

Good pharmacovigilance planning in Japan: Proposals from the “task force for good pharmacovigilance planning in Japan” of Japanese Society for Pharmacoepidemiology (JSPE)

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“JSPE Task force for good pharmacovigilance planning in Japan”

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1. Background

Japanese reexamination system was inaugurated, ahead of the world, in April 1980 when the amendment of Pharmaceutical Affairs Law (PAL) in October 1979 was enforced. The aim of the reexamination system was to reconfirm the quality, effectiveness and safety of new drugs and medical devices using the new information accumulated after the approval of the products. The importance of the reexamination system is currently increasing as the number of drugs with new pharmacological mechanisms and indications for rare diseases and special patient populations has increased in recent years, while the safety information for those products available before the approval is often limited. In addition, it is not rare that a new drug is marketed at the same time in the world and some drugs may be marketed in Japan for the first time in the world under the new “sakigake” strategy. What was aimed in the reexamination system when it was started in 1980 is still appropriate at the present time. Nevertheless, in general, any system can become truly useful or lose substance depending on how it is operated. Under the recognition that the current Japanese pharmacovigilance practice is facing various problems as mentioned below, and its underlying cause is in the inappropriate operation of the reexamination system, we have decided to publish our proposals for a change.

2. Emerging problems

- ICH-E2E “Pharmacovigilance Planning”, which was issued as a notification (September 16, 2005) No. 0916001 by Director, Evaluation and Licensing Division and No. 0916001 by Director, Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (MHLW), provided key methods to help the industry select the way to address individual problems summarized by the Safety Specification. However, neither the industry nor the regulatory body was serious about implementing ICH-E2E; to date, ICH-E2E has been a “forgotten document”.

- The notification “Risk Management Plan Guidance” (April 11, 2012), No. 0411-1 by Director, Evaluation and Licensing Division and No. 0411-2 by Director, Safety Division, put in place guides to developing the risk management plan (RMP), including the risk minimization plan to lower the risk of drugs. It is stated in the notification (“RMP notification”) that “with regard to the methods available for pharmacovigilance, the annex of ICH-E2E ‘Pharmacovigilance Methods’ should be referred, including methods such as pharmacoepidemiological studies utilizing medical databases”. Despite this, pharmacovigilance methods in the risk management plans submitted by industries and published online* still heavily depend on the traditional “drug use results surveys and specific use results surveys” (**Note 1**), even after the “RMP notification” was enforced.

* <http://www.pmda.go.jp/safety/info-services/drugs/items-information/rmp/0001.html>

(Note 1) The traditional “drug use results surveys and specific use results surveys” are studies with the following designs that have been used in Japanese pharmacovigilance for more than 30 years. The traditional “drug use results surveys” are studies without a comparator group, conducted mainly to detect so-far unknown adverse drug reactions occurring with a specific frequency (e.g., 0.1%) with a specific target number (e.g., 3,000) of patients. The traditional “specific use results surveys” are essentially the same as the traditional “drug use results surveys” but the target patients are restricted to those with specific attributes (e.g. in terms of age, concurrent diseases, etc.) or the study period is longer (e.g., 1 year) than that in the traditional “drug use results surveys” (typically 3-6 months).

(Note 1a for English version) In the appendix 1 of the current proposals, examples of 139 Japanese RMPs, as of September 27, 2015, submitted and published online after the enforcement of the “RMP notification” in April 1, 2013 are presented. In almost all RMPs so far submitted and published, essentially the same traditional “drug use results survey” design without a comparator is selected as the method of pharmacovigilance.

- Both industries and regulatory bodies are keen to collect a large number of spontaneous reports and to estimate the incidence proportion. However, they have little interest in how to evaluate the collected information (e.g., assessing causality, specifying risk factors, etc.). Indeed, there have been very few studies where the comparison (comparison with a comparator or comparison using a self-controlled design) is the main focus.
- A ministerial ordinance “Good Post-marketing Study Practice (GPSP)” and related

notifications do not have a concept of comparison. Without comparison, the evaluation of the causality of adverse events is virtually impossible except when the background incidence is negligibly small.

- In the “RMP notification” which is now stipulated in the amendment of another ministerial ordinance “Good Vigilance Practice (GVP)”, the industry is required to summarize the important identified risks of a drug, important potential risks, and important missing information in the Safety Specification. Nevertheless, in almost all RMPs so far submitted by pharmaceutical industries, the traditional “drug use results surveys” or the “specific use results surveys” are selected as a research tool to address the problems specified in the Safety Specification because the GPSP ordinance requires that the industry should normally select these traditional methods. In other words, two ministerial ordinances (GPSP and GVP) are poorly connected with each other.

Other types of emerging problems include ineffective use of the new development of conditions and potential resources which may help the appropriate operation of the reexamination system. These include the following.

