1st Vietnam-Japan Symposium

The 1st Vietnam-Japan Symposium was held in Hanoi, Vietnam on October 8, 2019, jointly hosted by Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and the Drug Administration Department of Vietnam (DAV). JPMA and the Japanese Pharmaceutical Association in Vietnam (JPAV) assisted with the running of the symposium as supporting organizations. The aim of the symposium was to enhance Vietnam's and Japan's mutual understanding of each other's regulatory systems and to promote advancement of pharmaceutical regulations and development. This was the first time that the public and private sectors involved in the registration of pharmaceuticals in Vietnam and Japan had gathered together under one roof. After the keynote speech, delegates from both countries gave presentations on the three themes of Overview of the Regulatory System, Pharmaceutical Review, and Pharmacovigilance. The attendees asked many questions and there was lively discussion in all three sessions.

Group photograph

Introduction

The venue for the symposium was the Pullman Hanoi, a hotel close to Vietnam's Ministry of Health. A total of 199 delegates attended the symposium, 38 of whom were Vietnamese government representatives and experts, with nine from Japanese government authorities, and 71 representatives of Vietnamese companies. There were 81 delegates from Japanese companies, including from members of the JPAV in Vietnam. The Embassy of Japan in Vietnam was also represented by First Secretary, Takaya Shimizu.

PMDA's Chief Executive, Dr. Yasuhiro Fujiwara, and DAV Deputy Director, Mr. Do Van Dong, made welcoming speeches to open the delegation. Mr. Dong remarked that Vietnam and Japan had built up an excellent relationship through political, economic, and cultural exchange since diplomatic relations were established in 1973 and that Japan was Vietnam's largest contributor of Official Development Assistance (ODA) between 2000 and 2016. It was noted that such assistance had extended into wide-ranging fields such as education, agriculture, and energy, and that there have been many projects in the area of health and medicine, including a project currently in progress for the transfer of technology for the manufacture of combination vaccines, through the Japan International Cooperation Agency (JICA). With high-level meetings between the two nations' health authorities, in particular, the attendance of representatives of Vietnam's Ministry of Health at the 2nd Asian Network Meeting in April 2019, the cooperative relationship between Vietnam and Japan is going from strength to strength. Dr. Fujiwara concluded his remarks by expressing the hope that this symposium would lead to the further strengthening of the relationship between the two nations.

An overview of the presentations follows.

■Keynote Speech

PMDA Chief Executive **Dr. Yasuhiro Fujiwara**

After briefly outlining his own professional background, Dr. Fujiwara explained the organization and roles of the PMDA.

The PMDA is taking the lead in the pursuit of the “4 F’s” (Patient First, Access First, Safety First, Asia First) that the Chief Executive himself declared when he assumed the position. Review (approval adjudication), Safety (safety measures), and Relief (relief from health damage), which are together known as the “safety triangle,” are the three major roles of PMDA. In its international activities, PMDA is actively engaged in the development of the Grand Design for Asian Pharmaceutical and Medical Device Regulatory Harmonization. It is also actively supporting the enhancement of pharmaceutical and medical device approval frameworks in ASEAN Member States. To date, PMDA reviews have been referenced in Thailand, Taiwan, Indonesia, and Malaysia, and there are hopes that, through deeper cooperation and collaboration, PMDA will contribute to the improvement of health and hygiene in these countries. The PMDA Asia Training Center (PMDA-ATC) holds training seminars in Japan and overseas and plays a role in the development of young regulators in various countries around the world, particularly in Asia. PMDA has held bilateral symposiums with many countries to date and hopes to assist in the improvement of access to pharmaceuticals and the establishment of universal health coverage (UHC) in Vietnam.

■Overview of the Regulatory system

Overview of the Regulatory system

Senior Director for International Programs, Pharmaceuticals and Medical Devices Agency (PMDA)
Dr. Nobumasa Nakashima

Dr. Nakashima explained three points, namely Japan’s review system, consultation system, and systems for accelerated practical application.

