

# Future Perspectives for Pharmacovigilance in Japan

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Drugs are sophisticated intellectual products that have been evolving and specializing. For the efficient use of a drug, while enhancement of pre-marketing review is important, post-marketing monitoring is also essential, since it has been demonstrated that pre-marketing data provide only a limited understanding of the risks involved in the use of drugs. From the perspective of identifying concerns for future pharmacovigilance in Japan, safety measures for recent Adverse Drug Reactions (ADRs) are compared between Japan and the United States of America (U.S.A.) and are classified into the following three main categories: category one for cases in which ADR problems have not become apparent due to “drug lag” in Japan, category two for cases in which Japanese idiosyncrasies have become apparent, and category three for adverse events for which assessment of the causal relationship is difficult. Particularly, category one and category two are peculiar to Japan, and category three is also on the increase in Western countries. Regarding trends in international pharmacovigilance, the results of analysis of trends in safety measures indicated that there is an active movement, mainly in Japan and Western countries, for adoption of the Data Mining method using the databases of ADR reports (spontaneous reports) submitted by medical institutions or companies, and epidemiological studies have been conducted to improve assessment of risk, to facilitate development of a more active safety-monitoring system. In conclusion, as simultaneous, global developments and approvals have been realized in Japan, safety measures should also be implemented simultaneously, efficiently, quickly, and accurately with internationally harmonized approaches in the future.

**Key words** — drug lag, pharmacovigilance, data mining, epidemiological study, causality assessment

## INTRODUCTION

The term “pharmacovigilance” refers to the post-marketing monitoring of drug safety.<sup>1)</sup> Expressed in a more concrete fashion, the specific objective of pharmacovigilance is an intent to identify signals of potential drug-induced adverse events efficiently, and as soon as possible. Drugs are sophisticated intellectual products that have been evolving and specializing. For the efficient use of a drug as a substrate, while enhancement of pre-marketing review is important, post-marketing monitoring is also essential, since it has been demonstrated that pre-marketing data provide only a limited understanding of the risks involved in the use of drugs. One of the objectives of using a drug is to treat a disease by changing the environment in the body by actively taking a drug into the “human body.” However, as occurs in the natural environment, a compli-

cated human environment may subsequently cause various problems in the individual. Meanwhile, Japan also needs to deal with the drug lag problem represented by the treatment of mucopolysaccharidoses. Since there are fewer mucopolysaccharidosis patients in Japan than in Western countries, necessary clinical trials to review drug efficacy and safety have not been conducted smoothly, causing delays in drug development, approval, and application.

In addition, in Western countries, although backgrounds and circumstances are a little different, regulatory authorities have successively enforced policies to strengthen pharmacovigilance, including suspension of drug sales. Currently, international harmonization of pharmaceutical regulations, including safety measures, has been promoted, which may have an impact on the Japanese system in the future.

In this context, the backgrounds of recent adverse drug reactions (ADRs) are analyzed, with specific examples, including category one for cases in which ADR problems have not come to the surface due to “drug lag” in Japan and category two for cases in which Japanese particularities have come

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to the fore. Concerns for future pharmacovigilance are also discussed. In the context of the current situation, trends in pharmacovigilance in Western countries have been studied with consideration of the Japanese role in international society. Trends in safety measures are also analyzed, and I identify noteworthy methods that will become particularly important in the future. The future direction of Japanese pharmacovigilance is discussed.