- Since 1996 when Japanese Society for Pharmacoepidemiology (JSPE) was established, JSPE has tried to encourage the use of pharmacoepidemiology in the society and published several proposals and has been involved in the enlightenment activities to meet this end. From 2012, JSPE started the certification system for “pharmacovigilance specialist” to foster human resources. In addition, thanks to the creation of several departments and schools of universities to teach epidemiology, including pharmacoepidemiology, and the continued efforts over the years of a few incorporated foundations to foster human resources, the number of individuals who have certain level of knowledge of pharmacoepidemiology is gradually increasing, although still insufficient in number. The current reexamination system, however, impedes epidemiologically sound inputs from these precious human resources to be reflected in organizational actions, with a consequence that proper involvement of these individuals being rare in designing and conducting studies in the reexamination system.
- Despite the emergence of the big data and real world data related to the medical services, no consensus has been reached about the proper use of medical databases in the reexamination system. This is due to difficulty in positioning such use under the current regulations governing the reexamination system (Note 2).

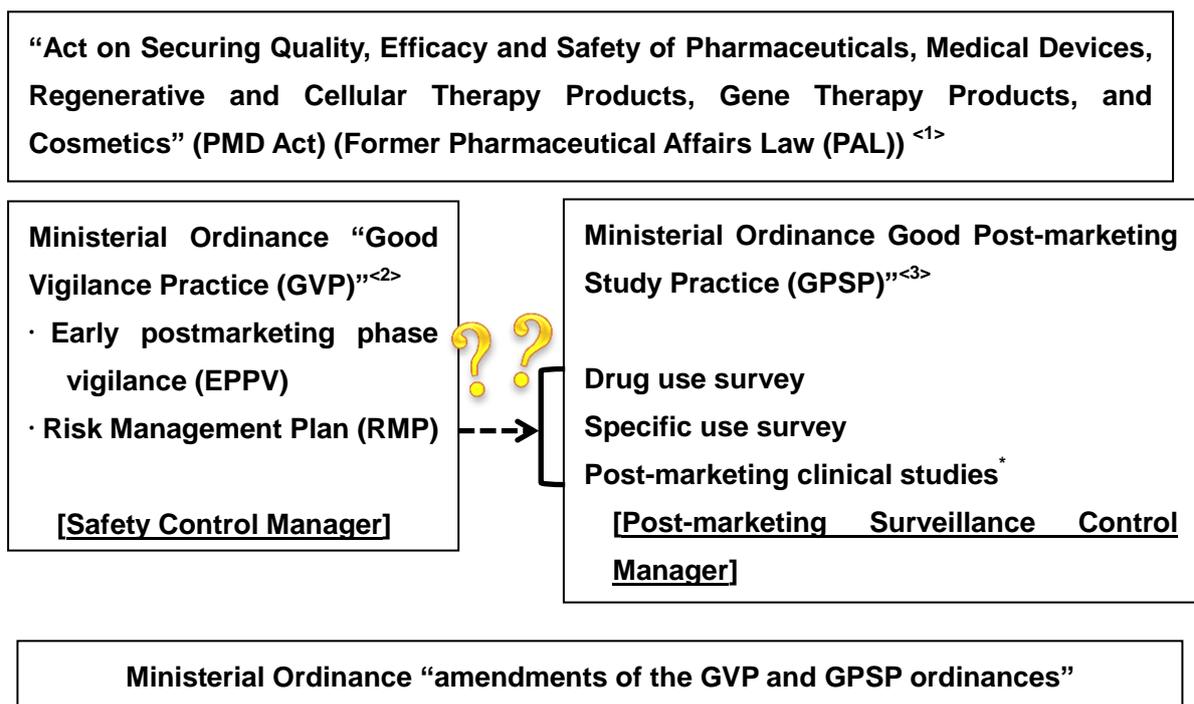
(Note 2) In general, a database study can provide good evidence leading to the

good decision making in safety measures. Nevertheless, when the indices for the outcome and other key variables are not well validated or the information of key variables is not confirmed by the source documents, a database study may be regarded merely as a screening tool to judge whether the next action, including conducting a study involving primary data collection, is needed.

3. Underlying cause

The emerging problems outlined in the above section represent the end results derived from the underlying cause. The underlying cause of the malfunction of pharmacovigilance practice is the inappropriate operation of the reexamination system which should be changed to create an enabling environment in Japan for contributing to the worldwide proper use of drugs. Figure 1 depicts the current structure of the regulation of pharmacovigilance in Japan.

Figure 1 Current framework for the regulation of pharmacovigilance



<1> <http://law.e-gov.go.jp/htmldata/S35/S35HO145.html>

<2> <http://law.e-gov.go.jp/htmldata/H16/H16F19001000135.html>

<3> <http://law.e-gov.go.jp/htmldata/H16/H16F19001000171.html>

* The term “clinical studies” here is used to indicate interventional studies or “clinical trials”

The Pharmaceutical and Medical Device Act (PMD Act, former PAL) stipulates the reexamination of newly marketed drugs in Article 14-4. The following descriptions are given in Articles 14-4(2)4 and 14-4(2)6 (The underline was given by the authors of the current proposals).

