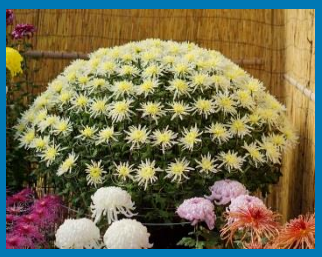

Chrysanthemum × morifolium Ramat.

PMDA Updates

October, 2016

News

1. The 7th International Meeting of World Pharmacopoeias (September 13 to 14)

From September 13 to 14, the 7th International Meeting of World Pharmacopoeias was held in Tokyo, cohosted by the WHO and MHLW/PMDA. The International Meeting of World Pharmacopoeias was first convened in 2012 under the leadership of the WHO, to facilitate information exchange and discussion of international cooperation and harmonization among the world's pharmacopoeial organizations. Delegates from the WHO and 14 pharmacopoeias attended the meeting. The establishment of Good Pharmacopoeial Practices (GPhP), which are created primarily to promote the international harmonization of pharmacopoeial standards, approaches, and policies, has been discussed since the 1st International Meeting. At this 7th International Meeting, the additional chapters to the GPhP regarding Compounded preparations and Herbal medicines as well as the Glossary, which the participants had agreed to incorporate into the GPhP, were each discussed and the participants reached agreement in principle on how to proceed towards finalizing these materials.

Actions and proposals for the upcoming meeting were also discussed as this meeting's main objective of discussing the GPhP texts drew close to completion. It was proposed that Japan, as the host of this year's meeting, and the future hosts of the International Meeting collaborate to draft a proposal as well as conduct a survey regarding the impact and value of the GPhP for consideration during the 8th International Meeting of World Pharmacopoeias.

The 8th International Meeting of World Pharmacopoeias will be held in June 2017 in Brazil, and will be co-hosted by the Brazilian Pharmacopoeia.

2. Japanese Pharmacopoeia 130th Anniversary Symposium (September 15)

Floor audiences (top) and Panelists (bottom)

On September 15, Japanese Pharmacopoeia 130th Anniversary Symposium was held in Tokyo, hosted by PMDA and MHLW. Delegates from main pharmacopoeias overseas were invited to this symposium to mark the 130th anniversary of the establishment of JP as well as the establishment of the Japanese Pharmacopoeia 17th edition, and 400 attendees from industry, government and academia in and outside of Japan participated in the symposium. In Part 1 of the symposium: Japanese Pharmacopoeia 130th Anniversary Ceremony, the Address by Mr. Toshihiko Takeda, Director - General, Pharmaceutical and Environmental Health Bureau, MHLW, and the Salute from the Organizer by Dr. Tatsuya Kondo, Chief Executive, PMDA were followed by speeches by industry, government and academia representatives expressing expectations for further internationalization of the JP, making use of the JP in education in universities , and encouraging listing of products using the latest technology in the JP. In Part 2 of the symposium: Japanese Pharmacopoeia 130th Anniversary Symposium, lectures were delivered on the Japanese Pharmacopoeia's history and future roles in the progress of globalization, and also

overviews were provided by each of the 5 pharmacopoeias overseas and the JP on latest trends and initiatives for internationalization towards globalization. In the Roundtable Discussion, questions from the audience were answered by the representatives from each pharmacopoeia, and a common understanding was achieved that GPhP, which were under development by the 7th International Meeting of World Pharmacopoeias held on September 13 and 14, would provide a fundamental and important framework for prospective harmonization of pharmacopoeias.

This symposium is expected to improve supply chain integrity at global level by further promoting international collaboration and cooperation among pharmacopoeias, and understanding the Japanese principle of quality based on the JP.

3. The 10th IMDRF Management Committee Meeting (September 12 to 15)

From September 12 to 15, the 10th International Medical Device Regulators Forum (IMDRF) Management Committee (MC) Meeting was held in Florianópolis, Brazil, and two staff members from Office of International Programs attended as the MC Members. The first and the third day of the meeting were dedicated to the closed sessions for regulators and officially invited observers only, where, in addition to the guidance documents developed by each working group, the new membership was discussed, and Singapore was unanimously accepted into MC as the 9th member. On the second day, IMDRF Stakeholders Forum, which is open to all stakeholders, was held with approximately 220 participants including Members from MC and industries, and active discussions on the concern of medical device industries took place. At the forum, up-to-date information of Japanese medical device regulations, and the progress report of the Adverse Event Terminology Working Group (chaired by PMDA), as well as the overview of ISO14155 and its ongoing revision, were provided by the Japanese MC Members.