In addition to the regular review arrangements, Japan’s review program also has a range of other schemes, including the Priority Review Scheme, Rare Diseases Review Scheme, Sakigake Designation Scheme, and Conditional Accelerated Approval Scheme. The applicable criteria and conditions, as well as their target review periods, are indicated for each of these scheme. Efforts have been made to reduce review periods and those efforts have produced some results. PMDA sets targets for reviews, which it discloses to ensure transparency and predictability, and makes efforts to achieve those targets. PMDA’s consultation program provides consultation at each stage from the early stages of development until after approval, including clinical trial consultation, regulatory science strategy consultation, and advance evaluation consultation. Fees are set for these consultation services. The consultation program is contributing greatly to the mitigation of development costs and shortening of review periods through such efforts as the optimization of clinical trial design. This benefits both the regulatory authorities and the drug companies. PMDA has also established new schemes, such as the Sakigake Designation Scheme, which promotes the accelerated practical application of innovative drugs, and the Conditional Accelerated Approval Scheme that can be applied in cases of serious diseases that have few treatment options but small numbers of sufferers makes clinical trials difficult, or that would take a long time to trial. In this way, the Agency aims to improve patient access to pharmaceuticals.

Overview of the Registration in Vietnam

DAV, Drug Registration Division, Deputy Director **Dr. Nguyen Ngoc Anh**

An explanation was given of pharmaceutical registration in Vietnam.

The Drug Registration Division has four departments, namely domestic pharmaceuticals, imported pharmaceuticals, vaccines and biological agents, and pharmaceutical information/adverse reactions/advertising. As of 2018, there were 20,857 pharmaceuticals registered in Vietnam, 6,203 of which were imported drugs. Drug registrations are valid for a maximum of five years, while new drugs, vaccines and biological agents, and drugs requiring safety and efficacy monitoring may only be registered for a maximum of three years. Application documentation may be submitted in the ASEAN-CTD (Common Technical Document) format or International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) format. A priority review system is available for pharmaceuticals on the Orphan Drug List, pharmaceuticals that will meet treatment needs at times of emergency or disaster, and for drugs produced on manufacturing lines in Vietnam that have satisfied the requirements of the Pharmaceutical Inspection Convention and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) or the EU’s Good Manufacturing Practice (GMP) in the past 18 months, or in cases where a drug is an original

drug of an overseas manufacturer but its manufacture is to be transferred to Vietnam. The review of registration applications is conducted by technical reviewers (attached to universities, research facilities, etc.) divided into five groups, namely legal documentation, pharmacological documentation (package inserts/labels), quality documentation, clinical data, and bioavailability/ bioequivalence (BA/BE) studies. Pharmaceutical labeling is reviewed according to the requirements of Ministry of Health Notification 1 of 2018, and the technical requirements of application references are reviewed according to ASEAN technical guidelines.

The presentation concluded with an expression of the Vietnamese authorities' hopes for cooperation with Japan in the following areas.

- Sharing of information about legal documents concerning the approval of new drugs
- Results of inspections of overseas pharmaceutical manufacturing plants by Vietnamese and Japanese regulatory authorities
- Sharing of information about the safety and efficacy of Japanese pharmaceuticals
- Registration of and export assistance for Vietnamese herbal medicines
- Investment by Japanese pharmaceutical companies for the transfer of pharmaceutical manufacturing technology to Vietnam

■**Pharmaceutical Review**

Pharmaceutical Review

Planning and Coordination Officer, Office of International Cooperation, PMDA, Japan **Aya Myoenzono**

Ms. Myoenzono explained PMDA's actual review methods, touching on three key points – overall processes of new drug development and review, the requirements for approval and approval scope, and risk-benefit assessment in the review of new drugs.