Pharmaceutical and Medical Device Law (PMD Law)

Article 14-4(2)4 The applications specified in Paragraph 1 shall be made by means of an application form with data concerning the results of use of the drug and other data specified by MHLW ordinance attached. When the drug concerned in such applications is specified by MHLW ordinance, the data concerned must be collected and compiled in accordance with standards specified by MHLW Ordinance.

Article 14-4(2)6 Persons who have received approval of drugs specified in the items in Paragraph 1 as indicated in Article 14 shall investigate the results of use, for the drug concerned and perform other investigations as specified by MHLW ordinance and shall report these results to the Minister.

The PMD Law does not indicate any specific method to investigate “the results of use, etc.”; it states only that the methods are specified by the ministerial ordinance. In other words, in the PMD Law, the term “drug use results survey” or “specific use results survey” does not appear at all and only the word meaning “investigation” in general is used. As the PMD Law does not bind the method used in the reexamination system, we do NOT propose the change of the PMD Act.

It is the ministerial ordinance GPSP (the ordinance 171, December 20, 2004, and the ordinance 87 in the latest amendment on July 30, 2014) which specifies the methods to investigate “the results of use, etc.” given in the PMD Law. In the GPSP, the term “investigation of the results of use, etc.” in the PMD Law is replaced by the term “post-marketing surveillance”. Article 2 of the GPSP ordinance indicates that “post-marketing surveillance” include 3 methods: “drug use results survey”, “specific use results survey” and “post marketing clinical studies”.

The GPSP ordinance (definition)

Article 2 Definitions of the main terms used in this Ordinance are as specified below.

1. ‘Post-marketing surveillance’ indicates drug use results surveys or post-marketing clinical studies implemented by marketing authorisation holders or holders of special approval for foreign manufacture of medicinal products, etc. (hereinafter collectively referred to as marketing authorisation holders) to collect, obtain, verify or validate information on the quality, efficacy and safety of medicines.

2. 'Drug use results surveys' indicates surveys implemented as part of post-marketing surveillance in which marketing authorisation holders obtain or verify information on the incidence of adverse drug reactions by disease type and information on medicine quality, efficacy and safety in medical practice, with no conditions specified for patients using the medicine in question.
3. 'Specific use results surveys' indicates drug use surveys implemented as part of post-marketing surveillance in which marketing authorisation holders obtain or verify information on the incidence of adverse drug reactions by disease type and medicine quality, efficacy and safety, with conditions imposed on the use of the medicine in medical practice. Such conditions include administration to juvenile, elderly, or pregnant patients, patients with renal or hepatic dysfunction, long-term administration to patients and other specified drug use conditions.
4. 'Post-marketing clinical studies' indicates clinical studies implemented as part of post-marketing surveillance in compliance with approved administration, dosage, indications and effects of the medicine in question pursuant to the provisions of Article 14, Paragraphs 1 or 9 (including cases of application mutatis mutandis in Article 19-2, Paragraph 5) or Article 19-2, Paragraph 1 of The Law to enable marketing authorization holders to validate assumptions obtained from results of clinical studies or usage results surveys , or to collect information which cannot be acquired in medical practice relating to the quality, efficacy and safety of medicinal products.

Source: Thomson Reuters CORTELLIS™ Regulatory Intelligence, GOOD POST-MARKETING STUDY PRACTICE (MHLW Ordinance No.171 dated December 20, 2004) translated by Thomson Reuters.

The GPSP ordinance and related notifications are the root causes of the malfunctioned operation of the reexamination system in Japan. In the GPSP ordinance, only three study designs are mentioned as methods to investigate “the results of use, etc.” in the PMD Law, namely, “drug use results survey”, “specific use results survey” and “post-marketing clinical studies”. This practically limits the available options. To limit the options for the post-marketing studies to these three is not compatible with what ICH-E2E requires where it is clearly stated that “the best method to address a specific situation can vary depending on the product, the indication, the population being treated and the issue to be addressed” in Section 3.2. All the related notifications presuppose that only these three options, but no other methods, are available for the studies in the reexamination system, thereby strengthen the narrow view of the GPSP ordinance. Desired study designs for studies in the RMP under the

GVP ordinance are not compatible with “post-marketing surveillance” in the GPSP ordinance. It has been already pointed out many times by several authors that virtually no useful information has been generated from the current studies conducted by drug companies using the traditional “drug use results survey” and “specific use results survey” designs stipulated in the GPSP ordinance, which lack the critical concept of comparison.

4. Proposals

Based on the above observations, we present the following proposals to help develop a good pharmacovigilance planning to achieve the good pharmacovigilance system and resultant good safety measures in Japan.

