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PMDA Updates

September, 2016

News

1. Asia-Pacific Economic Cooperation, Life Science Innovation Forum, Regulatory Harmonization Steering Committee (APEC-LSIF-RHSC) Meeting (August 16 to 17)

Dr. Tominaga

Asia-Pacific Economic Cooperation, Life Science Innovation Forum, Regulatory Harmonization Steering Committee (APEC- LSIF-RHSC) meeting was held in Lima, Peru from August 16 to 17. Key participants from Japan were Dr. Toshiyoshi Tominaga (Associate Executive Director for International Programs, PMDA), Dr. Junko Sato (Office Director, Office of International Cooperation, PMDA) and Dr. Nobumasa Nakashima (Office Director for International Regulatory Affairs, MHLW). RHSC meeting aims for "Promotion of the strategic framework for the convergence of medical products regulation". Dr. Tominaga is co-chair of the RHSC along with the US. Regulators from ten APEC economies and representatives from industry (pharmaceuticals, bio-pharmaceuticals, medical devices) participated in the meeting. APEC-LSIF-RHSC has been conducting pilot programs of upskilling of regulators and relevant persons to establish Center of Excellence (CoE) to offer such training. Out of the six working areas of RHSC, PMDA is to provide the pilot programs in the areas of MRCT/GCP in January 2017, and Pharmacovigilance and medical device vigilance in February 2017, respectively. At the meeting, the progress report was given on the preparation for the two pilot programs as well as the workshop which is to take place after the MRCT/GCP pilot program. Also, the procedure and guideline development leading to the establishment of formal CoE were discussed.

Next APEC-LISF RHSC meeting will be held in Viet Nam, in the first quarter of 2017.

2. Tripartite Meeting held between EMA, FDA and PMDA towards enhancing development for Antibacterial Agents (September 1 to 2)

From September 1 to 2, a tripartite face-to-face meeting was held between the EMA, FDA and PMDA at the EMA, London, which was the first meeting toward facilitating antimicrobial drug development. This meeting was held in response to the discussions at the G7 summits (in Schloss Elmau and Ise-Shima) and the proposal by Dame Sally Davies, Chief Medical Officer of the UK, where PMDA proposed the EMA and FDA to explore tripartite collaboration in developing guidelines. From PMDA, Mr. Yoshikazu Hayashi (Associate Center Director), Dr. Junko Sato (Office Director, Office of International Cooperation) and 2 other staffs attended the meeting.

In the two-day discussions, each region's current regulations and guidelines on all antimicrobial drugs were outlined, and approaches and experiences on consultations or reviews of drugs for Antimicrobial Resistance (AMR) infections were shared. As many diseases in this field affect only small numbers of patients and sporadic patients, clinical trials in this field may require different approaches from usual. Possible approaches for such situations were explored and discussed in the meeting as well.

Participants agreed to continue further discussion on the matter, including a thorough gap analysis among three regulatory systems.

The common summary of the outcome of the meeting is available at web sites of the three agencies.

Please refer to the following web site for Tripartite Meeting held between EMA, FDA and PMDA towards enhancing development for Antibacterial Agents.

http://www.pmda.go.jp/english/int-activities/outline/0018.html

3. PMDA provides training to Taiwan Food and Drug Administration, Ministry of Health and Welfare (TFDA) (September 5 to 8)

From September 5 to 8, PMDA provided training on Good Clinical Practice (GCP) inspections to 2 staffs from Taiwan Food and Drug Administration, Ministry of Health and Welfare (TFDA). This training was offered as part of the activities of GCP Working Group at the Joint Conference of Taiwan and Japan on Medical Regulation which has been held since 2013. This four-day training included lectures and case studies as well as a site visit, covering topics on PMDA's principles on conducting overseas inspections and GCP inspections for bioequivalence studies. On the last day of the training, the participants were asked to give presentations to introduce TFDA's GCP inspections and related regulations, and also to summarize the training. Through the training, the participants were able to gain further details on GCP inspection methods in Japan, and both regulatory authorities were able to deepen the mutual understanding.

