In fact, analysis of disease condition and current treatment options, which are also topics of Patient-Focused Drug Development public meeting, are two of five factors in FDA's Benefit-Risk Framework. FDA's Benefit-Risk Framework is an initiative to improve clarity and transparency of the U.S. FDA's decision-making by using a template comprised of five decision factors, which include analysis of condition, current treatment options, benefit, risk, and risk management. In Japan, it might also be beneficial to consider how the Japanese agency could learn even more about patients' perspectives about diseases in a systematic manner.

1) <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm430885.htm>

2) <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf>

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

Current situation of CDER's novel new drugs approval

In addition to an efficient review by regulatory agencies, dialogue between regulator and drug sponsors during early stage of drug development is thought to be important for faster access to a new drug therapy by patients. Through these early communications, critical issues of clinical study designs (including the selection of study populations, study end points, and drug doses) can be discussed, and quantitative methods such as modeling and simulations often play critical roles. PMDA may consider utilizing these quantitative methods to facilitate efficient review of drug products and offer sophisticated consultations.

Recent use of expedited development and regulatory review tools by CDER appears to lead to more efficient approval of novel therapies¹⁾. Each year, CDER approves hundreds of drugs such as new molecular entities (NMEs) under New Drug Applications (NDAs), new therapeutic biologics under Biologics License Applications (reviewed by CDER not CBER), new dosage forms of already approved products, and generic drug products. In January, 2015, CDER published a report of approving 41 novel therapies (NMEs and new therapeutic biologics) in 2014¹⁾. This number is more than that in any other year since 2005 (e.g. on average, about 25 novel therapy approvals each year between 2005 and 2013). The report also indicated that 78% of these novel therapies were approved after their first review cycle. In comparison, the Office of Medical Policy in CDER also investigated the reasons for denial of FDA approval of initial applications for novel therapies (Sacks LV., et al., JAMA, 311(4): 378-384 (2014)). Among approved 222 novel drugs between 2000 and 2012, 68.0% (151/222) were approved when first review cycles. One can consider that utilization of quantitative methods such as modeling and simulations have contributed the increase in number of approval novel drugs and approval success rate on the first review cycle.

Physiologically based pharmacokinetic (PBPK) modeling and simulation, which I am learning during my training in FDA, is one of the advanced tools that may help efficient regulatory review and communications with the sponsors. As I mentioned in my previous report, the number of submissions containing PBPK modeling and simulation works has increased in recent years. PBPK model, which is constructed by incorporating patients' physiological component and drug-dependent pharmacokinetic component, can simulate drug pharmacokinetics by taking into account the patients' conditions. The use of PBPK modeling and simulation has facilitated decisions on when and how specific clinical pharmacology studies to evaluate the effects of intrinsic and extrinsic factors should be conducted and appropriate labeling language. (Zhao P., et al., Clin Pharmacol Ther., 89 (2): 259-268 (2010)). I would like to improve my understanding of PBPK modeling methodology during my training, and continuously share the latest knowledge and review cases in FDA utilizing PBPK modeling and simulation with you.

- 1) Novel new drugs 2014 summary
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM430299.pdf>

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

Dispatch to Center for Devices and Radiological Health, U.S. FDA (1)

I am Rie Fukaya from the Office of Medical Devices I, PMDA. I have been in a three-month dispatch program at the U.S. FDA Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), Division of Cardiovascular Devices (DCD) which is scheduled from April 13 to July 7. DCD reviews Investigational Device Exemptions (IDE) for clinical trials/studies and 510(k) and Premarket Approval (PMA) marketing submissions in the cardiovascular devices area.

At CDRH, I have been engaging in discussions and information sharing on PMDA's review process for specific device areas (especially the areas for which I am responsible at PMDA*), joining internal team discussions and sponsor meetings, learning the guidance document development process, and visiting several research laboratories involving some device areas where we are interested.

Additionally, benefit/risk balance principles, Quality Management System (QMS) inspection and review, combination product review, teamwork/role-sharing process, and professional development will be discussed. I would like to learn a lot from them and share various kinds of information in a timely manner. I am dedicated to establishing a stronger cooperative relationship between FDA and PMDA through the discussion of review and other issues about cardiovascular devices, above and beyond the achievements of the Harmonization By Doing (HBD) activities. I hope my report from CDRH will be informative and interesting to you.

*Cardiovascular surgery and interventional devices

Detailed information on HBD is available at following URL.
<http://www.jfmدا.gr.jp/hbd/e/index.html>

Ms. Rie Fukaya
Visiting Reviewer at CDRH, U.S. FDA in the U.S.A.

Dispatch to Center for Devices and Radiological Health, U.S. FDA (2)

I am Takehiro Ichikawa, Office of Medical Devices II in PMDA. I have been dispatched to the Office of Device Evaluation, Center for Devices and Radiological Health (CDRH), U.S. FDA since April 13 2015. My dispatch period is about 3 months. During this period I am part of the Contact Lens and Retinal Devices Branch in the Division of Ophthalmic and Ear, Nose, and Throat Devices (DOED).

I have been engaging in collecting information on processes and review disciplines for ophthalmic and Ear, Nose and Throat (ENT) medical devices and have been attending internal meetings. In addition, I attended a meeting of the Medical Devices Advisory Committee Panel.

Furthermore, through information sharing and exchange of opinions in addition to information gathering, I would especially share the matters in review policy for innovative medical devices as well as the bottleneck in the review for existing ones that both U.S. FDA and PMDA are facing.

I hope that developing awareness of similarities and differences between U.S. FDA and PMDA will be of help to strengthen cooperation between both agencies.

Finally I wish that the information delivered during my short dispatch period will be beneficial to you.

Mr. Takehiro Ichikawa
PMDA's International Officer at CDRH, U.S. FDA in the U.S.A