[Proposal 1] The GPSP ordinance should be completely revised to encourage referring the annex “pharmacovigilance methods” in “Pharmacovigilance planning” (issued as a notification of No 0916001, September 16, 2005) and not to limit the methods for pharmacovigilance and studies for generating evidence to certain types of designs (**Note 3**).

(Note 3) All the notifications related to the GPSP ordinance should be revised. Several measures such as organizing expert groups to examine the problems of the current regulation may be needed to achieve the full range of revision of all the related notifications. It is beyond the scope of the current proposals to present the full range of the required changes to these notifications.

[Proposal 2] The GVP ordinance provides the standards for the safety management in the post-marketing phase, including the early post-marketing phase vigilance (EPPV). The EPPV, mentioned in the annex of “pharmacovigilance planning” may be maintained in the future. However, the use of this scheme should be restricted to the epoch-making drugs marketed at the same time in the world or marketed for the first time in Japan. In such a situation, the EPPV may detect a new risk for the first time in the world.

[Proposal 3] The notification on March 11, 2013 (No 0311-7) about the ministerial ordinance of “Enforcement of Ministerial Ordinance to Partially Revise the Ministerial Ordinance on GVP for Drugs, Quasi-drugs, Cosmetics, and Medical Devices and the Ministerial Ordinance on Good Post-marketing Study Practice for Drugs” connects the GVP ordinance with the GPSP ordinance. The notification describes “close and mutual

relationship” between the Safety Control Manager for the risk management (per GVP) and the Post-marketing Surveillance Control Manager for the post-marketing studies in the pharmaceutical industry (per GPSP). This relationship should not be simply “liaison and coordination” and “information sharing”, as it is currently described, but should be revised to include a prescription that “the Safety Control Manager encourage the Post-marketing Surveillance Control Manager to develop a pharmacovigilance plan according to the ICH-E2E guidelines as given in the RMP notification”.

[Proposal 4] Forms attached to the individual RMPs submitted to the regulatory body specified in the notification (No 0426-1 and No. 0426-2, on April 26, 2012) should be revised referring the example of the revised form as in the appendix 2 of the current proposals (Note 4).

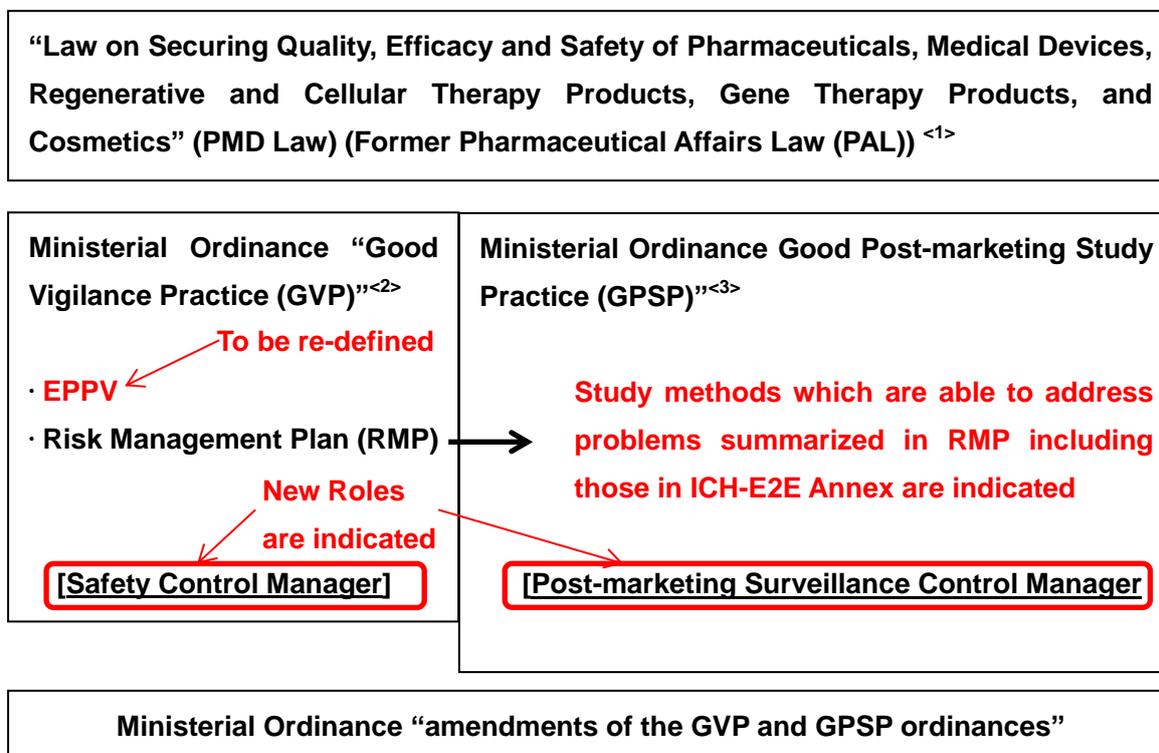
(Note 4) Though the terms “drug use results survey” and “specific use results survey” are used in the appendix 2 of the current proposals, this does not mean that the study designs should be restricted to the traditional “drug use results survey” and “specific use results survey”.

