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PMDA Updates

July, 2017

News

1. ICH Meeting in Montreal

Group photo of participants

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) met in Montreal, Canada from May 27 to June 1. The attendees included 33 staff in total from PMDA, including Dr. Toshiyoshi Tominaga, Associate Executive Director for International Programs who served as Vice-Chair of the Assembly and the Management Committee; and Mr. Naoyuki Yasuda, Office Director, Office of International Programs, as well as staff from Ministry of Health, Labour and Welfare (MHLW) including Dr. Nobumasa Nakashima, Office Director, Office of International Regulatory Affairs. The ICH Assembly approved the China Food and Drug Administration (CFDA) as a new Regulatory Member, and Pharmaceutical Inspection Co-operation Scheme (PIC/S) as a new Observer. In addition, 2 new topics were adopted: the revision of the ICH E8 guideline on general considerations for clinical trials, and extrapolation for paediatric medicines. The Working Group meetings achieved many outcomes including a tentative agreement on the draft guideline on ICH Q12 (Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management), and an adoption of the ICH M7 addendum to the guideline on Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.

The next ICH meeting will be held in November 2017 in Geneva, Switzerland.

MHLW's press release is available at the following link.

http://www.mhlw.go.jp/stf/houdou/0000168423.html (in Japanese)

2. 5th International Generic Drug Regulators Programme (IGDRP) Meeting

From June 5 to 9, the 5th International Generic Drug Regulators Programme (IGDRP) meeting was held in Ottawa, Canada, which was attended by about 40 participants from 15 countries/regions/organizations. From Japan, one staff member from the Office of International Programs and one staff member from MHLW participated in the Steering Committee meeting. In addition, 3 staff members from the Office of Generic Drugs and one staff member from the Office of International Programs participated in the Bioequivalence Working Group and the Quality Working Group meetings. In the Working Group meetings, papers describing the comparison between regulatory authorities were finalized as an output of working group activities, and current opinions regarding existing projects were shared among participants. In the Steering Committee meeting, a merger with the International Pharmaceutical Regulators Forum (IPRF) was discussed and agreed as a future direction of IGDRP.

The next IGDRP meeting will be held in Brasilia, Brazil from October 30 to November 3, 2017.

The details of the IGDRP are available at the following URL.

http://www.igdrp.com/

3. DIA 2017 53rd Annual Meeting

From June 18 to 22, the DIA 2017 53rd Annual Meeting was held in Chicago, U.S.A., and Dr. Tatsuya Kondo (Chief Executive), Mr. Shinobu Uzu (Chief Safety Officer), Dr. Toshiyoshi Tominaga (Associate Executive Director for International Programs), Dr. Yoshiaki Uyama (Office Director, Office of Medical Informatics and Epidemiology) and 7 other staff from PMDA attended. In the PMDA Town Hall session chaired by Dr. Tominaga, Dr. Kondo delivered a presentation on PMDA's new activities based on the concept of "Rational Medicine" Initiatives. Mr.

Kazuhiko Mori (Councilor, MHLW) explained regulations including Conditional Early Approval System and SAKIGAKE, which will stimulate practical realization of new medical products, in his presentation, and Mr. Uzu spoke on PMDA'S post-marketing safety measures and quality management. There were approximately 100 participants in the PMDA Town Hall session, and active discussions about PMDA's recent activities were held. In the DIAmond sessions, which were the prime sessions of DIA, Dr. Kondo and Mr. Mori participated as panelists in the "International Regulatory Convergence" and "Global Annual Meeting Executive Forum," respectively, and input initiatives by PMDA/MHLW. Dr. Tominaga delivered presentations in two sessions, "Global Perspective on ICH" and "Changing Environments with Pharmacovigilance". PMDA staff participated in a total of 7 sessions as a chair, panelist or speakers. In addition, PMDA staff contributed as a tutor of a short (training) course, a poster presenter, and booth exhibitors.

The next meeting will be held on June 24-28, 2018 in Boston, U.S.A.

