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PMDA Updates

August, 2016

News

1. PIC/S Committee Meeting (July 4 to 5)

PIC/S Committee Meeting was held from July 4 to 5 in Manchester, United Kingdom, and was attended by 41 out of 48 PIC/S Participating Authorities as well as by Applicants and Associated Partners, etc. under the chairmanship of Mr. Paul Hargreaves (United Kingdom's Medicines and Healthcare products Regulatory Agency; MHRA). The participants from Japan included 3 staffs from Office of Manufacturing/Quality and Compliance and Office of International Programs, PMDA and 1 staff from Ministry of Health, Labour and Welfare (MHLW). In the meeting, the committee gave their assent to the proposal for training "Japan/PMDA GMP training course with the support of PICS" (to be held in Toyama on December 5-9, 2016) which had been suggested by Japan. Also, the membership of Thailand's Food and Drug Administration (Thai FDA) was approved, and Thai FDA became the 49th PIC/S Participating Authority.

The next PIC/S Committee Meeting will be held in Geneva, Switzerland in February, 2017.

2. CVIT 2016 HBD Town Hall Meeting (July 7)

On July 7, Harmonization By Doing (HBD) Town Hall Meeting was held in Tokyo in conjunction with the 25th Annual Meeting of the Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT 2016), where Dr. Yuka Suzuki, Director, Office of Medical Devices II and six staffs from PMDA participated. In this session entitled "expectations and potential risks with the latest technology (device)", presentations and discussions were held by participants from government, industry, and academia of Japan and the U.S. including U.S. FDA on the topics such as the introduction of activities of HBD promoting global clinical trials, and clinical performance of the latest technology (bioabsorbable stents, etc.) as well as the appropriate study patients and the proper use based on the clinical performance. With an audience at full capacity, a high level of interest in HBD activities and the latest technology was observed. Also, on the same day, HBD face-to-face meeting was held and attended by about 50 participants from government, industry, and academia of Japan and the U.S. Active discussions took place about the topics to be addressed by HBD in the future and also the agenda for the next Town Hall Meeting.

The next HBD Town Hall Meeting will be held on October 30 in Washington, D.C. at Transcatheter Cardiovascular Therapeutics (TCT) 2016, as HBD West 2016 Think Tank Meeting.

3. PMDA provides JICA training program "Roles of regulatory systems and pharmacists on ensuring proper access to quality assured medicines" (July 12, 14 and 26)

PMDA accepted seventeen officers from Brazil, China, Fiji, Ghana, Indonesia, Iraq, Myanmar, Nigeria, Papua New Guinea, South Africa, Sri Lanka and Tanzania, and gave training on outlines of PMDA's organization, Good Manufacturing Practice (GMP) case study, new drug review case study, post-marketing safety measures and risk management plan (RMP) and RMP case study.

This training was provided upon the request from Japan International Corporation of Welfare Services (JICWELS), based on

Group photo of trainees with Mr. Masayoshi Shibatsuji (Office Director, Office of New Drug V)

the contract between JICWELS and Japan International Cooperation Agency (JICA) which organized the JICA Knowledge Co-Creation Program "Roles of regulatory systems and pharmacists on ensuring proper access to quality assured medicines". PMDA received positive feedback from the participants who found it very worthwhile. This training aimed to contribute to promoting better public health of the participants' countries/regions as well as the rest of the world by sharing PMDA's accumulated knowledge and experience with other regulatory authorities.

4. PMDA-ATC Pharmaceuticals Review Seminar 2016 (July 25 to 29)

From July 25 to 29, PMDA held PMDA-ATC Pharmaceuticals Review Seminar 2016, the very first seminar after the launch of PMDA Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC). This seminar was designed for officials of regulatory agencies overseas engaged in drug reviews, and participated by a total of 13 regulators from 7 regulatory agencies (i.e. China, Hong Kong, Indonesia, Korea, Malaysia, Taiwan, and Thailand). In the seminar, lectures were delivered on clinical trials, consultations, product reviews, package inserts, safety measures, risk management plan (RMP), the relief system for sufferers from adverse drug reactions and capacity building. In addition, group discussions on consultations and product reviews, presentations by the participants on drug regulations of their regulatory authorities, lectures by industry representatives, etc. took place and the participants actively engaged in discussions throughout the seminar.