[Proposal 5] The above notification (No. 0426-1 and No. 0426-2, on April 26, 2012) should be revised to add 2 new subsections to the beginning of the notification section “1. On the formulation of RMP” as: “(a) the need for additional pharmacovigilance plan should be judged by careful consideration to the medical and scientific importance of the additional information, the need for an alternative treatment comparator, the required level of the accuracy of the information, required swiftness for the provision of the information, and the burden on the health professionals.”; and “(b) when an additional pharmacovigilance plan is developed, the study design acceptable to the health professionals involved in the study should be used by referring the annex ‘pharmacovigilance methods’ in ‘pharmacovigilance planning’ issued as a notification (No. 0916001 on September 16, 2005)”.

[Proposal 6] When the drug is marketed in the countries outside Japan as well, it is not rational, either from scientific or economic viewpoint, to answer all research questions that arise from problems corresponding to the Safety Specification based only on data from studies in Japanese patients. It should be stated in the ordinance and related notifications that additional investigations to evaluate the causal relationship, to find the high risk populations, and to examine the risk factors may be conducted by the divisional cooperation in several countries in the world or may be conducted as a

non-clinical study (e.g., molecular level studies, genome-wide association study) if appropriate.

Figure 2 Diagrammatic summary of the proposal



Acknowledgement: We would like to thank Dr. Yoichi Ii, Statistical Research & Consulting, Pfizer Japan Inc. for providing valuable suggestions in proofreading of the English version of the proposal.

Appendix 1 Examples of 139 RMPs submitted and published online after the after the enforcement of the “RMP notification” in April 1, 2013

No	Submission date	Drugs	Indication	Safety Specification	*Post-marketing surveillance**				EPPY	Postmarketing Clinical Trials *
					Study Design	Comparator	Follow-up period	Size		
1	October 2014	Aflibercept (Genetical Recombination)	[1] Age-related Macular Degeneration (AMD), [2] Macular edema due to retinal vein occlusion (RVO), [3] Choroidal neovascularization due to pathologic myopia (CNV), [4] Diabetic Macular Degeneration (DMD)	[1] Endophthalmitis [2] Intraocular pressure increased [3] Retinal tear/detachment [4] Traumatic cataract [5] Events due to Arterial thromboembolism etc.	Specific use-results study	No	1-3 years	5200	Yes	Yes
2	October 2014	Anagrelide Hydrochloride Hydrate	Essential thrombocythemia	[1] Cardiac Toxicity [2] QT/QTc prolongation [3] Haematotoxicity [4] Thrombocytopenic/Thrombotic Event [5] Interstitial Lung Disease [6] Headache etc.	use-results study	No	1 year	474	Yes	Yes
3	August 2014	Riociguat	[1] Chronic thromboembolic pulmonary hypertension, [2] Pulmonary arterial hypertension	[1] Hypotension [2] Upper-gastrointestinal motility disorder [3] Haemoptysis/Pulmonary haemorrhage etc.	use-results study	No	1 year	1000	Yes	Yes
4	August 2014	metronidazole infusion	[1] Infection with anaerobic bacteria [2] Infectious enteritis [3] Amoebic dysentery	[1] Central nervous system disorder [2] Peripheral nerve disorder [3] Aseptic meningitis [4] Toxic Epidermal Necrolysis [5] Acute pancreatitis [6] Leukopenia/Neutropenia etc.	use-results study	No	8 weeks	100	Yes	No
5	July 2014	Vilanterol Trifenatate	Various symptoms of Chronic Obstructive Pulmonary Disease (COPD)	[1] Cardiovascular event [2] Asthma-related intubation/death	use-results study	No	1 year	2000	Yes	No
6	March 2014	Everolimus	[1] Advanced/metastatic renal cell carcinoma [2] Pancreatic neuroendocrine tumor [3] Advanced/recurrent breast cancer [4] Renal angiomyolipoma with tuberous sclerosis [5] Subependymal giant cell astrocytoma with tuberous sclerosis	[1] Interstitial Lung Disease [2] Severe infection [3] Hypersensitivity [4] Stomatitis [5] Serum creatinine increased/protein urea/renal failure [6] Hypoglycaemia/diabetes mellitus [7] Leukopenia [8] Hemorrhage [9] Thromboembolic event [10] Acute respiratory distress syndrome etc.	Specific use-results study	No	up to 1 year	1590	Yes	Yes
7	April 2014	Tofogliflozin Hydrate	Type 2 diabetes mellitus	[1] Hypoglycemia [2] Polyuria/Pollakiuria [3] Events related to fluid loss [4] Genital infection [5] Urinary tract infection [6] Blood ketone body increased [7] Renal impairment [8] Bone fracture [9] Malignancies [10] Cardiovascular diseases etc.	Specific drug use-results study	No	3 years	3000	Yes	Yes
8	March 2014	Fluticasone Furoate, nasal spray	Allergic rhinitis	[1] Anaphylaxis [2] Nasal septum perforation [3] Systemic effect of corticosteroid [4] Growth retardation	Specific use-results study	No	24 weeks	1500	Yes	No
9	October 2014	Donepezil Hydrochloride	[1] Alzheimer's disease [2] Dementia with Lewy Bodies	[1] Bradycardia, heart block, sinus arrest, Ventricular tachycardia [2] Peptic ulcer [3] Parkinson's syndrome [4] Myocardial infarction/heart failure [5] Liver injury [6] Parkinson's syndrome [7] Neuroleptic malignant syndrome [8] Rhabdomyolysis [9] Dyspnea [10] Acute pancreatitis etc.	Specific use-results study (studies for new indication, dementia with lewy bodies)	No	52 weeks	500	Yes	Yes
10	July 2014	Alectinib Hydrochloride	Advanced ALK-positive non-small cell lung cancer	[1] Interstitial lung disease [2] Impaired liver function [3] Neutropenia/Leukocytopenia [4] Bradycardia [5] QT prolongation [6] Visual disturbances [7] Gastrointestinal perforation [8] Thromboembolism etc.	use-results study	No	18 months	1000	Yes	Yes