Left: (from left) Dr. Tominaga, Dr. Kondo, Mr. Mori and Mr. Uzu.
Right: Dr. Kondo (second from left) as panelist in DIAmond session

4. PMDA-ATC Pharmaceuticals Review Seminar 2017

From June 26 to 30, PMDA held a seminar entitled "PMDA-ATC Pharmaceuticals Review Seminar 2017" in Tokyo and Toyama. This seminar was designed for officials of regulatory agencies overseas engaged in drug reviews, and participated by 28 regulators from Brazil, China, Hong Kong, Malaysia, Myanmar, The Philippines, Saudi Arabia, Singapore, Taiwan, Thailand and Vietnam.

Group photo of participants and PMDA executives and directors
Front row from left to right, Dr. Toshiyoshi Tominaga, Associate Executive Director for International Programs (3rd), Mr. Kenichi Mikami, International Senior Training Coordinator/Office Director, Office of New Drug I (4th), Dr. Junko Sato, Office Director, Office of International Cooperation (5th)

In the seminar, lectures were delivered by PMDA staff on consultations, clinical trials, toxicology, GCP/GLP inspections, product reviews (for new/generic drugs), package inserts, safety measures, Risk Management Plan (RMP), the relief system for sufferers from adverse drug reactions, and recent challenge to accelerate drug development in Japan. Also, lectures on new drug development from an industry viewpoint were presented by a Japan Pharmaceutical Manufacturers Association (JPMA) representative. Besides these lectures, the program in Tokyo included group discussions on product reviews, and presentations by the participants on the regulations of their regulatory authorities. The program in Toyama included a site visit of a manufacturing facility to observe a patch manufacturing process and its quality control, and lectures on some OTC drugs that are approved by a prefectural governor. The participants actively engaged in discussions throughout the seminar.

On the final day of the seminar in Tokyo, the Course completion certificates were handed to each one of the participants by Mr. Kenichi Mikami, International Senior Training Coordinator/Office Director, Office of New Drug I.

Please refer to the following web site for the details of PMDA-ATC Pharmaceuticals Review Seminar 2017.
http://www.pmda.go.jp/english/symposia/0105.html

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
Suiny	anagliptin	June 26
Duac	clindamycin phosphate hydrate/ benzoyl peroxide	July 10

Safety Information

Pharmaceuticals and Medical Devices Safety Information No. 344, June 27, 2017

1. Revision of Instructions for Package Inserts of Prescription Drugs
2. Precautions Concerning Recurrent and Similar Medical Accidents
3. Important Safety Information
   (1) Treprostinil
   (2) Bosutinib
4. Revision of Precautions (No. 285)
   Treprostinil (and 3 others)
5. List of Products Subject to Early Post-marketing Phase Vigilance
   (Posted on June 27, 2017)

http://www.pmda.go.jp/english/safety/info-services/drugs/medical-safety-information/0015.html

Pharmaceuticals Revisions of PRECAUTIONS, July 4, 2017

- Tramadol hydrochloride
- Tramadol hydrochloride/acetaminophen
- Dihydrocodeine phosphate/dl-methylephedrine hydrochloride/chlorpheniramine maleate
- Dihydrocodeine phosphate/diprophylline/dl-methylephedrine hydrochloride/diphenhydramine salicylate/acetaminophen/bromovalerylurea
- Codeine phosphate hydrate/cherry bark extract
- Dihydrocodeine phosphate/platycodon fluidextract/glycyrrhiza extract/plantago herb extract/peony root extract
- Codeine phosphate hydrate
- Dihydrocodeine phosphate
- Dihydrocodeine phosphate/ephedrine hydrochloride/ammonium chloride
- Products containing codeine phosphate hydrate and products containing dihydrocodeine phosphate(OTC drugs) (preparations with the administration for patients younger than 2 years old)
- Products containing codeine phosphate hydrate and products containing dihydrocodeine phosphate(OTC drugs) (preparations with the administration for patients younger than 12 years old and without the administration for patients younger than 2 years old)
- Products containing codeine phosphate hydrate and products containing dihydrocodeine phosphate(OTC drugs) (preparations without the administration for patients younger than 12 years old)
- Loxoprofen sodium hydrate (Cataplasms/Gel Patches)
- Loxoprofen sodium hydrate (Tape)
- Loxoprofen sodium hydrate (Gel)
- Loxoprofen sodium hydrate (Spray)
- Hydroxocobalamin
- Nivolumab (genetical recombination)
- Fluconazole
- Fosfluconazole
- Patch test products containing gold (I) sodium thiosulfate
- Loxoprofen sodium hydrate (dermatologic preparation) (guidance-mandatory drugs)

http://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0005.html

Risk Information which some safety measures might be taken (July 14, 2017)