## MATERIALS AND METHODS

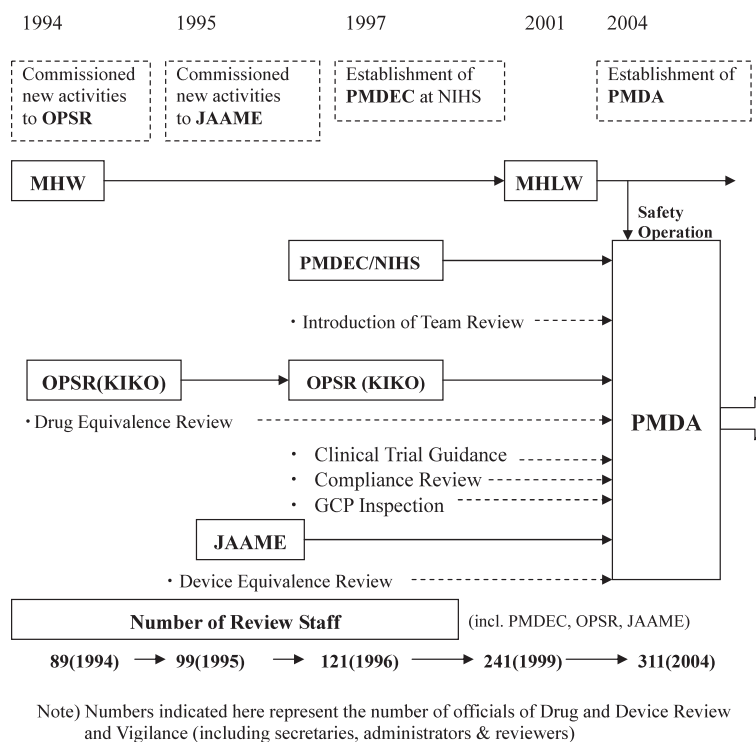
Information used in this study was obtained mainly from web sites related to “Information for Pharmaceuticals and Medical Devices” of the Pharmaceuticals and Medical Devices Agency (PMDA) and safety information provided by the Food and Drug Administration (FDA). Safety information was obtained from the official Web sites of each country, *i.e.*, the Ministry of Health, Labour and Welfare (<http://www.mhlw.go.jp>) and the PMDA (<http://www.info.pmda.go.jp/>) in Japan, the FDA

(<http://www.fda.gov/cder/drug>) in the United States of America (U.S.A.), and the European Medicines Agency (<http://emea.eu.int/>) in European countries.

## RESULTS AND DISCUSSION

### Comparison between Safety Measures in Japan and the U.S.A. with Specific Examples

Many books have been already published<sup>1)</sup> that describe the history of drug safety measures in Japan, therefore, I will not repeat the history here. The system and the organization in Japan have been developed through historical events described below (Fig. 1), in a similar fashion to the historical development of safety measures in Western countries. While Japan had some cases that differed from those in Western countries, such as Subacute Myelo-optic Neuropathy (SMON) induced by clioquinol, some tragic ADRs including thalidomide and human immunodeficiency virus (HIV) infection induced by blood products have spurred the development of the system. After joining the World Health Organization (WHO) in 1972 as an ADR-monitoring country,



**Fig. 1.** The Development of the Drug Regulatory System in Japan

This figure shows the history of the development of the drug regulatory system in Japan. The Ministry of Health, Labour and Welfare (MHLW), formerly MHW (Ministry of Health and Welfare) has been the center of drug regulation for many years. Since 1994, the Ministry has been outsourcing its review work to related organizations: OPSR (Organization for Pharmaceutical Safety and Research), JAAME (Japan Association for the Advancement of Medical Equipment), the PMDEC (Pharmaceuticals and Medical Devices Evaluation Center at National Institute of Health Sciences) and the PMDA.

Japan has cooperated with WHO/Uppsala Monitoring Centre (UMC)<sup>2)</sup> and has discussed harmonization of safety. Japan has also played an international role in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and is one of the three poles of harmonization of drug regulations between Japan, the U.S.A., and European countries.

After the tragic events of HIV infection and ADRs caused by sorivudine (1993), no new, serious ADR has been identified in Japan. From the perspective of identifying concerns for future pharmacovigilance, safety measures for pharmaceutical products were analyzed based on recent ADRs reported in Japan and the U.S.A., which were classified into the following three categories. The first two categories were peculiar to Japan.

*Cases in Which ADR Problems Have Not Come to the Surface Due to "Drug Lag" in Japan:* When rofecoxib (an anti-inflammatory drug: Vioxx)<sup>3)</sup> and tegaserod (a drug which improves bowel function: Zelnorm)<sup>4)</sup> were recalled from the market after discussion of the ADRs for several years in Western countries, they were under development and were not yet approved in Japan, which avoided a disaster in this country (Table 1). In addition, certain drugs with cardiovascular risks had not been approved

in Japan when these risks were dealt with, including rosiglitazone (Avandia),<sup>5)</sup> for which a black-box warning was recently added, and alvimopan (Entereg),<sup>6)</sup> for which strict post-marketing monitoring was required at approval; they were not therefore recognized as a major problem in Japan (Table 2). Had these drugs also been on the market at the same time as in Western countries, without a drug lag, post-marketing monitoring and safety measures would also have been required in Japan. Since Japan has been working for improvement of the review system in order to reduce the drug lag, the development of a system to deal with pharmacovigilance is also required.