* Observational studies for pharmacovigilance planning; b Interventional clinical trials for pharmacovigilance where the size is usually much smaller than that in the observational "post-marketing surveillance" and often have a control group.

No	Submission date	Drugs	Indication	Safety Specification	*Post-marketing surveillance**				EPPV	Postmarketing Clinical Trials ^b
					Study Design	Comparator	Follow-up period	Size		
11	April 2014	Enzalutamide	Prostate Cancer refractory to castration	[1] Seizure [2] Thrombocytopenia [3] Interaction with CYP2C8 inhibitor [4] Psychoneuropathy	Specific use-results study	No	2 years	900	Yes	Yes
12	September 2014	Levetiracetam	Partial seizures with/without secondary generalisation	[1] Aggression [2] Suicidal behaviour/ Suicidal ideation [3] Toxic Epidermal Necrolysis / Stevens-Johnson Syndrome [4] Drug-induced hypersensitivity syndrome [5] Blood disorder (Pancytopenia, Agnucytosis, Leukopenia, Neutropenia, Thrombocytopenia) [6] Hepatic Failure / Hepatitis [7] Pancreatitis [8] Rhabdomyolysis [9] Withdrawal symptom / Rebound psychosis [10] Reproductive toxicity etc.	[1] Use-results study [2] Specific use-results study	[1] No [2] No	[1] 16 weeks [2] 2 years	[1] 3000 [2] 600	Yes	No
13	June 2014	Interferon Gamma-1a	[1] Renal cancer [2] Severe infection associated with Chronic granulomatous disease [3] Mycosis fungoides / Sezary's syndrome	[1] Interstitial pneumonia [2] Shock [3] Depression (serious) [4] Acute renal failure [5] Heart failure [6] Leukopenia, thrombocytopenia, pancytopenia [7] Autoimmune disorder [8] Diabetes mellitus [9] Liver disorder (serious) [10] Retinopathy etc.	Specific use-results study (Mycosis fungoides / Sezary's syndrome)	No	1 year	100	No	No
14	Jun 2015	Ramosetron Hydrochloride	Diarrhoea predominant irritable bowel syndrome	[1] Constipation / Hard stool [2] Acute ischaemic colitis	Specific use-results study	No	52 weeks	600	Yes	No
15	February 2015	Efractocog Alfa	Bleeding tendency in Patients with Coagulation factor VIII deficiency	[1] Neutralizing antibodies [2] Shock, Anaphylaxis	Use-results study	No	[1] 2 years (New patients) [2] 1 year (Previously treated patients)	[1] 20 [2] 100	Yes	No
16	March 2015	Insulin Glargine (Genetical Recombination)	Diabetes requiring insulin	[1] Hypoglycemia [2] Hypersensitivity reaction (anaphylaxis with shock, angioneurotic edema, pruritus, exanthema) [3] Injection site reaction [4] Neoplasia [5] Anti-insulin antibody	Specific use-results study	No	1 year	1000	No	No
17	October 2014	Infiximab (Genetical Recombination)	[1] Rheumatoid arthritis [2] Psoriasis vulgaris, Psoriatic arthropathy, Pustular psoriasis, Erythrodermic psoriasis [3] Crohn's disease (severe), Ulcerative colitis (severe)	[1] Serious infection [2] Interstitial pneumonia [3] Tuberculosis [4] Lupus-like syndrome with anti-dsDNA antibody positive [5] Hepatitis B aggravated [6] Demyelination disorder [7] Blood disorder (Pancytopenia, Thrombocytopenia, Leukopenia, Agnucytosis, Haemophagocytic syndrome) [8] Rhabdomyolysis [9] Malignancy [10] Abscess (perianal, colon), Intestinal stenosis / obstruction (Crohn's disease) etc.	[1] Use-results study (Rheumatoid arthritis) [2] Specific use-results study (Psoriasis) [3] Specific use-results study (Crohn's disease, ulcerative colitis)	No	[1] 1 year [2] 1 year [3] 2 years	[1] 1000 [2] 100 [3] 300	No	Yes
18	April 2015	Acidinium Bromide	Symptoms due to airway obstruction in Chronic Obstructive Pulmonary Disease	[1] Cardiovascular events [2] Bronchospasm	Specific use-results study	No	1 year	1000	Yes	No
19	May 2015	Aripiprazole	[1] Schizophrenia [2] Manic state in Bipolar disorder [3] Depression / Depressive state (refractory)	[1] Neuroleptic malignant syndrome [2] Extrapyramidal symptoms [3] Paralytic ileus [4] Anaphylaxis [5] Rhabdomyolysis [6] Hypoglycemia, Diabetic ketoacidosis, Diabetic coma [7] Hypoglycemia [8] Seizure [9] Agnucytosis, leukopenia [10] Pulmonary embolism / Deep venous thrombosis etc.	Specific use-results study	No	up to 1 year	2420	Yes	No
20	April 2014	Enzalutamide	Prostate Cancer refractory to castration	[1] Seizure [2] Thrombocytopenia [3] Interaction with CYP2C8 inhibitor [4] Psychoneuropathy	Specific use-results study	No	2 years	900	Yes	Yes