Trainees from TFDA (left side) and staffs of the Office of Non-clinical and Clinical Compliance

4. Call for application to PMDA-ATC Medical Devices Seminar 2016 starts

PMDA Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) will hold a seminar entitled "PMDA-ATC Medical Devices Seminar 2016" from November 7 to 11, 2016. This seminar is designed for officials from overseas regulatory agencies who are engaged in the review of medical devices and in vitro diagnostics. The Seminar will cover wide range of topics including regulations, consultations (scientific advices), product reviews, and GCP/GLP/QMS. In addition, group discussions and site visit to manufacturing facilities are planned as part of the seminar. The objective of the seminar is to provide the participants an opportunity to reflect on and enhance their regulatory systems.

Please refer to the following web site for the details of PMDA-ATC Medical Devices Seminar 2016.
http://www.pmda.go.jp/english/symposia/0092.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
Zafatek	trelagliptin succinate	August 30

Safety Information

Pharmaceuticals and Medical Devices Safety Information No. 336, September 6, 2016

1. Precautions Relating to Interstitial Lung Disease During Administration of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors
2. Genome Research Relating to Drug-induced Serious Skin Disorders
3. Important Safety Information
   (1) Olanzapine
   (2) Azosemide
4. Revision of Precautions (No. 277)
   Imatinib mesilate (and 4 others)
5. List of Products Subject to Early Post-marketing Phase Vigilance

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

Pharmaceuticals Revisions of PRECAUTIONS, September 13, 2016

- Natalizumab (genetical recombination)
- Nartograstim (genetical recombination)
- Filgrastim (genetical recombination)
- Filgrastim (genetical recombination) ［filgrastim biosimilar 1］
- Filgrastim (genetical recombination) ［filgrastim biosimilar 2］
- Filgrastim (genetical recombination) ［filgrastim biosimilar 3］
- Lenograstim (genetical recombination)
- Pegfilgrastim (genetical recombination)
- Eltrombopag olamine
- Afatinib maleate
- Corticorelin （human）

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

Events

Conferences/Meetings PMDA hosts or participates in:

Date	Title	Location
October 4	3rd Brazil-Japan Seminar on Regulations on Pharmaceuticals and Medical Devices	Sao Paulo
October 11-13	11th International Summit of Heads of Medicines Regulatory Agencies / International Coalition of Medicines Regulatory Authorities (ICMRA)	Interlaken
October 12-13	3rd Self-Medication Collaborative Regulator Expert Roundtable annual meeting	Nagoya
October 17-21	4th Meeting of the International Generic Drug Regulators Programme (IGDRP)	Mexico City
October 25-26	CoRE Advisory Board Meeting	Singapore
November 5-10	ICH Week	Osaka
November 7-11	PMDA-ATC Medical Devices Seminar 2016	Tokyo
November 15-17	APEC-LSIF-RHSC Good Review Management Workshop	Taipei
November 29-December 2	17th International Conference of Drug Regulatory Authorities (ICDRA)	Cape Town

Reports from overseas

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

Performance of new drug pre-market review in Japan and EU

EMA issued its Annual Report 2015 in May 2016[1)], and PMDA published its FY 2015 performance report in August 2016. In the press release by EMA related to announcement of the annual report, it is mentioned that the number of positive recommendations for new drug approval was 98, including 39 for new active ingredients, in 2015[2)]. On the other hand, in Japan, 116 products, including 42 products with new active ingredients, were approved in FY 2015. These positive recommended/approved numbers have remained similar for recent couple of years in both Japan and EU.

In addition, as shown in the table below, both reports include the information on pre-market review period for brand new drugs:

Table Pre-market review period of brand new drugs in 2015 (EU)/FY 2015 (Japan)

	Authority time	Applicant time	Total
EU (Average)	8.7 months	4.3 months	13.0 months
Japan (60th percentile)	5.5 months	5.0 months	10.8 months

According to the pre-market review periods for recent years, the reviews have been conducted steadily in both Japan and EU. Collaborative activities between PMDA and EMA are continuously advanced, which is expected to contribute to maintaining/improving time and quality of pre-market review of drug.