*Cases in Which Particularities of Japanese or Asian Population Have been Prominent:* For the past few years, it has been pointed out that the incidence of serious ADRs, such as interstitial pneumonia caused by gefitinib (a therapeutic for lung cancer: Iressa)<sup>7)</sup> or leflunomide (an antirheumatic drug: Arava)<sup>8)</sup> are exceptionally high only in the Japanese. It has also been pointed out that Asian people are highly sensitive to irinotecan (an anti-neoplastic agent: Campto)<sup>9)</sup> and rosuvastatin (anti-hyperlipidemia: Crestor),<sup>10)</sup> and therefore, their dosage regimen is clearly different (Table 3).

Regarding ethnic differences, discussions have been conducted from various perspectives at regu-

**Table 1.** Examples of Recent Withdrawals in the U.S.A.

Components (Product Name)	U.S.A. Approval Date	U.S.A. Withdrawal Date	Japanese Approval Date
(COX-2 Selective NSAIDs)			
celecoxib (Celebrex)	December 31, 1999	—	January 26, 2008
rofecoxib (Vioxx)	May 20, 1999	September 30, 2004	—
valdecoxib (Bextra)	November 16, 2001	April 7, 2005	—
(drug for irritable bowel syndrome)			
tegaserod (Zelnorm) <sup>a)</sup>	July 2, 2002	March 30, 2007	—

—: not available (or not approved yet). *a)* Tegaserod can still be used at an Investigational New Drug (IND) level.

**Table 2.** Examples of Recent Restricted Use in the U.S.A.

Components (Product Name)	U.S.A. Approval Date	U.S.A. risk identification after marketing	Japanese Approval Date
(drug for diabetes mellitus)			
rosiglitazone (Avandia)	April 4, 2000	June 14, 2007 <sup>a)</sup>	—
exenatide (Byetta)	April 28, 2005	August 18, 2008	—
(drug for improvement of bowel function)			
alvimopan (Entereg)	May 20, 2008	May 20, 2008	—

*a)* Nissen Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes NEJM Vol.356, 2457–2471 (June 14, 2007).

**Table 3.** Recent Examples of Unusual ADRs in Japan and Asian Countries

Ingredients (Product Name)	Therapeutic categories	Approval date in U.S.A.	Approval date in Japan
(Interstitial Pneumonia in the Japanese population)			
pemetrexed (Alimta)	for malignant pleural mesothelioma	February 2004	January 2007
leflunomide (Arava)	for rheumatoid arthritis	September 1998	September 2003
bortezomib (Velcade)	for multiple myeloma	May 2003	December 2006
gefitinib (Iressa)	for non-small cell lung cancer	May 2003	July 2002
(Sensitivity in Japanese or Asian population)			
irinotecan (Camptosar)	for colorectal cancer	April 2000	January 1994 <sup>a)</sup>
rosuvastatin (Crestor)	for hyperlipidemia	August 2003 <sup>b)</sup>	January 2005

a) MHLW issued an instruction for additional information on dose adjustment in June 2008. b) FDA issued a warning to Asian patients in March 2005.

latory review for approval through assessment under the ICH/E5 guideline, and factors that cause differences have also been thoroughly discussed. It is very difficult to interpret ethnic differences in efficacy in some diseases. However, it has become clear that the variation in drug-metabolizing enzymes is a major cause of the pharmacokinetic differences. In addition, there has been energetic development and advocacy of biomarkers as surrogates for assessment of efficacy and safety. Therefore, the biomarkers should be used for acceleration of the regulatory review for approval or detection of a signal in the early phase of post-marketing surveillance.