^a Observational studies for pharmacovigilance planning; ^b Interventional clinical trials for pharmacovigilance where the size is usually much smaller than that in the observational "post-marketing surveillance" and often have a control group.

No	Submission date	Drugs	Indication	Safety Specification	Post-marketing surveillance**			EPPV	Postmarketing Clinical Trials 3		
					Study Design	Comparator	Follow-up period			Size	
21	July 2015	Lidocaine-Proprilocaine cream	Pain relief in Laser therapy / Vessel puncture	[1] Methaemoglobinemia [2] Shock, Anaphylaxis [3] Consciousness disturbance, tremor, Convulsion [4] Central nervous system depression (Somnolence, Convulsion, Parosities etc.) / Cardiac function depression (Cyanosis, Cardiac arrest, Hypoxia etc.) [5] Carcinogenicity	[1] Use-results study [2] Specific use-results study (children)	No	[1] 1 week [2] 1 week	[1] 3000 [2] 300	Yes	No	
22	April 2015	Umeclidinium Bromide (dry powder inhaler)	Symptoms due to airway obstruction in Chronic Obstructive Pulmonary Disease	Cardiovascular events	Use-results study	No	1 year	1000	No	No	
23	February 2015	Nitisinone	Tyrosinemia type I	[1] Ophthalmopathy [2] Thrombocytopenia, Leukopenia, Granulocytopenia [3] Blood tyrosine increased [4] Development / Cognitive disorder [5] Reproductive / Embryological toxicity etc.	Use-results study	No	up to 7 years		8	Yes	No
24	July 2014	Nivolumab (Genetical Recombination)	Malignant melanoma (non-resectable)	[1] Interstitial pneumonia [2] Hepatic dysfunction [3] Thyroid function abnormal [4] Infection reaction [5] Excessive immunisation reaction	Use-results study (all-case surveillance)	No	12 months	All cases in 30 months after marketing (estimated as \$50)	Yes	No	
25	April 2015	Macitentan	Pulmonary arterial hypertension	[1] Anemia, Decreased hemoglobin [2] Teratogenicity [3] Hypotension [4] Pulmonary oedema in patients with Pulmonary veno-occlusive disease [5] Hepatic dysfunction [6] Thrombocytopenia [7] Leukopenia [8] Menstrual disorder [9] Ovarian cyst [10] Testicular disorder, Male infertility	Specific use-results study (long term)	No	up to 3 years	1050	Yes	Yes	
26	August 2015	Olanexidine gluconate	Disinfectant (surgical operation)	[1] Shock	Use-results study	No	30 days	5000	Yes	No	
27	April 2015	Colistin Sodium Methanesulfonate	Infection of colistin-sensitive Escherichia coli, Citrobacter, Klebsiella, Enterobacter, Pseudomonas aeruginosa or Acinetobacter resistant to other antibiotics	[1] Escherichia coli, Citrobacter, Klebsiella, Enterobacter, Pseudomonas aeruginosa or Acinetobacter resistant to other antibiotics [2] Neurotoxicity [3] Pseudomembranous colitis	[1] Use-results study [2] Specific use-results study (on trend of Minimum Inhibitory Concentration, MIC)	No	[1] Not specified [2] trend over 3 years	[1] 200 [2] not applicable	Yes	No	
28	July 2014	Eftrenonacog Alfa (Genetical Recombination)	Bleeding tendency in Patients with Coagulation factor IX deficiency	[1] Neutralizing antibodies [2] Shock, Anaphylaxis [3] Thromboembolism	Use-results study	No	2 years	100	Yes	Yes	
29	May 2015	Gadobutrol	Contrast media for MRI	[1] Shock, Anaphylaxis [2] Seizure [3] Nephrogenic systemic fibrosis, NSF [4] Acute renal failure	Use-results study	No	Not specified	3000	Yes	No	
30	July 2014	Canagliflozin Hydrate	type 2 Diabetes Mellitus	[1] Hypoglycemia [2] Events associated with hypovolemia [3] Genital infection [4] Urinary tract infection [5] Polyuria / Pollakiuria [6] Renal disorder [7] Bone fracture [8] Malnutrition [9] Effect of weight loss [10] Effect of Blood ketone body increased etc.	[1] Specific use-results study (elderly) [2] Specific use-results study (Long term)	No	[1] Up to 1 year [2] 3 years	[1] all old cases (265) within 3 months after marketing [2] 10000	No	Yes	