1) http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2016/05/WC500206482.pdf
2) http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/05/news_detail_002531.jsp&mid=WC0b01ac058004d5c1

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

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Health Canada's bioequivalence evaluations of orally inhaled drug products for treatment of patients with asthma and/or chronic obstructive pulmonary disease

Health Canada published guidances for short-acting beta2-agonist metered dose inhaler in 1999 [1)], quality of aqueous solutions including inhaled aqueous solutions in 2005 [2)], quality of inhalation and nasal products in 2006 [3)], and draft guidance document regarding safety and effectiveness of inhaled corticosteroid products for treatment of asthma in 2011 [4)].

Within Health Canada, the Generic Drugs Quality Division in the Bureau of Pharmaceutical Sciences (BPS) is responsible for the evaluation of quality and in vitro studies, whereas the Division of Biopharmaceutics Evaluation in BPS is responsible for the evaluation of pharmacokinetic studies, and the Allergy and Respiratory Drugs Division of the Bureau of Cardiology, Allergy and Neurological Sciences (BCANS) evaluates the pharmacodynamic or clinical endpoint studies.

With respect to generic drug development for inhaled aqueous solutions, Health Canada may accept a biowaiver if the provided generic product meets the criteria regarding relative differences in formulation, physicochemical property, and device attributes compared to the innovator product. On

the other hand, Health Canada requires bioequivalence evaluations with in vitro, pharmacokinetic, and pharmacodynamic or clinical endpoint studies in the following cases:

・Inhaled aqueous solutions that do not satisfy the above criteria

・Dry powder inhaler and metered dose inhaler products

Although there have been generic submissions reviewed for these products, no products have currently been approved in accordance with these requirements.

In Japan, the Ministry of Health, Labour, and Welfare (MHLW) published the basic principles on the bioequivalence evaluation for the generic dry powder inhaler drug products in March 2016 [5)6)]. I expect that guidelines on the quality for the aqueous solution, dry powder inhaler, and metered dose inhaler products will be developed in Japan, and would like to pay attention to the contents of these guidelines.

1) Health Canada. 1999. Guidance to Establish Equivalence or Relative Potency of Safety and Efficacy of a Second Entry Short-Acting Beta2-Agonist Metered Dose Inhaler (MDI) http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/mdi_bad-eng.pdf

2) Health Canada. 2005. Guidance for Industry: Pharmaceutical Quality of Aqueous Solutions http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/aqueous_aqueuses-eng.pdf

3) Health Canada. 2006. Guidance for Industry: Pharmaceutical Quality of Inhalation and Nasal Products http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/inhalationnas-eng.pdf

4) Health Canada. 2011. Draft Guidance Document Data Requirements for Safety and Effectiveness of Subsequent Market Entry Inhaled Corticosteroid Products for Use in the Treatment of Asthma for Industry http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/consultation/drug-medic/draft_inhal_ebauche_corticost-eng.pdf

5) MHLW. 2016. Basic principles on the bioequivalence evaluation for the generic dry powder inhaler drug products. http://www.pmda.go.jp/files/000210452.pdf (In Japanese)

6) Bioequivalence Evaluations of Generic Dry Powder Inhaler Drug Products: Similarities and Differences Between Japan, USA, and the European Union. Kuribayashi R, Yamaguchi T, Sako H, Takishita T, Takagi K. Clin Pharmacokinet. 2016 Jul 26. [Epub ahead of print].

Mr. Ryosuke Kuribayashi
Bureau of Pharmaceutical Sciences of the Therapeutic Products Directorate
Health Canada in Canada

Basic Principles for Pharmacopoeia Preparation

The United States Pharmacopeial Convention (USP) transferred to the 2015-2020 cycle last year. The 2015-2020 work plan for each expert committee (EC) is posted to the USP website[1)]. The work plan includes the focus areas, the structure of the committee, and the standards to be listed, so that many stakeholders easily can know their direction. For example, Excipient Monograph 2 Expert Committee is responsible for global harmonization activities that include: retrospective harmonization of excipient monographs, excipient related General Chapters for the Pharmacopoeial Discussion Group (PDG) work plan and works closely with other ECs (GCCA: General Chapters – Chemical Analysis, GCPA: General Chapters - Physical Analysis, B&B: Biologic and Biotechnology) on General Chapters, B&B General Chapters and ICH Q6A chapters (guideline for test procedures and acceptance criteria). The committee is also responsible for developing new and revising existing excipient monographs, their associated

reference standards for pharmaceutical excipients and for new excipient-related General Chapters development and updates. The EC reviews global harmonization activities, including PDG, bilateral harmonization projects with other pharmacopoeias, monograph modernization fitting for a global supply chain, development of new excipient monographs, development of excipient-related General Chapters and other key issues as defined by the work plan published on the USP website.