*A High Incidence of Adverse Events for Which Assessment of the Causal Relationship is Difficult:* In 1991, anterograde amnesia caused by triazolam (Halcion) became a big problem, resulting in suspension of sales in the United Kingdom (U.K.). In an extreme case, it was suspected that the ADR might have led to a murder, which indicated the difficulty of evaluation for a causal relationship. Subsequently, throughout the world, there have been many ADRs (mainly psychoneurotic ADRs) for which evaluation of a causal relationship is difficult. Examples include suicidal ideation in patients treated with the antidepressant paroxetine (Paxil) or the drug varenicline, used for smoking cessation (Chantix; Champix in Japan).<sup>11)</sup> Since these events originally occur in patients who already have depression or those who are quitting smoking, it is difficult to evaluate an individual causal relationship. However, it should be noted when there is an increase in the risk in a given population. A similar event is the abnormal behavior caused by oseltamivir (anti-influenza virus drug: Tamiflu)<sup>12, 13)</sup> that was reported as an ADR for the first time in

Japan and subsequently became the center of public attention. Assessment of any causal relationship is still under way. Psychoneurotic adverse events such as suicidal ideation, abnormal behavior, or disturbance of consciousness could lead to serious events including suicide, fatal falls, or accidental death; therefore, strengthening of monitoring and rigorous and quick review should be conducted. The causal relationship between pramipexole (BI-Sifrol) for treatment of Parkinson disease and sudden disturbance of consciousness has been recognized, mainly in older people; therefore those receiving pramipexole have recently, again been instructed not to drive.<sup>14)</sup>

As measures used to identify these cases, risk assessment by epidemiological cohort study and case-control study has been considered. In order to put these measures into practice, a sufficiently large database is required. In other words, the development of an appropriate database for epidemiological study is required in Japan.

### Trends in International Pharmacovigilance

After regulatory authorities were criticized over measures taken for safety issues, energetic discussions to improve pharmacovigilance have been taking place in Western countries.

*Movement toward Improvement of the Methodology of Pharmacovigilance:* In pre-marketing clinical studies, the randomized comparative clinical trial (RCT), which was developed approximately 60 years ago, has been considered an established approach for the evaluation of efficacy. However, there is no globally established approach for pharmacovigilance. Therefore, signals have been empir-

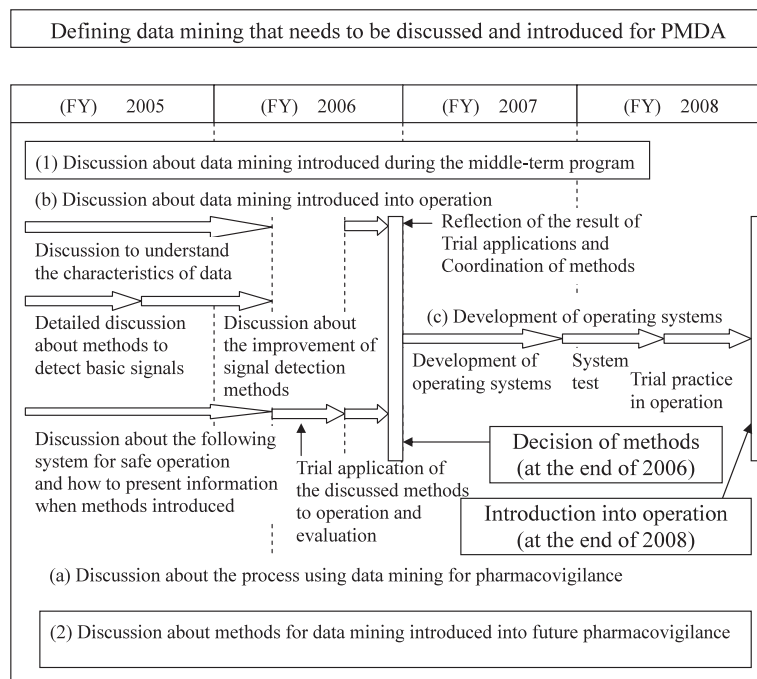
ically detected from the databases of ADR reports submitted by medical institutions or sponsors. Currently, with the remarkable progress seen in drug development, and an increase in the types of drug available, there is a movement for adoption of Data Mining methods that use databases containing ADR reports (spontaneous reports) submitted by medical institutions or companies, mainly in Japan and Western countries.<sup>15,16)</sup> In Japan, the development of the Data Mining method has been promoted in accordance with the schedule shown in Fig. 2.<sup>17)</sup> To make the Data Mining method an established approach for pharmacovigilance, the method needs to be improved,<sup>18)</sup> and this is under development. Each country is also required to pay close attention to developments, and hold discussions on more efficient methods (Fig. 3).

