Prunus mume at Kairakuen-park in Mito City

PMDA Updates

March, 2017

News

1. PMDA-ATC Pharmacovigilance Seminar 2017

From February 6 to 9, PMDA held a seminar entitled "PMDA-ATC Pharmacovigilance Seminar 2017".

This seminar, focusing on pharmacovigilance, was designed for officials from overseas regulatory authorities who are engaged in the pharmacovigilance area, and held as a Center of Excellence Pilot Workshop for the Pharmacovigilance/Medical Device Vigilance Priority Work Area in the APEC-LSIF-RHSC (Asia-Pacific Economic Cooperation, Life Science Innovation Forum, Regulatory Harmonization Steering Committee).

The seminar was participated by 28 regulators from Brazil, Chile, China, Chinese Taipei, India, Indonesia, Korea, Malaysia, Myanmar, Nepal, Peru, Philippines, Poland, Singapore, and Thailand.

Group Photo of Participants and PMDA executive staff members. From the left end, Dr.Junko Sato, Office Director, Office of International Cooperation, Dr. Shoji Takamatsu, Office Director, Office of Safety II, Mr. Shinobu Uzu, Chief Safety Officer, Dr. Toshiyoshi Tominaga, Associate Executive Director (for International Programs), Dr. Tatsuya Kondo, Chief Executive, and Mr. Haruo Akagawa, Director of PMDA-ATC in the front low.

The program of the seminar included lectures by staff from PMDA as well as regulatory authorities overseas, Japan Pharmaceutical Manufacturers Association (JPMA), academic institutions such as universities on the topics including adverse event reporting, labeling, Risk Management Plan (RMP), risk communication for patients and health care providers, and pharmacoepidemiology. Besides the lectures, group work with case studies were provided as well, and the participants had active discussions throughout the seminar.

Please refer to the following web site for the details of PMDA-ATC Pharmacovigilance Seminar 2017.
http://www.pmda.go.jp/english/symposia/0096.html

2. HBD Town Hall Meeting at Cardiovascular Research Technologies (CRT) 2017

In conjunction with the Cardiovascular Research Technologies (CRT) 2017 conference held in Washington D.C. from February 17 to 21, one-day Harmonization By Doing (HBD) Town Hall Meeting entitled "Japan FDA"session was held on February 20, which Dr. Yuka Suzuki, International Coordination Officer (for medical devices), 4 staff members of the Office of Medical Devices Review, and a staff member of the Office of International Programs from PMDA, as well as one staff member from MHLW, attended.

In the Town Hall Meeting, there were 4 sessions on the topics of Introduction of HBD activity and its significance, HBD for children, Real world evidence and Peripheral vascular devices, and presentations were given by the speakers from academia, industry and regulators of both the US and Japan, many of

whom were members of HBD. The participants of PMDA presented the current situations of Japan and the regulatory view, and joined in the discussions as panelists in all sessions. There were total of about near capacity 60 participants throughout the sessions, notably US FDA, physicians, as well as stakeholders from industry, engaging in active Q & A and intensive opinion exchange. Those discussion were introduced in the CRT2017 Daily News published on the following day. Also, the first face-to-face meeting of the HBD for children working group which intends to discuss on the effective development of medical devices for pediatric use, and another face-to-face meeting to review overall HBD activities were respectively held in the morning and in the evening of the same day, and the current status of work items and future directions were discussed.

3. Asia-Pacific Economic Cooperation, Life Sciences Innovation Forum, Regulatory Harmonization Steering Committee (APEC-LSIF-RHSC) Meeting

Dr. Tominaga (2nd left) with other chairs/co-chaires

Asia-Pacific Economic Cooperation, Life Sciences Innovation Forum, Regulatory Harmonization Steering Committee (APEC-LSIF-RHSC) meeting was held in Nha Trang, Vietnam from February 20 to 21. 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 a co-chair of the RHSC along with the US. Regulators from 13 APEC economies and representatives from industry (pharmaceuticals, bio-pharmaceuticals, medical devices) and academia participated in the meeting. APEC-LSIF-RHSC has been conducting pilot programs of capacity building of regulators and relevant persons to establish Center of Excellence (CoE) to offer such training. Out of the six priority work areas of RHSC, PMDA provided the pilot programs in the areas of MRCT/GCP inspection in January 2017, and Pharmacovigilance and medical device vigilance in February 2017, respectively. Based on the outcomes of these pilot programs, the meeting approved the formal establishment of CoE at PMDA.