Similarly, the Japanese Pharmacopoeia (JP) transferred to the new 5-year cycle for the development of the JP 18th edition after the JP 17th edition was published on May 7, 2016. The JP has been prepared based on the basic principle, which is composed of primary objectives and specific work plans. Public comments were invited regarding the draft of the JP 18th basic principle from August 19, 2016 to September 18, 2016.

As mentioned above, both pharmacopoeias have published their respective work plans in efforts to maintain transparency with our stakeholders. I would like to exchange information effectively between USP and PMDA while keeping in mind their principles and work plans. By doing so, I hope to contribute to the bilateral harmonization project and the PDG harmonization activity.

1) 2015-2020 Work Plans of the USP Expert Committees
   http://www.usp.org/expert-committees

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

Dispatch to Center for Drug Evaluation and Research, U.S. FDA

I am Shinichi Kijima, Advanced Review with Electronic Data Promotion Group, PMDA. I have been dispatched to the Division of Pharmacometrics (DPM), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS), Center for Drug Evaluation and Research (CDER), U.S. FDA since July 2016. The dispatch period will be for 1 year.

In the DPM, reviewers mainly evaluate the results of quantitative data analyses in pharmacokinetics and clinical pharmacology area of application of pharmaceuticals including modeling and simulation for regulatory decisions.

PMDA will start to receive electronic data of clinical study from October 2016. On the other hand, U.S. FDA already started to receive electronic data of clinical study more than 10 years ago. In the DPM, reviewers are conducting analyses by themselves for regulatory decisions.

Furthermore, regulatory science research is conducted to create new knowledge based on the accumulated data available at U.S. FDA, e.g., data from New Drug Application (NDA) submission, and articles for efficient drug development and better regulatory decisions.

The objective of my dispatch is to learn the review process for new drugs and regulatory science research methodology utilizing submitted electronic data in U.S. FDA. I will attend to review teams for some NDA and also conduct regulatory science research. I hope the information would be useful for the advanced review with electronic data in PMDA.

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

Dispatch to the U.S.FDA

I am Ken Sakushima, and have been dispatched to the Office of Strategic Programs (OSP) in CDER, U.S.FDA on September 1, 2016 for one year. Mission of this dispatch is mainly to learn about the development, testing, and adoption of Clinical Data Interchange Standards Consortium (CDISC) clinical study data standards, and moreover, to promote collaboration and harmonization on CDISC standards

between the PMDA and the U.S. FDA. I have superseded Mr. Hiroshi Sakaguchi who dispatched to the OSP from May to August in 2016.

The OSP[1) 2)] supports agency officials concerning the performance of the U.S.FDA CDER planning, analysis, and business informatics activities; leads Center-wide strategic and operational planning and analysis. Electronic data standards, including CDISC standards, are vital in efficient and effective regulatory review process. The OSP has a robust data standard development framework and processes on the development, testing and adoption of electronic data standards. The U.S.FDA already conducts new drug reviews with electronic study data using CDISC standard with the OSP supports. The PMDA starts accepting electronic study data from October 2016 with a transitional period until March 2020. I would like to learn about effective utilization of electronic study data in the review process and contents of support by the OSP and other Offices. Moreover, I would like to facilitate and strengthen the communication and collaboration between the PMDA and the U.S.FDA on data standard topics.

I'm going to report not only what I learned in the U.S.FDA but also various topics related to new drug reviews and CDISC standards on this "Reports from Overseas".

1) Center for Drug Evaluation and Research
http://www.fda.gov/downloads/AboutFDA/CentersOffices/OrganizationCharts/UCM439876.pdf
2) Office of Strategic Programs
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm292121.htm

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