In Western countries, epidemiological studies have also been conducted to enhance risk assessment procedures for the development of a more active safety monitoring system,<sup>19)</sup> and environmental improvement, including the development of medical databases, has been promoted. While most of the databases are administered by private insurance companies in the U.S.A., the FDA has announced a “Sentinel Initiative”<sup>20)</sup> to accelerate improvement

of the infrastructure for both private- and public-led epidemiological studies. In Europe, especially in the U.K., the General Practice Research Database (GPRD)<sup>21)</sup> system, in which medical records are compiled into a database by the National Health Service (NHS), has actually been put into practice.

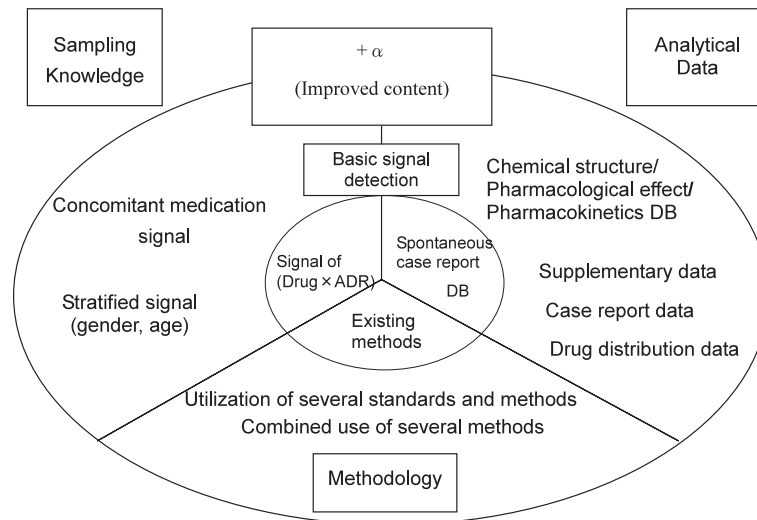
Improvement of databases for these epidemiological studies is necessary for the construction of better pharmacovigilance; therefore, people concerned should cooperate in the development of Japanese databases that can withstand world-class risk assessment.

*The Progress of Pharmacogenomics and Its Utilization in Safety Measures:* pharmacogenomic (PGx) studies that utilize genetic factors for the assessment of efficacy or safety have been performed, and guidelines for the studies have been prepared in cooperation between the Japanese authority, the FDA, and European Union (EU).<sup>22)</sup> There have been some cases in which the results of studies were used in regulatory review for approval or safety measures. As mentioned above, the ethnic differences that were proved by the results of the studies have been taken into consideration by the FDA, to determine the dosage regimen of the anticancer drug irinotecan and the lipid-lowering drug rosu-



**Fig. 2.** The Development Program in PMDA (PMDA Published Data, Original Japanese)

This figure shows the introduction design of the data mining method into Japan (PMDA). A fiscal year in Japan starts in April and ends the following March. The progress up to 2007 FY has been published (PMDA Website, Japanese only) and the project has been progressing well. Therefore, it is expected that the data mining method will be introduced into PMDA's pharmacovigilance as an additional method at the end of March 2009 when the 2008 FY ends.



**Fig. 3.** Data Mining and Signal Detection in Pharmacovigilance

Data mining is expected to be a method which would be able to improve the basic signal-detection methods that we use to detect signals from databases of spontaneous case reports, the only available analytical data at present, with the existing experimental methods.

**Table 4.** Additional Safety Information Based on PGx in Japan

Ingredients	Dates	Additional Information on Labeling
Warfarin	November 2006	Precautionary update
	April 2007	Pharmacogenomics topic (Pharmaceuticals Medical Devices Safety Information No.235, April 2007)
Carbamazepine	April 2008	Precautions regarding severe epidermal reactions association between HLA-B*502 and ethnicity
Irinotecan	June 2008	Dosage precautions taking PGx (UGT1A1 polymorphism) into consideration

vastatin. To be more specific, in 2006, the dose of irinotecan was required to be based on the use of an *in vitro* diagnostic (IVD) test that determines activity of the enzyme UDP-glucosyltransferase (UGT1A1), which detoxifies the active metabolites of irinotecan (SN-38) by glucuronidation.<sup>23)</sup> In Japan, these procedures for determining the dosage of irinotecan were put into place after approval of IVD in June 2008.

The current situation of safety measures for PGx in Japan is provided in Table 4. From now on, further expansion of PGx studies should be promoted, to ensure the safety of pharmaceutical products. As a specific example, Japan has cooperated with the FDA and European Medicines Evaluation Agency (EMA) to identify an additional biomarker for examination of renal toxicity,<sup>24)</sup> and this activity will be further promoted.

