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PMDA Updates

December, 2016

News

1. ICH Meeting in Osaka (November 6-10)

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was held in Osaka, Japan from November 6 to 10. Thirty-five staffs in total from PMDA, including Dr. Toshiyoshi Tominaga, Associate Executive Director (for International Programs; who served as Vice-Chair of the Assembly and Chair of Management Committee) and Mr. Naoyuki Yasuda, Office Director, Office of International Programs attended the meeting. Mr. Kazuhiko Mori, Minister's Secretariat (for Pharmaceutical Affairs), Dr. Nobumasa Nakashima, Office Director for International Regulatory Affairs and other staffs also attended from Ministry of Health, Labour and Welfare (MHLW). In the Assembly, the new Members were approved as Regulators other than Funding Regulatory Members, Standing Regulatory Members for the first time. The key achievements of the Working Group meetings included ICH E6 on "Guideline for Good Clinical Practice", ICH M8 on "Electronic Common Technical Document (Questions and Answers)", ICH E2B on "Electronic Submission of Individual Case Safety Reports (Questions and Answers)", and ICH Q3C on "Guideline for Residual Solvents" which all reached Step 4, as well as ICH Q11 on "Development and Manufacture of Drug Substances" and ICH E11 on "Clinical Investigation of Medicinal Products in the Pediatric Population" which reached Step 2b. The next ICH meeting will be held in May 2017 in Montreal, Canada.

Group photo of participants including Dr. Tominaga and Mr. Mori (3rd and 5th right on the front row), Mr. Yasuda (2nd right on the 2nd row) and Dr. Nakashima (2nd right on the 3rd)

2. PMDA-ATC Medical Devices Seminar 2016 (November 7-11)

From November 7 to 11, PMDA held PMDA-ATC Medical Devices Seminar 2016. This Seminar was designed for officials of regulatory agencies overseas engaged in the review of medical devices and in vitro diagnostics, and participated by a total of 28 regulators from 13 regulatory agencies (i.e. Australia, Brazil, Chinese Taipei, Hong Kong, India, Indonesia, Malaysia, Myanmar, Singapore, South Africa,

Group photo of participants and PMDA Executives and DIrectors. From the 2nd left on the front row, Dr. Junko Sato, Director of Office of International Cooperation, Mr. Akagawa, Dr. Tatsuya Kondo, Chief Executive and Mr. Shinichi Takae, International Senior Training Coordinator.

Sri Lanka, Thailand and Zambia). In the Seminar, lectures were delivered by PMDA staff on the topics including medical device product reviews, consultations, clinical trials, GCP/GLP inspections, Quality Management System (QMS) inspections, post-marketing safety measures, package inserts, patient registration system, medical device standards (utilization of international standards, etc.), in vitro diagnostics product reviews, capacity building, and international regulatory updates. The Seminar also included group discussions on consultations and product reviews, presentations by the participants on the regulations of their Regulatory Authorities, and site visit to manufacturing facilities recommended by The Japan Federation of Medical Devices Associations. The participants actively engaged in discussions throughout the seminar.

On the final day of the Seminar, the Course completion certificates were handed to each participant by Mr. Haruo Akagawa, Director of Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs.

3. Special training given by staff from U.S.FDA (November 14)

On November 14, Dr. Gerald J. Dal Pan, Director of the Office of Surveillance and Epidemiology, U.S.FDA visited PMDA and gave a special lecture entitled "Assessing the impact of pharmacovigilance: Predictors and correlates" to PMDA staff members.

Dr. Dal Pan explained the importance of assessing the regulatory and societal impact of pharmacovigilance activities, and provided the results of a study that examined the impact Scheduled Safety Summary Analyses on subsequent safety measures. He also explained how U.S.FDA utilizes information from external sources for pharmacovigilance.

The attendees gained a better understanding of the U.S.FDA's principles of assessing pharmacovigilance and risk management activities.


Dr. Dal Pan

4. 2016 APEC Good Registration Management Regulatory Science Center of Excellence Pilot Workshop (November 15-17)

On November 15-17, PMDA cohosted 2016 APEC Good Registration Management Regulatory Science Center of Excellence Pilot Workshop with Regulatory Affairs Professionals Society (RAPS) Taiwan and Taiwan Food and Drug Administration. The objective of Good Registration Management (GRM) is for Regulatory Agencies and Industry to cooperatively promote Good Review Practice (GRevP) and Good Submission Practice (GSubP) to foster mutual communication and to contribute to effective product development and product review in APEC member economy. The workshop was designed for reviewers from Regulatory Agencies as well as applicants from Industry who make regulatory submissions.