Grroup photo of trainees with Dr. Kondo (Center), Dr. Toshiyoshi Tominaga (Associate Executive Director for International Programs, the 2nd from the right) and Dr. Junko Sato (Office Director, Office of International Cooperation, the 2nd from the left) on the front row.

At the end of the seminar, the Course completion certificates were handed to each one of the participants by Dr. Tatsuya Kondo, Chief Executive.

Please refer to the following web site for the details of PMDA-ATC Pharmaceuticals Review Seminar 2016.

http://www.pmda.go.jp/english/symposia/0090.html

5. PMDA provides training to staff from National Pharmaceutical Regulatory Agency of Malaysia (August 1 to 3)

From August 1 to 3, PMDA provided training on cellular and tissue-based products to a staff from National Pharmaceutical Regulatory Agency of Malaysia. The training was facilitated by staff from Office of Cellular and Tissue-based Products, who instructed on topics including regulatory outlines for cellular and tissue-based products and points to consider before commencement of clinical trials. Also, the participant had an opportunity to visit CPC (Cell Processing Center) in the training period. This training is expected to promote practical application of advanced science technology into products including cellular and tissue-based products, and safety measures for those products in Asia.

Trainee and PMDA staffs

6. Call for application to PMDA-ATC Pharmaceuticals Review Seminar 2016 in Bangkok, Thailand starts

PMDA-ATC will hold its first seminar entitled "PMDA-ATC Pharmaceuticals Review Seminar 2016 in Bangkok, Thailand" from September 26 to 29, 2016. This seminar is the very first one to be organized by the PMDA-ATC in abroad, and designed for officials of regulatory agencies overseas who are engaged in drug reviews. At the seminar, the details of PMDA's regulatory works for pharmaceuticals including consultation (scientific advice) and product reviews will be shared, including comparison with the regulations in other countries/regions. In addition, group discussions on the regulatory decision making and discussion session with industry on Multi-Regional Clinical Trial (MRCT) in Asia are planned.

The aims of the Seminar are to provide chances for the participants to refer back to their work and to find any additional opportunity for enhancement of the participant's regulatory system.

For the details of PMDA-ATC Pharmaceuticals Review Seminar 2016 in Bangkok, Thailand, see the following web site.

http://www.pmda.go.jp/english/symposia/0091.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
NovoThirteen	catridecacog (genetical recombination)	July 21
Emulsion-adjuvanted Cell-culture Derived Influenza HA Vaccine (Prototype) for Intramuscular Injection "KAKETSUKEN"	emulsion-adjuvanted cell-culture derived influenza HA vaccine (prototype)	August 8
Efient	prasugrel hydrochloride	August 10
Strensiq	asfotase alfa (genetical recombination)	August 10
Remicade	infliximab (genetical recombination)	August 10

Safety Information

Medical Devices Revisions of PRECAUTIONS

Precautions in the Package Insert of Power Morcellators

(Posted on July 26, 2016, Originally Posted in Japanese on July 25, 2016)

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

Administrative Notice

Administrative Notice: Notice concerning Revisions to the "Standard Workflow for the Revision of Drug Product Package Inserts"

Reference material: Standard Workflow for the Revision of Drug Product Package Inserts

(Posted on July 29, 2016, Originally Posted in Japanese on November 25, 2014)

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

Pharmaceuticals and Medical Devices Safety Information No. 335, August 2, 2016

1. Precautions Relating to the Teratogenicity of Mycophenolate Mofetil Preparations
2. Important Safety Information
   (1) Nintedanib Ethanesulfonate
   (2) Ombitasvir Hydrate/Paritaprevir Hydrate/Ritonavir
   (3) Sofosbuvir, Ribavirin
   (4) Ledipasvir Acetonate/Sofosbuvir

3. Revision of Precautions (No. 276)
Diclofenac Sodium (and 6 others)
4. 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, August 4, 2016

- Olanzapine (Tablets)
- Olanzapine (Tablets)
- Olanzapine (Fine granules)
- Olanzapine (Injection)
- Azosemide
- Imatinib mesilate
- Imatinib mesilate
- Dasatinib hydrate
- Nilotinib hydrochloride hydrate
- Bosutinib hydrate
- Sitafloxacin hydrate