The next IMDRF MC Meeting will be held from March 14 to 16, 2017 in Canada (place to be decided).

The details of the 10th IMDRF MC Meeting are available at the following URL.

http://www.imdrf.org/meetings/meetings.asp

4. Regulatory Affairs Professionals Society (RAPS) 2016 (September 17 to 20)

From September 17 to 20, the Regulatory Affairs Professionals Society (RAPS) 2016 annual conference and associated workshops were held in San Jose, U.S.A., from September 17 to 20. Dr. Toshiyoshi Tominaga, Associate Executive Director (for International Programs), 6 staff members collectively from Office of International Programs, Office of Manufacturing/Quality and Compliance, and Office of Safety I of PMDA, and a staff member from MHLW, participated in the meeting. On September 18, a full-day Japan Workshop, chaired by a staff member of Office of International Programs, was held, with opening remarks given by Dr. Tominaga and presentations delivered by industry and regulatory authorities, including 3 PMDA staff members, on such topics like the current situations of medical device and in vitro diagnostics regulations, the overview of approval review and QMS inspection, safety measures, GCP, and the combined efforts of industry and regulators in these areas.

Dr. Tominaga

The formal sessions of RAPS were held from the evening of September 18 to 20, and in the session entitled "What's New in Japanese MD/IVD Regulation" held on September 19, chaired by Dr. Tominaga, a staff member of Office of International Programs delivered a presentation. Dr. Tominaga also delivered presentations in the sessions entitled "Breakthrough Therapy Designation/Accelerated Approval/EMAs PRIME" and "Efficient Registration of Medical Products through APEC Good Registration Management (GRM)" on the same day. On September 20, a staff member of Office of International Programs participated in the sessions entitled "Update on Rare Disease and Orphan Drug

Designations US/EU/Japan" and "Interaction with Health Authorities" and a staff member of Office of Manufacturing/Quality and Compliance participated in "Medical Device Single Audit Program (MDSAP)", as the presenters. Vigorous discussion took place in each of the sessions, indicating a high level of interest in the Japanese regulations and the ongoing efforts.

PMDA ran an exhibition booth also in this year, where interaction with the visitors was actively promoted for; 1) disseminating information on the current regulations in Japan, 2) enhancing recognition of PMDA, and 3) providing information on the Japanese pharmaceuticals and medical device, as well as PMDA's efforts for enhanced visibility of review and safety measures. There were more than 300 visitors conclusively.

The next RAPS annual conference will be held in National Harbor, U.S.A. from September 8 to 11, 2017.

5. PMDA-ATC Pharmaceuticals Review Seminar 2016 in Bangkok, Thailand (September 26 to 29)

From September 26 to 29, PMDA Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) held its first seminar outside of Japan entitled "PMDA-ATC Pharmaceuticals Review Seminar 2016 in Bangkok, Thailand". This seminar was designed for officials of regulatory agencies overseas engaged in drug reviews, and participated by 13 regulators from Hong Kong and Thailand. In the seminar, lectures were delivered by PMDA staff on the regulatory flow from clinical trial notification to approval, PMDA's latest initiatives, product reviews, safety measures, the relief system for sufferers from adverse drug reactions, etc. Besides these lectures, group discussions on product reviews, presentations by the participants on drug regulations of their regulatory authorities, lectures by Japan Pharmaceutical Manufacturers Association (JPMA) representatives took place and the participants actively engaged in discussions throughout the seminar.

Group photo of participants with Mr. Haruo Akagawa, Director of PMDA-ATC (the 4th left on frot line) and Dr. Sato (the 5th left on front line)

On the final day of the seminar, the Course completion certificates were handed to each one of the participants by Dr. Junko Sato, Office Director, Office of International Cooperation.