Lecturers and participants at group discussion

The participants included 28 officials from Regulatory Agencies of Chile, Indonesia, Malaysia, Mexico, Papua New Guinea, Peru, Philippines, Taiwan, Thailand and Vietnam. In the workshop, PMDA staffs facilitated lectures and group discussions on regulator/ applicant communication, points to be considered for a good review, and review management. Also, in the applicant-specific sessions, lectures by the representative of Japan Pharmaceutical Manufacturing Association and group discussions were held, and the attendees participated actively in the discussions throughout the workshop.

5. PMDA workshop "Toward promoting pediatric drug development: what we can do for children's future (November 28)

Dr. Yamori

Dr. Shikano (left end) at Panel DIscussion

On November 28, a PMDA workshop entitled "Toward promoting pediatric drug development: what we can do for children's future" was held in Tokyo, hosted by PMDA Pediatric Drugs Working Group, and attended by about 350 people who actively participated in discussion. Dr. Takao Yamori, Executive Director, Mr. Yoshikazu Hayashi, Associate Center Director (for New Drug Review), Dr. Mayumi Shikano, Associate Center Director (for Advanced Review with Electronic Data Promotion and Science Board) and many staff from PMDA participated in the workshop. The workshop was started by the key note lecture by Dr. Susumu Itoh, professor emeritus, Kagawa University, which was followed by lectures by regulators, industry and academia as well as EMA on the two themes (i.e. "pediatric extrapolation" and the "timing of initiation of pediatric drug development") and subsequent panel discussion with seven panelists and participants on those themes.

In the workshop, it was shared that the basic principle of the use of "pediatric extrapolation" in Japan was not much different from that of the US and the Europe. It was also shared that when pediatric use is anticipated, integrating the pediatric drug-development program earlier in the overall drug development program including the one for adults to collect necessary data would consequently allow for efficient development, with "pediatric extrapolation" and participation in multi-regional clinical trials. Moreover, it was recognized that collaborations (among industry, academia and regulators as well as international collaboration) would be important.

Please refer to the following web site for the details of the workshop.
http://www.pmda.go.jp/review-services/symposia/0055.html

6. 17th International Conference of Drug Regulatory Authorities (November 29-December 2)

Dr. Tominaga

The 17th International Conference of Drug Regulatory Authorities (ICDRA) was held in Cape Town, South Africa from November 27 to December 2. Dr. Toshiyoshi Tominaga, Associate Executive Director (for International Programs), Mr. Naoyuki Yasuda, Office Director, Office of International Programs, and 1 staff from PMDA as well as Dr. Nobumasa Nakashima, Office Director for International Regulatory Affairs, Ministry of Health, Labour and Welfare (MHLW) participated in the conference as speakers and moderators. ICDRA is the biennial meeting among pharmaceutical Regulatory Authorities organized by WHO, and the 17th ICDRA held under the theme of "Patients are waiting: How regulators collectively make a difference" consisted of Pre-ICDRA Meeting (November 27-28) which was open to Industry, and ICDRA (November 29-December 2) which was for Regulators only. Topics discussed during the conference included "Regulatory convergence and vision on future collaboration" and "Regulating medical devices: the involvement of stakeholders" in the Pre-ICDRA Meeting, and "Good Regulatory Practices", "Safety of herbal medicines" and "Global scenery of regulatory convergence initiatives" in the main ICDRA. Approximately 300 people participated from the world and many African countries, and had an active exchange of views on each topic. The next ICDRA meeting will be held in 2018 in Ireland.

7. Debrief meeting with EMA Visiting Expert (November 30)

Chief Executive
Dr. Tatsuya Kondo (left) and
Dr. Saint Raymond (right)

On November 30, a debrief meeting for PMDA staff entitled "A European as visiting expert at PMDA" was held with Dr. Agnès Saint Raymond, who had been dispatched to PMDA as a visiting expert from EMA from October 3 and November 30.