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

Risk Information which some safety measures might be taken (August 19, 2016)

- Filgrastim (Genetical Recombination)
- Filgrastim (Genetical Recombination) (follow-on biologics/biosimilars1)
- Filgrastim (Genetical Recombination) (follow-on biologics/biosimilars2)
- Filgrastim (Genetical Recombination) (follow-on biologics/biosimilars3)
- Lenograstim (Genetical Recombination)
- Nartograstim (Genetical Recombination)
- Pegfilgrastim (Genetical Recombination)
- Eltrombopag Olamine
- Natalizumab (Genetical Recombination)
- Corticorelin (human)
- Afatinib Maleate

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
September 6-9	Global Coalition for Regulatory Science Research / Global Summit on Regulatory Science	Washington D.C.
September 13-14	7th International Meeting of World Pharmacopoeias	Tokyo
September 13-15	IMDRF Management Committee (MC) Meeting	Florianopolis
September 15	JP 130th Anniversary Symposium	Tokyo

September 17-21	RAPS' 2016 Regulatory Convergence	San Jose
September 26-30	PMDA-ATC Overseas Pharmaceuticals Review Seminar 2016	Bangkok
September 27-28	Ph. Eur. : Tackling future challenges of the Quality of Medicines together	Tallinn
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

Reports from overseas

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

Actions taken by EMA to introduce public hearings for pharmacovigilance

EMA has focused on promotion of involvement by civil society, including patients, in the pharmacovigilance field. In this context, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), where pharmacovigilance issues are openly discussed, has adopted the final rules of procedure for public hearings to be held by the Committee in April 2016. Opinions obtained from such public hearings will be discussed in PRAC and taken into account for a final decision.

The public hearing will not necessarily scope all the products that are discussed in PRAC, and the decision whether a product is included in the public hearing is made case by case. However, EMA has said that the first public hearing could take place as early as the fourth quarter of 2016, as soon as a relevant topic is identified.

In the meanwhile a "dry-run" of the public hearing was held in the July PRAC meeting. EMA staff volunteers participated in the hearing as public audiences and speakers. In the dry-run, a fictional product as well as issues that may be involved were prepared, which resulted in a rehearsal just like real one in terms of logistics and contents.

As EMA has also established with US FDA a new cluster related to patient engagement in June 2016, it is advancing activities to obtain more contributions from civil society.

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

Cooperation for the development of therapeutic area standards

From October 2016, PMDA will start to accept study data which is based on the data standards developed by Clinical Data Interchange Standards Consortium (CDISC), NPO in U.S. CDISC has developed general purpose foundational data standards which can be utilized and customized for clinical trials in every disease area. On the other hand, CDISC did not standardize the specific data elements for each disease area and the sponsors have been creating their own variations of custom domains to capture the disease specific data elements. These custom domains make cross studies reference difficult as the formats and contents varied from study to study.

To resolve this problem, CDISC started to create therapeutic area standards to standardize the typical endpoints result or background data for each disease area. These therapeutic area standards are developed mainly in the U.S., and U.S.FDA actively participates in the development. U.S.FDA specifies the endpoints which are recommended to be included in therapeutic area standards, and support the data standards development in CDISC, and test to confirm its ability to process, review and archive the format, standard, and terminology. Once U.S.FDA decides to support the therapeutic area standard, U.S.FDA will require sponsors to use the therapeutic area standards.

Turning to Japan, these therapeutic area standards might not be used smoothly if the medical situation in Japan is somewhat different from that in the U.S. Since dissemination of therapeutic area standards in Japan is expected to bring us the facilitation of multi-regional clinical trials as well as more efficient conduct of clinical research, research program granted by Japan Agency for Medical Research and Development (AMED) has stared this year in order to reflect Japanese medical practices to therapeutic area standards. PMDA cooperates with the research problem, and plans to ask cooperation for medical societies and JPMA for each disease area.

I learned how U.S.FDA contributes to the development of therapeutic area standards in order to consider future plan for the development of therapeutic area standards in Japan. In U.S.FDA, review division, in addition to the Center for Drug Evaluation and Research (CDER) Study Data Standards Working Group and the Office of Strategic programs, plays an important role in the therapeutic area standards development. I believe that accumulation of analysis in the actual review process in PMDA will produce meaningful opinion for the data standards. I went back to Japan on August 11, and I would like to contribute the development of therapeutic area standard in Japan based on my experience in U.S.FDA.