Regarding the organization of PMDA's review department, the composition of review teams, and the review process from PMDA's acceptance of an application to the drug's approval by the Minister for Health, Labour and Welfare, she introduced the Initial Interview and Review Report 1 and the Expert Discussions and Review Report 2, including when these reports are produced and what roles they play. She also spoke about the post-approval process for inclusion on the NHI drug price list, and reiterated the roles of Japan's two regulatory authorities, PMDA and MHLW. Specifically, PMDA is responsible for scientific review and discussions with external experts, while MHLW is responsible for administrative decisions, management of the Pharmaceuticals Sub-committee, and the NHI drug price list, etc. Next, Ms. Myoenzono explained the requirements for approval and its scope. The Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices stipulates the reasons for refusing approval of a drug or medical device. Meanwhile, regarding the maintenance of approvals, when approval is granted, the application for approval in Japan is issued as the approval dossier. If any changes need to be made to the contents of the dossier after approval, the manufacturer must either submit a change application or, in cases where the impact on quality or efficacy would be small, a notification of change. In Japan, the contents of the CTD attached to the dossier do not form part of the approval. In the content of the package insert, the product name, indications, and dosage and administration are approved matters, but all other sections are not. Finally, Ms. Myoenzono explained risk-benefit assessment in the review of new drugs. It is not that only pharmaceuticals that are completely free of risk are approved, rather, that risks can be mitigated through management. In the review stage, the reviewers check whether or not risk management is adequate, and if the benefits outweigh the risks, they will consider its approval as a pharmaceutical.

Evaluation of the ASEAN Common Technical Dossier (ACTD) for the Registration of Pharmaceuticals for Human Use, Part II Quality

National Institute of Drug Quality Control (NIDQC), Head of Raw Material Quality Control, MSc. Pharm. **Tran Thuy Hanh**

Ms. Tran Thuy Hanh explained the approval review procedures and quality requirements of Vietnam's registration application process.

The registration of pharmaceuticals is governed by the Ministry of Health Circular No. 32 of 2018 under the Pharmaceutical Law. This Circular came into force on September 1, 2019. The procedure for approval review is as follows: (1) the applicant submits the application documents to the DAV; (2) the DAV passes the application documents to the designated review expert (or expert body); (3) the review expert examines the dossier and prepares a review report, which is sent to the DAV; (4) the DAV checks the review report and, if the requirements are met, submits the application documents, review report, and other materials to the Advisory Council; (5) the Advisory Council assesses whether or not to issue a registration number (approval) and submits its opinion containing its final decision. The requirements for registration are

stipulated in the circular of drug registrations and circulars of drug labeling and drug quality management. For the technical documentation, in addition to the guidelines published by the DAV, applicants may also refer to the ASEAN Common Technical Dossier (ACTD) and ASEAN Common Technical Requirements (ACTR), and the guidelines or pharmacopeia of other countries and organizations, such as the ICH, World Health Organization (WHO), US Food and Drug Agency (US FDA), and the European Medicines Agency (EMA). In terms of quality standards, applicants may refer to the Vietnam Pharmacopeia, the British Pharmacopeia (BP), United States Pharmacopeia (USP), Japanese Pharmacopeia (JP), European Pharmacopeia (EP), and the International Pharmacopeia (IP) issued by the WHO. If the API is certified as complying with the EP (CEP), Parts S1 to S7 of the ACTD need not be submitted. If specifications and testing methods established by the manufacturer (in-house standards) are being registered, they must be more stringent than the standards of the Pharmacopeia and the applicant must submit an analysis validation report based on technical documentation such as ICH guidelines or pharmacopeia.

■**Pharmacovigilance**

Pharmacovigilance in Japan

Office of Pharmacovigilance II, Pharmaceuticals and Medical Devices Agency (PMDA) **Sayoko Fukuda**

Ms. Fukuda gave a presentation on Japan's Pharmacovigilance (PV) systems and PMDA's post-market safety measures.