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

http://www.pmda.go.jp/english/symposia/0091.html

6. Conference commemorating the publication of the 9th edition of the European Pharmacopoeia (September 27 to 28)

From September 27 to 28, an international conference to mark the publication of the 9th edition of the European Pharmacopoeia organized by EDQM was held in Estonia, and Dr. Takao Yamori, Executive Director and a staff member from Office of Standards and Guidelines Development, PMDA participated in the conference. At the conference, a plenary meeting and 4 workshops were held under the theme of "Tackling future challenges of the quality of medicines together". In the workshop: Setting Pharmacopoeial Standards for Biotherapeutic Products, Dr. Yamori delivered a presentation entitled "Perspective of the Pharmaceuticals and Medical Devices Agency on Biotherapeutics". In the plenary panel session, following the feedback from each workshop, active discussion took place among participants from industry, government, and academia, mainly in Europe, on future agendas towards drug quality assurance.

7. Call for application to PMDA-ATC GMP Inspection Seminar 2016 starts

PMDA Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) will hold a seminar entitled "PMDA-ATC GMP Inspection Seminar 2016" from December 5 to 9, 2016. This five-day Seminar is designed for GMP inspectors from regulatory authorities.

The Seminar includes lectures, group discussions and a mock inspection at the manufacturing facility with the objective of acquainting the participants with Risk-based GMP Inspection. The Seminar is supported by PIC/S.

Please refer to the following web site for the details of PMDA-ATC GMP Inspection Seminar 2016.
https://www.pmda.go.jp/english/symposia/0093.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
Miticure	-	October 5
Ofev	nintedanib ethanesulfonate	October 13

Safety Information

Pharmaceuticals and Medical Devices Safety Information No. 337, October 11, 2016

1. Summary of the Relief System for Adverse Drug Reaction and Request of Cooperation for the System
2. Amendment of Procedures for Bar Code Labeling on Prescription Drugs
3. Important Safety Information
   (1) Imatinib Mesilate (and 3 other tyrosine-kinases inhibitors)
   (2) Afatinib Maleate
   (3) Corticorelin (human)
4. Revision of Precautions (No. 278)
   Natalizumab (genetical recombination) (and 3 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, October 18, 2016

- Atorvastatin calcium hydrate
- Simvastatin
- Pitavastatin calcium hydrate
- Pravastatin sodium
- Fluvastatin sodium
- Rosuvastatin calcium
- Amlodipine besilate/ Atorvastatin calcium hydrate
- Warfarin potassium (Tablets)

- Warfarin potassium (Granules)
- Warfarin potassium (Fine Granules)
- Ustekinumab (genetical recombination)
- Nivolumab (genetical recombination)
- Daptomycin
- Voriconazole (Tablets)
- Voriconazole (Dry Syrup)
- Voriconazole (Injection)
- Itraconazole (Capsules)
- Itraconazole (Tablets)
- Itraconazole (Oral Solution)
- Itraconazole (Injection)
- Fluconazole (Capsules)
- Fluconazole (Dry Syrup)
- Fluconazole (Injections)
- Fosfluconazole
- Peramivir hydrate
- Miconazole (Oral Gel)
- Miconazole (Injection)

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
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
December 5-9	PMDA-ATC GMP Inspection Seminar* (*with the support of PIC/S)	Toyama
December 7-8	4th Joint Conference of Taiwan and Japan on Medical Products Regulation	Tokyo

Reports from overseas

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

Japan started participation in the international pharmacovigilance cluster from September 2016

Based on specified topics related to drug regulations, EMA and US FDA, with Japan and other regulatory authorities, share a variety of information and exchange opinions through regular meetings. This activity is called "cluster", and the clusters include paediatric medicinal products, biosimilar and oncology-haematology medicinal products as well as pharmacovigilance.

The international pharmacovigilance cluster is the sharing of information on drug safety issues and to provide advance notice of anticipated regulatory action, public information and communication prior to decision-making and publication. Product-related risk assessments with a special focus on emerging safety concerns, policies, guidance documents and regulations are typically exchanged during the cluster meetings.

Since lots of drugs are globally distributed now, it is useful for Japan that each regulator shares its safety information and views on the information at an early stage. Japan started participation in the pharmacovigilance cluster from September 2016. PMDA contributes on providing specific inputs or information based on data obtained under the pharmacovigilance system in Japan, which is expected to result in further contribution to drug safety securement and international collaborative activities.