*Increased Needs for Effective Safety Measures in Clinical Practice:* At the time of regulatory review, cautionary notices have been issued regarding approval, pharmacovigilance, and clinical practice; however, it has been pointed out that the cautions

might not be utilized in clinical practice. For example, frequent blood tests are required after administration of the anticoagulant ticlopidine to avoid serious ADRs such as leukopenia or liver injury (2002); however, there are some reports of serious ADRs due to lack of compliance with these cautions. There is also the problem of off-label use of pharmaceutical products. If discretion in clinical settings is uniformly regulated, it would remove the opportunity to experiment with new forms of medical practice; this is thus a difficult problem. However, it has been pointed out that off-label use may increase the incidence of unexpected ADRs,<sup>25)</sup> and there is therefore an increased need for sound safety measures for high-risk drugs in clinical practice, and taking countermeasures is a major issue which the regulatory authorities in European countries and the U.S.A. are facing.

The basic concept of a series of safety measures such as data collection, analysis and evaluation of risk specified in guideline E2E in ICH are agreed upon, and have been put into practice in each pole. In addition, comprehensive measures have been ini-

tiated, such as the Risk Management Plan (RMP) in Europe and Risk Evaluation and Mitigation Strategies (REMS) in the U.S.A.

In consideration of these trends, it is important to address post-marketing risk assessment and risk management using a team of experts in safety, pharmacoepidemiology, regulatory affairs, and clinical pharmacology, while performing regulatory review for approval in Japan.

*Trends in the East Asian Region:* At the private level, the infrastructure for an international collaborative study has already been developed in several East Asian countries notably Japan, China, and South Korea.<sup>26)</sup> Regarding pharmacovigilance, while regulatory authorities previously only exchanged short-term trainees, an official annual meeting was started in April 2008,<sup>27)</sup> held by the regulatory authorities for pharmaceutical affairs in Japan, China and South Korea. In the subsequent symposium, the three countries shared their current situations and future perspectives for pharmacovigilance. This means that there is a growing momentum for international harmonization of safety monitoring of pharmaceutical products in the East Asian region, as well as of regulatory review for approval. In these circumstances, Japan should play a positive, leading role in implementing safety measures in East Asia.

### Discussion of Future Perspectives for Pharmacovigilance in Japan

Based on the above-mentioned findings, the following should be taken into consideration when deliberating the direction of future pharmacovigilance.

After the recall of rofecoxib, pharmacovigilance and regulatory safety reviews have tended to be stricter due to the subsequent IOM report<sup>28)</sup> (January 2007), the enactment of the FDA Amendment Act in September 2007, and measures for pharmacovigilance including REMS.<sup>29)</sup>

Meanwhile, there was no rofecoxib problem in Japan partly because of drug lag; however, other ADRs have been reported frequently. Therefore, we should not regard developments in the U.S.A. solely as occurrences in another country but should view them as relevant to our country, and as points of reference that can be used to institute future measures.

The resolution of drug lag is not an isolated objective. We should identify conditions of approval that should be disclosed after marketing under strict review, and the conditions should be instituted as soon as possible after marketing. Examples include

orphan drugs, where we are compelled to make post-marketing surveillance a priority, because of the small number of patients in Japan. In other words, conducting a clinical study of these drugs takes a long time and is difficult, although getting them onto the market as quickly as possible is desired.

Application of new analytic methods used to assure safety, such as Data Mining and PGx are desirable, and their application should be further promoted in Japan.

It is considered important for pharmacovigilance that Japan continues to play an international role in ICH, CIOMS, and also in Asia.

Japan has enhanced the system of regulatory review for approval, in order to overcome the drug-lag problem. This implies a requirement for investing additional human resources and keeping the review system on the basis of primary review.<sup>30,31)</sup> In consideration of developments in Western countries, and the future role of Japan in the research and development of pharmaceutical products, and in the pharmaceutical affairs in Asia, this choice was considered reasonable and correct.

In conclusion, I believe that Japan should establish a primary pharmacovigilance system with a research function, to strictly evaluate the risks and benefits of pharmacovigilance, as one of the roles comparable to the Western countries, similarly enhancing as primary review for approval. Japan should also play a positive, international role in the construction of a wide-ranging pharmacovigilance system, especially in Asia.

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