



*Helianthus annuus*

# PMDA Updates

July, 2019

## News

### 1. ICH Meeting in Amsterdam

The 8th International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) met in Amsterdam, the Netherlands, from June 1 to 6. The 39 PMDA staff members attended including Dr. Nobumasa Nakashima (Senior Director for International Programs), and Mr. Naoyuki Yasuda (Office Director, Office of International Regulatory Affairs, Ministry of Health, Labour and Welfare (MHLW)) attended with other officers from MHLW.

Main outcomes from the meeting included the endorsement of 5 new topics, including "GCP Renovation" and "Non-clinical Biodistribution Studies for Gene Therapy Products" proposed by MHLW/PMDA. Work on 4 of these new topics will start by the next ICH meeting. Also, as a reflection paper outlining a strategic plan to future development of ICH guidelines, the document on "Strategic Approach to International Harmonization of Technical Scientific Requirements for Pharmacoepidemiological Studies Submitted to Regulatory Agencies to Advance More Effective Utilization of Real-World Data," which was originally proposed by MHLW/PMDA, was endorsed. A discussion group composed of experts will be established for further detailed discussion.

At ICH Assembly, the regulatory authorities of Argentina, Israel, Jordan, and Saudi Arabia have newly been accepted as Observers. ICH is now constituted by 16 Members and 32 Observers. In conjunction with the ICH meeting, the International Pharmaceutical Regulators Programme (IPRP) was held and an election for IPRP Management Committee Chair and Vice-Chair was held in this meeting. In this election, Dr. Junko Sato (Director of Office of International Programs) was elected as Chair.

The next ICH meeting will be held from November 16 to 21, 2019, in Singapore.



Group photo of participants

### 2. The International Coalition of Medicines Regulatory Authorities San Diego Meeting

The International Coalition of Medicines Regulatory Authorities (ICMRA) meeting was held in San Diego, the USA, on June 23. About 40 members from 18 nations and regions participated. Dr. Yasuhiro Fujiwara (Chief Executive), Dr. Nakashima, and one staff member of Office of International Programs attended the meeting from PMDA. Mr. Kazuhiko Mori (Councilor, MHLW), Mr. Yasuda and one staff members attended from MHLW. The update for ICMRA Innovation Project, statements for antimicrobial resistance and biosimilars as collaborative project with WHO, and other topics were discussed at the meeting. PMDA/MHLW presented an Informal Network for Innovation, which is a succeeding project of the Innovation project, of which Japan led the horizon scanning. PMDA also reported on the ICMRA website which is maintained and hosted by PMDA. The next ICMRA meeting will be held from October 28 to 30 in Rome, Italy.

### 3. DIA 2019 55th Annual Meeting

From June 23 to 27, the DIA 2019 55th Annual Meeting was held in San Diego, the USA, and Dr. Fujiwara, Dr. Hiroyuki Arai (Director of Center for Product Evaluation & Director of Center for Regulatory Science), Dr. Nakashima, Dr. Tatsuya Kondo (Honorary Chief Executive), and 8 other staff members from PMDA attended. In the PMDA Town Hall session chaired by Dr. Nakashima, Dr. Fujiwara delivered a presentation on PMDA's activities based on the concept of his priorities "4Fs (First)". Mr. Mori gave regulatory updates including how to facilitate early patient access in his presentation, and Dr. Arai spoke on the current initiatives of PMDA Regulatory

Science Center. Approximately 150 participants attended the PMDA Town Hall session, and discussions about Dr. Fujiwara's policy and PMDA's recent activities were held. In the ICMRA session, Dr. Fujiwara delivered a presentation as a panelist, and active discussions were held with other panelists. Dr. Nakashima delivered a presentation at "Convergence of the Regulatory Pathways for Advanced Therapy Medicinal Products". Dr. Fujiwara and Dr. Nakashima got interviewed by DIA. Thanks to his long contribution to DIA, Dr. Kondo was elected as a Fellow of DIA and the awards ceremony was held at DIA Inspire Awards and Fellows Induction Celebration. PMDA staff participated in a total of 6 sessions as a chair, panelist, or speakers. In addition, PMDA staff contributed as a poster presenter and booth exhibitors.