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 generic nasal drug products for treatment of patients with allergic rhinitis

Health Canada published guidances for quality of aqueous solutions including nasal aqueous solutions in 2005[1)], quality of inhalation and nasal products in 2006[2)], and guidance document regarding safety and effectiveness of generic steroid nasal products for treatment of allergic rhinitis in 2011[3)].

With respect to generic drug development for nasal aqueous solutions for treatment of allergic rhinitis, 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, with the exception of nasal aqueous solution (e.g., nasal aerosols and nasal dry powder) products, Health Canada requires bioequivalence evaluations with in vitro, pharmacokinetic, and clinical endpoint studies. Particularly, with respect to the clinical endpoint study, Health Canada recommends conducting the following study.

Study design: Double blinded, placebo-controlled, parallel group design
Study Duration (Treatment period): Two or three weeks
Subject: Seasonal allergic rhinitis patients
Primary endpoint: Change from baseline in the reflective Total Nasal Symptom Score (TNSS)
Secondary endpoint: Change from baseline in the Immediate (instantaneous) TNSS
Bioequivalence criteria: 90% confidence interval of ratio is within 80% to 125%.

Some generic drug products have been already approved based on the Health Canada's guidances 4). I think the sample size of clinical endpoint study is a notable matter.

In Japan, there is no document regarding bioequivalence evaluations for nasal products. I expect that various documents on the bioequivalence evaluations for the nasal products will be developed in Japan.

I finished my temporary dispatch at the end of September. During three months, I had the opportunity to learn a lot, and these three months have been very meaningful. The Bureau of Pharmaceutical Sciences members taught me many details of review for generics in Health Canada. I would like to use this experience to contribute to future international activities.

Finally, I would like to express my sincere appreciation to Dr. Scott Appleton, and thank everyone of Health Canada and PMDA who supported my dispatch.

1) 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
2) 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
3) Health Canada. 2011. Guidance document Data Requirements for Safety and Effectiveness of Subsequent Market Entry Steroid Nasal Products for Use in the treatment of Allergic Rhinitis http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/nas-rhin/nas_rhin-eng.pdf
4) Health Canada. Drug Product Database Online Query http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp

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

Modernization of Analytical Technology for Pharmaceutical Quality Assurance

The modernization of general test methods and monographs to maintain their relevance given scientific advances and evolving manufacturing and regulatory approaches is one of the resolutions approved by USP (United States Pharmacopeial Convention) for the 2015-2020 cycle. The analytical procedures for elemental impurities which USP's scientific experts concluded should be updated to incorporate modern up to date methods, also is being discussed on the workplan of the PDG (Pharmacopoeial Discussion Group). Since the revision of these methods has a significant impact on USP monographs and general chapters, this topic has been discussed not only in the General Chapters – Chemical Analysis Expert Committee (EC) which has the direct responsibility for these chapters, but also in the other ECs cooperatively which are impacted by the updated procedures. The topic was discussed in the Excipient Monograph 2 EC face-to-face meeting which was held on September 20-21. In addition, stakeholders have been invited to comment on a Stimuli article on the Future of Element Specific Chapters1) as well as participate in a stakeholder forum outlining USP's approaches to the control of Elemental Impurities2).

Similarly, improvements of pharmaceutical quality by proactive application of latest science and technologies is one of policies in the draft of the Basic Principles for Preparation of Japanese Pharmacopoeia 18th Edition. The control method of elemental impurities has been discussed as a specific work plan to achieve this policy.

The cooperation among countries is important to modernize pharmaceutical technologies for fitting with needs derived from changes of environment surrounding pharmaceuticals while adjusting with the globalizing pharmaceutical market. I will try hard to facilitate information sharing promptly between USP and PMDA while paying attention to the movements for modernization of pharmaceutical technologies.

1) Pharmacopeial Forum 42 (4) Stimuli to the Revision Process: Future of Element-Specific Chapters in the USP-NF
2) Webinar Excipients (September 29, 2016): Outcomes 4a USP Overview on Elemental Impurities
http://www.usp.org/meetings-courses/stakeholder-forums/excipients/webinar-2016

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