Next APEC-LISF RHSC meeting will be held in Vietnam, in the third quarter of 2017.

4. Call for application to PMDA-ATC Pharmaceuticals Review Seminar 2017 starts

PMDA Asia Training Center (PMDA-ATC) will hold the "PMDA-ATC Pharmaceuticals Review Seminar 2017" from June 26 to 30. This seminar is designed for new drug application reviewers from overseas regulatory authorities. The objective of the seminar is to provide the participants with opportunities to acquire knowledge and perspectives on a wide range of topics including clinical trials, product application review, GCP/GLP, and post-marketing safety measures through lectures and case studies, and consequently apply them to enhance the regulatory system in the participants' own country or region.

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
Viekirax	ombitasvir hydrate/ paritaprevir hydrate/ritonavir	February 24
Talion	bepotastine besilate	February 27
Tresiba [Partial Change Approval]	insulin degludec (genetical recombination)	February 27
Acoalan	antithrombin gamma (genetical recombination)	March 6
Allergen Scratch Extract Positive control "TORII" Histamine Dihydrochloride	histamine dihydrochloride	March 9
Laserphyrin	talaporfin sodium	March 9
Adsorbed Cell Culture-derived Influenza Vaccine H5N1 "Kitasato Daiichi Sankyo"	adsorbed cell culture-derived influenza vaccine (H5N1)	March 10
Cosentyx [Partial Change Approval]	secukinumab (genetical recombination)	March 10
Eylea	aflibercept (genetical recombination)	March 15
Botox	botulinum toxin type A	March 15
Artist	carvedilol	March 15
Kenketu Glovenin-I	freeze-dried polyethylene glycol treated human normal immunoglobulin	March 15

Medical Devices

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

Brand Name	Generic Name	Posting date
HAL for Medical Use (Lower Limb Type)	biosignal-responsive motor function improvement device	February 24

Safety Information

Risk Information which some safety measures might be taken (February 24, 2017)

- Aluminum Potassium Sulfate Hydrate, Tannic Acid
- Alprazolam
- Eszopiclone
- Estazolam (Tablets)
- Estazolam (Powders)
- Etizolam (Fine Granules)
- Etizolam (Tablets)
- Oxazolam (Tablets ・Powder)
- Oxazolam (Fine Granules)
- Quazepam
- Cloxazolam
- Clotiazepam (Granules)
- Clotiazepam (Tablets)
- Clorazepate Dipotassium
- Chlordiazepoxide (Tablets)
- Chlordiazepoxide (Powders)
- Diazepam (Powders)
- Diazepam (Tablets)
- Diazepam (Syrup)
- Diazepam (Injection)
- Zopiclone
- Zolpidem Tartrate (Tablets)
- Zolpidem Tartrate (Oral Solution)
- Triazolam (Tablets)
- Nimetazepam
- Haloxazolam
- Fludiazepam
- Flutazolam
- Flutoprazepam
- Flunitrazepam (Tablets)
- Flurazepam Hydrochloride
- Brotizolam (Tablets)
- Bromazepam
- Mexazolam
- Medazepam
- Rilmazafone Hydrochloride Hydrate
- Ethyl Loflazepate (Fine Granules)
- Ethyl Loflazepate (Tablets)
- Lorazepam
- Lormetazepam
- Clonazepam
- Clobazam
- Diazepam (Suppository)

- Midazolam (products with an indication to treat status epilepticus)
- Nitrazepam (Powder)
- Nitrazepam (Fine Granules)
- Nitrazepam (Tablets)
- Amobarbital
- Secobarbital Sodium
- Pentobarbital Calcium
- Phenobarbital (Oral dosage form)
- Phenobarbital (Injection)
- Phenobarbital Sodium (Suppository)
- Phenobarbital Sodium (Injection)
- Phenytoin/Phenobarbital
- Phenytoin/Phenobarbital Combination
- Primidone
- Triclofos Sodium
- Bromovalerylurea
- Chloral Hydrate (Suppository)
- Chloral Hydrate (Enema)