The next meeting will be held from June 14 to 18, 2020 in Washington, D.C., the USA.



Dr. Fujiwara as panelist in ICMRA session



Dr. Fujiwara as speaker in PMDA Town Hall

#### 4. Call for participation to PIC/S Committee Meeting and Seminar 2019 starts

MHLW and PMDA have honor to announce that registration is now open for the PIC/S Committee Meeting and Seminar, hosted by MHLW and PMDA from November 11 to 15, 2019 in Toyama, JAPAN. The Seminar is a training event for regulators only. The Seminar, entitled "Quality Assurance of Sterile Medicinal Products - PIC/S GMP Guide Annex1-" will consist of interactive discussions, presentations, and workshops. The workshop will be supported by the use of videos filmed at manufacturing sites. These practical manufacturing operation videos will stimulate active discussions. The Seminar is open to the participation of inspectors from Medicines Regulatory Authorities from around the world. For registration and further details regarding the Seminar, please visit <http://pics-toyama.com/>.



## 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	Non-proprietary Name	Posting date
Adcetris [Partial Change Approval]	brentuximab vedotin (genetical recombination)	June 24
Otezla [Initial Approval]	apremilast	June 27
Maviret [Initial Approval]	glecaprevir hydrate/pibrentasvir	July 2
Suglat [Partial Change Approval]	ipragliflozin L-proline	July 11

## Safety Information

### Pharmaceuticals and Medical Devices Safety Information No. 364 (July 2, 2019)

1. Interstitial lung disease by abemaciclib
2. Review of "glaucoma" as a contraindication for anticholinergic drugs
3. Important Safety Information
  1. Abemaciclib
  2. Nivolumab (genetical recombination)
  3. Baloxavir marboxil
4. Revision of Precautions (No. 304)
  1. Eletriptan hydrobromide
  2. Zolmitriptan
  3. Naratriptan hydrochloride
  4. Rizatriptan benzoate (and 6 others)
5. List of Products Subject to Early Post-marketing Phase Vigilance

<https://www.pmda.go.jp/english/safety/info-services/drugs/medical-safety-information/0017.html>

### Pharmaceuticals Revisions of PRECAUTIONS (July 9, 2019)

- Febuxostat
- Topiroxostat
- Epoprostenol sodium
- Nivolumab (genetical recombination)
- Pembrolizumab (genetical recombination)
- Palbociclib
- Cedar pollen extract powder
- Dermatophagoides pteronyssinus extract/dermatophagoides farina extract
- Standardized cedar pollen extract (liquid, those for sublingual administration only)
- Dermatophagoides pteronyssinus extract bulk powder/dermatophagoides farinae extract bulk powder
- Tramadol hydrochloride (oral dosage form)
- Tramadol hydrochloride/acetaminophen
- Tramadol hydrochloride (injection)
- Codeine phosphate hydrate (prescription drugs)
- Dihydrocodeine phosphate (prescription drugs)
- Dihydrocodeine phosphate/platycodon fluidextract/glycyrrhiza extract/plantago herb extract/peony root extract (prescription drugs)
- Dihydrocodeine phosphate/dl-methylephedrine hydrochloride/ chlorpheniramine maleate (prescription drugs)
- Dihydrocodeine phosphate/diprophylline/dl-methylephedrine hydrochloride/diphenhydramine salicylate/acetaminophen/bromovalerylurea (prescription drugs)
- Dihydrocodeine phosphate/ephedrine hydrochloride/ ammonium chloride (prescription drugs)
- Products containing codeine phosphate hydrate (OTC drugs)
- Products containing dihydrocodeine phosphate (OTC drugs)