- Warfarin potassium
- Laninamivir octanoate hydrate
- Azithromycin hydrate

http://www.pmda.go.jp/english/safety/info-services/drugs/risk-communications/0001.html

Events

Conferences/Meetings PMDA hosts or participates in:

Date	Title	Location
July 31-August 4	PMDA-ATC GMP Inspection Seminar* (*with the support of PIC/S)	Yamaguchi
August 15-18	8th CIMDR (China International Medical Device Regulatory Forum)	Hangzhou
September 10-12	RAPS (Regulatory Affairs Professional Society) Annual Conference	Washington, D.C.
September 11-12	PIC/S (Pharmaceutical Inspection Cooperation Scheme) Committee	Taipei
September 19-21	12th IMDRF Management Committee Meeting	Ottawa

Reports from overseas

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

One year passed since PRIME implementation

One year has passed since PRIME (PRIority MEdicines), the similar system to Sakigake Designation System in Japan, was implemented in EU. EMA hosted a workshop on 19 May 2017 to share the experience of the 1-year implementation and exchange opinions of the future of PRIME with participation from a variety of stakeholders, including actual applicants of PRIME, industries, academia, patient groups, HTA organizations and regulators, including those outside EU.

In this workshop, results of a feedback survey conducted among EFPIA were shown. The results as well as opinions during the workshop were mostly supportive to PRIME. One outstanding note raised in the workshop is the importance of continuous monitoring of PRIME implementation in terms of actual performance and benefits after PRIME designation, as it is still too early to assess the points.

Positive remarks about proposals to make PRIME better, including when the most suitable timing of PRIME designation is, were also provided. As some proposals might be applicable to Sakigake Designation in Japan, I will pay continuous and close attention to the implementation of PRIME.

Mr. Hideyuki Kondo
PMDA's International Liaison Officer stationed at EMA in the United Kingdom

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USP Quality Standards for Pharmaceutical Continuous Manufacturing Expert Panel Face-to-Face Meeting

Pharmaceutical Continuous Manufacturing has been identified as a National Priority Technology in the U.S. In the ADVANCED MANUFACTURING: A Snapshot of Priority Technology Areas Across the Federal Government,

which has been published by the U.S. government, it is expected to help mitigate the public health threat arising from drug shortage and various patient demands by providing a rapid response to them through improving the agility, flexibility, and robustness in the manufacture of pharmaceuticals as well as reduce manufacturing costs [1]. Although currently 2 pharmaceutical products made by using continuous manufacturing have been approved in the U.S., industry and academia are pursuing development of various technologies for increasing of continuous manufacturing in the pharmaceutical industry.

USP has formed the Quality Standards for Pharmaceutical Continuous Manufacturing Expert Panel to provide recommendations for a road map for the development and implementation of compendial quality standards for Pharmaceutical Continuous Manufacturing. This expert panel held a face-to-face meeting on June 8-9 [2]. In this meeting, the experts discussed terminology specific for Pharmaceutical Continuous Manufacturing, process control strategies and statistical tools required for analytical methods using process analytical technology, material characterization required for processes specific for Pharmaceutical Continuous Manufacturing, and others. The recommendations prepared based on these discussions will be published on the website of Pharmacopeial Forum [3] to invite public comments.

I guess Pharmaceutical Continuous Manufacturing, which assures products quality by maintaining the state of control on processes, will influence pharmacopoeias which provide standards for pharmaceutical products. Therefore, I will pay close attention to trends of Pharmaceutical Continuous Manufacturing in the U.S. including this expert panel.