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

Pharmaceuticals and Medical Devices Safety Information No. 341, March 14, 2017

1. Revisions of Proper Control Procedures for Revlimid/Pomalyst (RevMate)
2. Research on Actual Status in Drugs and Medical Devices Safety Information Reporting System
3. Revision of Precautions (No. 282)
   Hydroxyzine hydrochloride, Hydroxyzine pamoate and the others
4. List of Products Subject to Early Post-marketing Phase Vigilance
   (Reference)
   Terminology of "Acute Kidney Injury"

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

PMDA Medical Safety Information No. 33 (September, 2002) (Revised, March, 2017)

Accidental Burns during Surgery using a Light Source, an Electric or Laser Scalpel

http://www.pmda.go.jp/english/safety/info-services/safety-information/0001.html

Pharmaceuticals Revisions of PRECAUTIONS, March 21, 2017

- Lamotrigine
- Aluminum Potassium Sulfate Hydrate, Tannic Acid
- Amobarbital
- Alprazolam
- Ethyl Loflazepate (Fine Granules)
- Ethyl Loflazepate (Tablets)
- Eszopiclone
- Estazolam (Tablets)
- Estazolam (Powder)
- Oxazolam (Tablets ・ Powder)
- Oxazolam (Fine Granules)
- Quazepam
- Cloxazolam
- Clorazepate Dipotassium

- Chlordiazepoxide (Tablets)
- Chlordiazepoxide (Powder)
- Diazepam (Powder)
- Diazepam (Tablets)
- Diazepam (Syrup)
- Diazepam (Injection)
- Diazepam (Injection)
- Secobarbital Sodium
- Zopiclone
- Zolpidem Tartrate (Tablets)
- Zolpidem Tartrate (Oral Solution)
- Triazolam (Tablets)
- Triclofos Sodium
- Bromovalerylurea
- Nitrazepam (Powder)
- Nitrazepam (Fine Granules)
- Nitrazepam (Tablets)
- Nimetazepam
- Haloxazolam
- Clotiazepam (Granules)
- Clotiazepam (Tablets)
- Phenobarbital (Oral dosage form)
- Phenobarbital Sodium (Suppository)
- Phenobarbital (Injection)
- Phenytoin/Phenobarbital
- Phenytoin/Phenobarbital/Caffeine and Sodium Benzoate
- Phenobarbital Sodium (Injection)
- Fludiazepam
- Flutazolam
- Flutoprazepam
- Flunitrazepam (Tablets)
- Bromazepam (Tablets ・ Fine Granules)
- Flurazepam Hydrochloride
- Brotizolam (Tablets)
- Pentobarbital Calcium
- Chloral Hydrate (Suppository)
- Chloral Hydrate (Enemas)
- Mexazolam
- Medazepam
- Rilmazafone Hydrochloride Hydrate
- Lorazepam
- Lormetazepam
- Clonazepam
- Clobazam
- Diazepam (Suppository)
- Primidone
- Midazolam (products with an indication to treat status epilepticus)
- Etizolam (Fine Granules)
- Etizolam (Tablets)

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

PMDA Alert for Proper Use of Drugs No. 11 (March 2017)

Dependence associated with Benzodiazepine Receptor Agonists
http://www.pmda.go.jp/english/safety/info-services/drugs/properly-use-alert/0001.html

Events

Conferences/Meetings PMDA hosts or participates in:

Date	Title	Location
April 5	5th Asia Partnership Conference of Pharmaceutical Associations	Tokyo
April 6-7	9th Asian Regulatory Conference	Tokyo
April 17-18	11th DIA Annual Conference in Japan for Asian New Drug Development	Tokyo
April 24	2nd India-Japan Medical Products Regulation Symposium	Tokyo
May 11	2nd Japan-Korea Joint Symposium on Medical Products	Seoul
May 16	3rd Japan-Indonesia Symposium	Jakarta
May 27- July 4	ICH Assembly meeting in Montreal	Montreal

Reports from overseas

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

Completion of a research project at EMA by Mr. Katsuaki Ura, Deputy Director of MHLW

Mr. Katsuaki Ura, Deputy Director of MHLW, stayed at EMA from September 2016 to February 2017. His research theme during his stay focused on support measures for drug development, innovation and early access, which are priority areas for EMA, especially Adaptive Pathways and Clinical efficacy and safety Guidelines.