<http://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0007.html>

### Pharmaceuticals Revisions of PRECAUTIONS (July 17, 2019)

- Suxamethonium chloride hydrate
- Etilefrine hydrochloride
- Phenylephrine hydrochloride
- Ozagrel sodium
- Purified tuberculin

<http://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0007.html>

### Risk Information which some safety measures might be taken (July 19, 2019)

- Ropinirole hydrochloride
- Pramipexole hydrochloride hydrate

- Talipexole hydrochloride
- Rotigotine
- Cabergoline
- Bromocriptine mesilate
- Pergolide mesilate
- Apomorphine hydrochloride hydrate
- Freeze-dried BCG vaccine
- Tofacitinib citrate

<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
August 15-16	APEC-LSIF-RHSC SOM <sub>3</sub> meeting	Puerto Varas
September 16-19	IMDRF Management Committee Meeting	Ekaterinburg
September 21-24	RAPS (Regulatory Affairs Professionals Society) Regulatory Convergence	Philadelphia

## Reports from overseas

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

### USP Workshop on Endotoxins and Pyrogen Testing

Because current Bacterial Endotoxins Test and Rabbit Pyrogen Test need to use LAL reagent derived from horseshoe crabs and rabbits respectively, testing methods without using animals or animal based reagents are expected to be practically applied from the viewpoint of protection of animals. The European Pharmacopoeia (Ph. Eur.) allows Monocyte Activation Test (MAT) as an official method of analysis, and has made a public consultation on the testing method using recombinant Factor C in January, 2019<sup>1)</sup>.

The United States Pharmacopoeia (USP) also published the Stimuli article<sup>2)</sup> on the testing method using recombinant Factor C<sup>3)</sup> in 2010, and continues to discuss about the alternative testing methods to Bacterial Endotoxins Test and Rabbit Pyrogen Test. Based on this discussion, USP held a workshop on Future of Endotoxins and Pyrogen testing on June 10 and 11<sup>4)</sup>. The workshop focused on a) potential new reference material, Naturally Occurring Endotoxin (NOE), that may be used as an analyte under appropriate conditions in place of the USP Endotoxin RS<sup>5)</sup>, b) Use of recombinantly derived (non-animal based) reagents as an alternate to the horseshoe crab derived LAL reagent for the Bacterial Endotoxins Test, and c) *in vitro* Pyrogen Tests (such as MAT) in place of the Rabbit Pyrogen Test. In this workshop, Ph. Eur. and the Japanese Pharmacopoeia (JP) introduced their current activity, too.

JP is also discussing about the General Information related to alternative testing methods to those tests towards JP 18th edition, based on the description of "Substitute with test methods that do not use animals (alternative tests)" as a concrete activity in "basic principles for preparation of JP 18th edition"<sup>6)</sup>.

1) <https://www.edqm.eu/en/news/new-general-chapter-test-bacterial-endotoxins-using-recombinant-factor-c-give-your-feedback>

2) "Articles published to stimulate discussion and continual review of Pharmacopoeial Standards."

3) USP PF 36(1) A Recombinant Factor C Procedure for the Detection of Gram-negative Bacterial Endotoxin

4) <https://www.usp.org/events-training/workshops/future-of-endotoxins-and-pyrogen-testing>

- 5) Endotoxin Reference Standard is used for calibration of Bacterial Endotoxins Test. In USP, only USP Reference Standard which has been calibrated to the WHO International Standard for Endotoxin is currently permitted. The attendees discussed about the usage of Reference Material from other suppliers and in-house Reference Material.
- 6) Advice from Pharmaceutical Affairs and Food Sanitation Council dated August 25, 2016. Abstract available: <https://www.pmda.go.jp/files/000220938.pdf>

Dr. Hiroshi Takeda  
PMDA's Liaison Officer stationed at USP in the U.S.A

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