Mr. Hiroshi Sakaguchi
Office of Strategic Programs, U.S. FDA in the U.S.A.

Concept of Biopharmaceutics Classification System (BCS) and BCS-based biowaivers in Canada

Health Canada adopted the Biopharmaceutics Classification System (BCS) and BCS-based biowaivers in 2014[1)]. BCS categorizes drugs into four classes based on solubility and permeability/absorption of the drug substance (Figure). When combined with the dissolution of the drug product, the BCS takes into account three major factors (dissolution, solubility, and permeability) that govern the rate and extent of drug absorption from immediate release drug products. This tool serves as an alternate method for drug approval rather than conventional bioequivalence studies during generic drug development and is referred to as the BCS-based biowaiver. For example, when a drug substance shows high solubility and high permeability (Class I), and the reference and generic drug products express very rapid in vitro dissolution, both products can be predicted to be bioequivalent. The Division of Biopharmaceutics Evaluation at Health Canada is responsible for the evaluation of BCS and BCS-based biowaivers submitted in support of new and generic drug applications. Health Canada promotes consistency in their decisions concerning BCS and BCS-based biowaivers because there is a single division that is responsible for these evaluations. In addition, regular division meetings are held in order to share scientific data and information regarding regulatory decisions. On the other hand, the PMDA will have to consider how we maintain consistency in our evaluations of BCS and BCS-based biowaivers because the different offices are responsible for reviewing new or generic drugs (the offices of New drugs are responsible for new drug review, while the office of Generic drugs is in charge of

reviewing the Generic drugs in the PMDA). The concept of BCS-based biowaivers has already been incorporated into the pharmaceutical regulations of many countries, including the USA and Europe[2-4]. I remain hopeful that BCS and BCS-based biowaiver guidelines will be developed and published soon in Japan.

Figure

		Solubility	
		High	Low
Permeability	High	Class I	Class II
	Low	Class III	Class IV

1) Health Canada. 2014. Release of Guidance Document: Biopharmaceutics Classification System Based Biowaiver. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/bcs_guide_ld_scb-eng.pdf

2) FDA. 2015. Draft Guidance for Industry, Waiver of in Vivo Bioavailability and Bioequivalence Studies for Immediate-release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070246.pdf#search='FDA%2C+BCS'

3) EMA. 2010. Guideline on the Investigation of Bioequivalence. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

4) Regulatory Considerations of Bioequivalence Studies for Oral Solid Dosage Forms in Japan. Kuribayashi R, Takishita T, Mikami K. J. Pharm. Sci. 2016; 105(8): 2270-7.

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

Dispatch to the USP

I am Yujiro Kameyama, technical officer in Office of Standards and Guidelines Development, PMDA. I have been dispatched to the United States Pharmacopeial Convention (USP) as a liaison beginning August 8, 2016 for a period of 18 months. This is the 5th dispatch from PMDA to USP. Similar to former PMDA liaisons, I participate in the excipients team as an Executive Exchange Officer, in charge of the development and revision of excipient monographs, and other standard setting activities as needed.

The USP is a scientific nonprofit organization that sets quality standards for medicines, food ingredients, and dietary supplements manufactured, distributed and consumed worldwide. The USP's mission is to improve world public health through public standards and related programs that help ensure the quality, safety, and benefits of medicines and foods. Similarly, PMDA announced an international strategic plan entitled "PMDA International Strategic Plan 2015" last year to contribute furthermore to world public health improvement. USP and PMDA, which has the role as the secretariat in Japanese Pharmacopeia, have worked for this common purpose and strengthened the partnership through our bilateral project for the prospective harmonization of pharmaceutical excipients. During my stay in the USP, I will reinforce the strengthened partnership between USP and PMDA by addressing our common purpose as well as finding solutions to the challenges of international harmonization. In this PMDA update, I will introduce a summary the ongoing projects as part of this collaboration, as well as provide additional information regarding USP's standard setting activities which may be of interest to PMDA stakeholders.

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