Thanks to considerable supports by EMA staff, I believe, his stay was extremely fruitful. He took the best advantage of the collaboration by daily discussions with the teams and performing relevant investigations as well as active networking. Therefore, not only did he obtain much for himself and MHLW/PMDA through these activities, but also contributed actively to complement activities of liaison work. He also gave a successful talk to EMA staff at the end of his stay to present the Japanese situation in relation to his work.

Mr. Ura at EMA talk session

His stay at this time is expected to contribute to strengthening cooperative relationship between EMA and MHLW/PMDA for the future. As it is significant and valuable that representatives from Japan, in addition to a liaison officer, stay at EMA to work on specific projects in order to have intensive discussions and research in common with EMA staff, I hope that such efforts are promoted systematically and positively.

Mr. Hideyuki Kondo

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

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Pharmaceutical Excipient Workshop Co-sponsored by FDA and USP

The FDA and USP Workshop on Standards for Pharmaceutical Products – "Critical Importance of Excipients in Product Development Why Excipients are Important Now and In the Future" was co-hosted by United States Pharmacopeial Convention (USP) and U.S. FDA at USP headquarters on February 27-28[1]. The total number of attendees exceeded the capacity of the main conference room at USP headquarters, demonstrating the high interest in pharmaceutical excipients. In this workshop, the modernization strategy for excipient monographs in USP, the concepts and the case studies concerned with excipients in the FDA drug review process, the challenges for excipients in emerging technologies such as continuous manufacturing and nanomedicines, as well as the influence of excipients in protein formulations and others were introduced. By attending this workshop, I was able to learn about the difficulties encountered in determining quality control of excipients solely using a specification described in a monograph because of unique impacts of excipients on functionality, stability and manufacturing process of finished products, depending on the specific formulation.

The USP general information chapter <1059> Excipient Performance contains information on additional methodologies, which may not be identified or specified in compendial monographs for excipients. The methods described in this chapter can assist the user by providing information about the physical and chemical properties of excipients that may be useful in ensuring desirable excipient performance depending on the particular application. The USP put out a call for expert candidates for this general chapter on the USP website last year[2] in order to update missing information with regards to excipients used in specialized dosage forms, such as biologics. Therefore, I will observe the activities of this Expert Panel as they work to revise the USP general information chapter <1059>.

1) http://www.usp.org/sites/default/files/events/workshops/2016/fda-and-usp-workshop-standards-pharmaceutical-products-critical-importance-excipients-product-development-why-excipients-are-imp/e-program-2017-02-27.pdf
2) https://callforcandidates.usp.org/node/4133

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

Important Dates on Electronic Regulatory Submission in the U.S.

In 2016, U.S. FDA published two communications concerning electronic regulatory submission in the U.S. Several important dates on using standardized data for new drug application (NDA) and IND are described below. U.S.FDA is starting a regulation for study data format, in both clinical study and nonclinical study, and submission using eCTD on these important dates.

The important dates for study data format are December 17, 2016 and December 17, 20171). (1) Study data started after December 17, 2016, must be submitted using standards specified in the FDA Data Standards Catalog such as CDISC standards for NDAs, BLAs, ANDAs, and subsequent submission to these types of applications. (2) Study data started after December 17, 2017, must be submitted using standards specified in the FDA Data Standards Catalog such as CDISC standards for commercial INDs.

The important dates for electronic regulatory submission using eCTD are May 5, 2017 and May 5, 20182). (3) Starting May 5th, 2017; NDAs, BLAs, ANDAs, and master files must be submitted in eCTD 3.2.2 format. Unless exempted, submissions not in eCTD format will not be filed or received. (4) Commercial INDs must be submitted using eCTD standards from May 5, 2018.

It should be noted that CDISC standards and eCTD will not be mandatory in research INDs. Details of this information are shown in the leaflet[s1)2)] and the movie[3)] on the FDA Website.

1) STUDY DATA STANDARDS: WHAT YOU NEED TO KNOW
https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM511237.pdf

2) eCTD SUBMISSSION REQUIREMENTS: WHAT YOU NEED TO KNOW
https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM511230.pdf
3) Electronic Regulatory Submission and Review
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm2007043.htm

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