1) ADVANCED MANUFACTURING-A Snapshot of Priority Technology Areas Across the Federal Government (April 2016): Continuous Manufacturing of Pharmaceuticals (P29-32)
http://www.whitehouse.gov/sites/whitehouse.gov/files/images/Blog/NSTC%20SAM%20technology%20areas%20snapshot.pdf
2) Quality Standards for Pharmaceutical Continuous Manufacturing
http://www.usp.org/meetings-courses/expert-committee-meetings/quality-standards-pharmaceutical-continuous-manufacturing
3) Pharmacopeial Forum
http://www.usp.org/usp-nf/pharmacopeial-forum

Dr. Yujiro Kameyama
PMDA's Liaison Officer stationed at USP in the U.S.A

Utilization of physiologically based pharmacokinetics (PBPK) modeling in new drug development

In PBPK models, individual organs relevant to pharmacokinetic and pharmacological 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. In recent years, the PBPK model analysis for new drug development has been increasing mainly with prediction of drug-drug interaction. The PBPK model analysis was utilized for new drug applications in 217 cases in the U.S.[1] and 17 cases in Japan[2] by 2016.

In March this year, the Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting hosted by U.S. FDA was held [3]. At the meeting, it was discussed what kind of information should be included in a PBPK submission to FDA and what criteria should be used to determine that the model is adequately verified. In addition, in May, a workshop hosted by FDA and University of Maryland was held [4]. At the workshop, utilization of PBPK modeling in new drug development was discussed mainly on modeling on oral absorption.

FDA has already published the drafting guidance "Physiologically Based Pharmacokinetic Analyzes, Format and Content" for PBPK model analysis reporting. Also, EMA has already published the draft guidance "Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modeling and simulation".

As mentioned above, in recent years, utilization of PBPK model analysis for new drug application has been increasing. And there has been usually a very lively discussion for utilization of PBPK modeling in new drug

development. Therefore, it is hoped to publish guidance for analysis of PBPK in Japan and harmonize policy among review agencies in the future.

I finished my dispatch this July. During one year, I had the opportunity to learn a lot, and this one year has been very meaningful. The Division of Pharmacometrics members taught me many details of review for New Drug Application and technique of Pharmacometrics in FDA. I would like to use this experience to contribute to future international activities. Finally, I would like to express my sincere appreciation to Dr. Ping Zhao, and thank everyone at FDA and PMDA who supported my dispatch.

1) Ping Zhao, ASPCT Annual Meeting 2017
http://www.ascpt.org/Portals/8/docs/Meetings/2017%20Annual%20Meeting/2017%20Presentations/Friday%203_17/Physiologically%20Based%20Pharmacokinetics_Ping%20Zhao.pdf?ver=2017-03-30-081430-643
2) M Sato, Y Ochiai, S Kijima, N Nagai, Y Ando, M Shikano, Y Nomura, CPT Pharmacometrics Syst Pharmacol, First Published:1 June 2017.
3) 2017 Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm535520.htm
4) Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development
http://pharmacy.umaryland.edu/centers/cersievents/dissolution-and-translational-modeling-strategies/

Mr. Shinichi Kijima
PMDA's Officer at CDER, U.S. FDA in the U.S.A

Safety Labeling Changes in U.S. FDA

U.S. FDA can require, when certain conditions are met, and, if necessary, order that holders of applications for approved products make labeling changes related to safety issues when FDA identifies the need to change labels based on new safety information obtained after approval. A variety of sources can be used as new safety information, including cases reported to FDA Adverse Event Reporting System, clinical trials, observational studies, the medical literature, and communications with foreign regulatory authorities. PMDA also uses similar information in pharmacovigilance activities. FDA provides information on approved safety labeling changes on its website [1)].

There are differences in labeling change processes between PMDA and FDA. For example, in FDA, the Office of New Drugs or the Office of Generic Drugs contacts marketing authorization holders (MAH) instead of the Office of Surveillance and Epidemiology, which assesses post-marketing safety information. The MAH must respond to a labeling change request from FDA within 30 days of the date that a notification letter is issued by FDA by implementing the labeling change, by proposing alternative labeling language, or by notifying FDA that it believes that a labeling change is not warranted and providing an explanation of its reasoning. In certain situations, FDA will enter into discussions with the MAH. FDA generally makes a final decision on the labeling change within 30 days since FDA receives MAH's responses.

FDA did not have an authority to require safety-related labeling changes before the passage of the Food and Drug Administration Amendments Act of 2007.

1) http://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/

Dr. Takashi Misu
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