The Marketing Approval Holder (MAH) is required to collect information about adverse drug reactions after marketing launch. In Japan, post-marketing vigilance is compulsory for new drugs until they are re-examined. In addition, many new drugs are subject to mandatory Early Post-Marketing Phase Vigilance (EPPV) for the first six months after marketing launch. Since the introduction of the EPPV system, which is specific to Japan, the number of reports of adverse reactions has increased. There have been cases in which adverse reactions have been discovered early and it is believed that the information collection framework has been strengthened. In Japan, there are three sources of reports of adverse drug reactions to PMDA: (1) from the MAH; (2) from healthcare professionals; and (3) from patients. The collected adverse reaction reports are entered into the PMDA database and shared with the MHLW. Unlike (1) and (2), reports from (3) patients are not mandated by law and patients make such reports voluntarily. Adverse drug reaction reporting by patients began on a trial basis in Japan in 2012. The system was formally adopted in March 2019, and PMDA aims to increase the number of reports through various awareness-raising activities targeting patients.

Next, Ms. Fukuda gave a detailed explanation of the composition and duties of PMDA's Office of Pharmacovigilance, and about the processes and time required from the receipt of adverse reaction information to the revision of package inserts. In terms of post-marketing safety measures, action by the MAHs to collect information from medical institutions is extremely important. Pharmaceutical risk information that is currently being assessed by PMDA and MHLW is posted on the PMDA website. Information about package insert revisions is also posted on the website, along with an overview of the review and reasons for the revision. For information that requires urgency and speedy action, the MAH, under the instructions of MHLW, will issue a Yellow Letter or Blue Letter to healthcare professionals. PMDA provides a service known as PMDA medi-navi that takes this information and communicates it by e-mail. This service is in Japanese only, but critical safety information and safety countermeasure action can also be viewed on the English-language pages of the PMDA website.

Pharmacovigilance Activities in Vietnam

The Vietnam National Centre of Drug Information & ADR Monitoring (DI&ADR Centre) **Nguyen Phuong Thuy**

Ms. Nguyen Phuong Thuy talked about the path of pharmacovigilance in Vietnam and initiatives that are being taken in this area.

Vietnam first started adverse drug reaction (ADR) monitoring in 1994, with the support of Sweden. Subsequently, DI & ADR Centers were established at Hanoi University in 2009 and at Cho Ray Hospital in Ho Chi Minh City in 2011. As PV activities, the DI & ADR Centers are engaged in the detection, assessment, risk minimization, and risk communication of ADRs. Since the establishment of the DI & ADR Centers, the number of ADR reports has increased approximately eight-fold, but unlike the US FDA and Japan, in Vietnam, these reports primarily come from healthcare professionals. As a risk communication initiative, as well as publishing papers and websites, the Centers also use Facebook to distribute information to their 12,000 followers. They also offer a free consultation service for healthcare professionals, responding to about 100 requests a year. They also provide PV training, predominantly for central and province-level hospitals. Initiatives conducted to date have produced results, but challenges remain. They include the low level of awareness of the importance of PV among healthcare professionals, the pharmaceutical industry, and private-sector medical facilities, shortfalls in the quantity and quality of human capital, and the gaps

between the national and regional levels. To solve these problems, the Centers need to partner with the Ministry of Health and various related facilities to integrate laws and regulations, technical guidelines, protocols, and standard operating procedures (SOP), to promote PV activities at all levels.

Conclusion

The symposium ended with closing remarks from Dr. Nakajima of PMDA and the Dr. Nguyen Ngoc Anh of DAV.

They both expressed their appreciation that the symposium had been held and that it was a success, their views that it had been a productive forum, and their hopes that similar symposia would be held again in the future.

This was the first such symposium to be held between Japan and Vietnam, so there were some hiccups with its operation, but overall, the forum was deemed a success. It is hoped that the symposium will develop into a regular event as a platform for deepening mutual understanding and pursuing cooperation between the public and private sectors of Vietnam and Japan, and that it will help to improve access to innovative pharmaceuticals by the citizens of the two nations and the rest of Asia.

Scene from the venue

(Vietnam Team Leader, Asia Committee, Masayo Higashiyama)