Dr. Saint Raymond explained EMA's role in the EU public health, how EMA is organized, EMA's participation in global cooperation, and based on her experience at PMDA, spoke about the cooperation in activities of PMDA working groups of pediatric drugs and orphan drugs (drugs for rare diseases in small patient populations for which limited data are available) as well as the opinion exchange with Advanced Review with Electronic Data Promotion Group. In the subsequent questions and answers session, a range of topics were covered including pediatric drug regulations in the EU, strategies to create official English documents and to foster effective communication at EMA with staff from non-English speaking backgrounds.

The attendees obtained further understanding of EMA's operations as well as international regulatory challenges for PMDA and EMA to solve in cooperation with each other.

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
Yervoy	ipilimumab (genetical recombination)	December 5
Harvoni	ledipasvir acetonate/sofosbuvir	December 6
Pomalyst	pomalidomide	December 13

Regenerative Medicines (cellular and tissue-based products)

https://www.pmda.go.jp/english/review-services/reviews/approved-information/0004.html

Brand Name	Generic Name	Posting date
HeartSheet	human (autologous) skeletal myoblast-derived cell sheet	December 2

Safety Information

Pharmaceuticals Revisions of PRECAUTIONS, November 22, 2016

- Polaprezinc (Granules)
- Polaprezinc (Tablets)
- Formalin
- Formalin/Cresol
- Cresol/Formalin/Clove oil/Zinc oxide mixt

- Formalin/Guaiacol
- Allopurinol
- Alogliptin benzoate
- Alogliptin benzoate/Pioglitazone hydrochloride
- Linagliptin
- Teneligliptin hydrobromide hydrate
- Alogliptin benzoate/Metformin hydrochloride
- Zoledronic acid hydrate
- Famciclovir

http://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0004.html

Pharmaceuticals Revisions of PRECAUTIONS, November 25, 2016

- Duloxetine hydrochloride
- Venlafaxine hydrochloride
- Milnacipran hydrochloride

http://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0004.html

Risk Information which some safety measures might be taken (December 9, 2016)

- Interferon Beta-1b (genetical recombination)
- Iguratimod
- Lenalidomide Hydrate

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

Pharmaceuticals and Medical Devices Safety Information No. 339, December 20, 2016

1. Precautions for Driving, etc. under the Treatment with Milnacipran Hydrochloride, Duloxetine Hydrochloride, or Venlafaxine Hydrochloride
2. Suspected Adverse Reactions to Influenza Vaccines in the 2015 Season
3. Safety of Influenza Antiviral Drugs
4. Important Safety Information
   (1) Polaprezinc
   (2) Allopurinol
   (3) Alogliptin benzoate, Linagliptin, Teneligliptin hydrobromide hydrate
5. Revision of Precautions (No. 280)
   Formalin (and 4 others)
6. List of Products Subject toEarly Post-marketing Phase Vigilance

http://www.pmda.go.jp/english/safety/info-services/drugs/medical-safety-information/0014.html

Events

Conferences/Meetings PMDA hosts or participates in:

Date	Title	Location
January 23-26	PMDA-ATC MRCT Seminar 2017	Tokyo
January 26	PMDA-ATC MRCT Workshop	Tokyo
February 2-3	The 4th Thailand-Japan Symposium	Bangkok

February 6-9	PMDA-ATC Pharmacovigilance Seminar 2017	Tokyo
February 9-10	PIC/S (Pharmaceutical Inspection Cooperation Scheme)	Geneva

Reports from overseas

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

Official participation in programme to rationalise international GMP inspections of active pharmaceutical ingredients/active substances manufacturers

International cooperation activities relating to GMP include the development of relevant ICH guidelines and information sharing of GMP inspections through PIC/S, in which PMDA is very actively involoved. Most recently, it was decided in November 2016 that PMDA would officially participate in the programme to rationalise international GMP inspections of active pharmaceutical ingredients/active substances (APIs) manufacturers.

The programme is conducted by international regulators such EMA, U.S.FDA and Therapeutic Goods Administration (TGA), a regulatory authority of Australia. Under the programme, information about GMP inspections such as inspection plan, inspection outcome, and its follow-up, for mutually-interesting API manufacturers outside each country/region, which is expected to allow each regulators, for example, to allocate appropriate GMP inspection resources and to perform a joint inspection.

Requirements to participate in the programme include: Adequate inspection capacity and performance for API manufacturers, adoption of international GMP standards and guidelines, foundation to share confidential information and confidence has been established with existing participants.

Therefore, this official participation by PMDA indicates the domestic and international activities/contributions by Japan in the GMP field got high evaluation internationally once again.

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

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Biotechnological/Biological Products

Biologics Monographs 1 – Peptides & Insulins Expert Committee and Biologics Monograph 2 – Proteins Expert Committee held a face-to-face meeting at the United States Pharmacopeial Convention (USP) headquarters on November 16-17 and November 29-30, respectively. These committees discussed the setting and replacement strategies of reference standards, and the latest analytical methods for characterizing proteins which have complex structure, as well as the monographs for which they are responsible. Also, they have prepared basic principles and general information suitable for various types of biotechnological/biological products. I found that they were actively trying to ensure consistency with the other pharmacopoeias by comparing with the relevant standards in the other pharmacopoeias when they developed or revised these standards.

The development of the basic principles on quality assurance for biotechnological /biological products and inclusion of new monographs for these products is one of the specific work plans in the Basic Principles for Preparation of Japanese Pharmacopoeia 18th Edition. Accordingly, it is expected that various standards for these products will be developed.

A lot of discussion about biotechnological/biological products will be generated in USP and JP, therefore I would like to develop my understanding of each pharmacopoeia's strategy for these products in order to properly share information between both pharmacopoeias.

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

Communication with Applicant Concerning Electronic Study Data

PMDA started to receive electronic data of clinical study in October 2016. Whereas, the U.S. FDA already started to receive electronic data of clinical study more than 10 years ago. In the U.S.FDA, reviewers are conducting analyses by themselves to make regulatory decisions. Regarding the electronic data to be submitted, it is necessary to follow the rules stipulated in the guidance documents.1) In order to receive relevant data, communication with the applicant is very important.

In the U.S.FDA, technical aspects of the submission are generally discussed at the pre-NDA/BLA meeting. If technical aspects of the submission have not been adequately addressed with the applicant, an electronic presubmission meeting may be held at the discretion of the review division 30-60 days prior to the submission of the application.

On the other hand, PMDA does not discuss technical aspects of the submission at Pre-NDA/BLA Meeting. They are discussed at "consultation on data format of submission of electronic study data". The applicant can apply for the consultation for any number of times at any time.

In the U.S.FDA, in addition to the Study Data Reviewer's Guide on Analysis Data Reviewers Guide on CDISC standard data, in the case of pharmacometric analyses, documents describing the explanation and usage of files are generally required. Regarding what becomes clear after the submission (lack of files, lack of explanation, etc.), the review team issues information requests to the applicant and asks for explanation and correction. In this way, the U.S.FDA continues to communicate with the applicant concerning electronic study data towards the end of review.

In the PMDA, in the case of pharmacometric analyses, "explanation of electronic data package on clinical pharmacology" and "the program procedures" are expected to be submitted for conducting analyses. Thus, I think the future issue is how PMDA would communicate with the applicant regarding what becomes clear after the submission.

1) Advanced Review with Electronic Data Promotion Group
http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html
2) CDER 21st Century Review Desk Reference Guide
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.htm

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

Trainings for Data Analysis in the U.S. FDA

The review staffs in the U.S. FDA analyze electronic data of clinical trials as part of a new drug review process. There are well-organized infrastructures and training resources to support the review staffs.

Hands-on trainings on analytical tools for electronic data are provided for reviewers. A lot of trainings are also provided as recorded training materials. Staff can utilize those recorded materials to learn how to use the tools effectively. These training infrastructures for data analysis provide a solid learning environment for reviewers and can help overcome limitations in availability of hands-on training. In addition, there are plenty of recorded training materials to learn about new drug review

process and related matters. These materials can be beneficial not only for fellowship staff to learn effectively, but also review staff in continuous education.

These recorded training materials seem to be similar to the education resources of distance learning or preparatory schools in Japan. Plenty of recorded training materials provide trainings 8and supports for innovative project efficiency at the U.S. FDA. Many public training materials for general topics and webinars for recent topics are provided on the U.S. FDA's website [1),2)]. These materials can be useful for you.

1) Training and Continuing Education
http://www.fda.gov/Training/default.htm
2) CDER Webinars
http://www.fda.gov/Drugs/ucm273272.htm

Dr. Ken Sakushima
Office of Strategic Programs, U.S. FDA in the U.S.A.