a Observational studies for pharmacovigilance planning; b Interventional clinical trials for pharmacovigilance where the size is usually much smaller than that in the observational "post-marketing surveillance" and often have a control group.

Appendix 2 Proposal for revision of forms attached to the individual RMPs submitted to the regulatory body specified in the notification (No 0426-1 and No. 0426-2, on April 26, 2012) (See Proposal 4)

Attachment

Appended Form 1

New Drug Product Post-marketing Study Master Plan

Date:

To: Director, Evaluation and Licensing Division

Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Address: (Address of primary place of business of the corporation)

Name: (Name of corporation and name of company representative)

Signature of company representative:

Post-marketing Study Director

Department:

Name:

Summary information about the product is presented below.

Overview of Product

Date of marketing approval application:

Therapeutic category:

Expected reexamination period:

Application category:

Brand name:

Active ingredient:

Content and dosage form:

Expected dosage and administration:

Expected indications:

Comments:

(Appended Form 1: Draft revisions to the last half, and sample completed form)

Overview of Post-marketing Study (PMS) Protocol		
Safety specification	Whether PMS will be conducted Objective of PMS	Date of PMS protocol preparation
Skin disorders (identified risk)	Will PMS be conducted? (<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes [<input type="checkbox"/> Surveillance study <input type="checkbox"/> Clinical study]) The risks of experiencing this event have already been identified, and the company will make every effort to ensure that the risks are minimized.	Jan. 1, 2016
Malaise (identified risk)	Will PMS be conducted? (<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes [<input type="checkbox"/> Surveillance study <input type="checkbox"/> Clinical study]) The risks of experiencing this event have already been identified, and the company will make every effort to ensure that the risks are minimized.	Jan. 1, 2016
Liver disorder (identified risk)	Will PMS be conducted? (<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes [<input type="checkbox"/> Surveillance study <input type="checkbox"/> Clinical study]) The risks of experiencing this event have already been identified, and the company will make every effort to ensure that the risks are minimized.	Jan. 1, 2016
Neutropenia (identified risk)	Will PMS be conducted? (<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes [<input checked="" type="checkbox"/> Surveillance study <input type="checkbox"/> Clinical study]) Whether or not the risk of developing neutropenia is within the expected range will be checked, particularly for patients who normally have low neutrophil counts, such as women and persons with low body weight.	Jan. 1, 2016
Nausea/vomiting (potential risk)	Will PMS be conducted? (<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes [<input checked="" type="checkbox"/> Surveillance study <input type="checkbox"/> Clinical study]) After a certain period has passed post-marketing, an observational study will be conducted using, for example, health insurance claims data.	Jan. 1, 2016
Hypercalcemia (potential risk)	Will PMS be conducted? (<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes [<input type="checkbox"/> Surveillance study <input type="checkbox"/> Clinical study]) Early post-marketing phase vigilance (EPPV) will be conducted for 6 months, and additional post-marketing vigilance activities will be considered if the specified number of reports is exceeded.	Jan. 1, 2016
Serious mental condition (potential risk)	Will PMS be conducted? (<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes [<input type="checkbox"/> Surveillance study <input type="checkbox"/> Clinical study]) EPPV will be conducted for 6 months, and additional post-marketing vigilance activities will be considered if the specified number of reports is exceeded.	Jan. 1, 2016
Anaphylactic shock (potential risk)	Will PMS be conducted? (<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes [<input type="checkbox"/> Surveillance study <input type="checkbox"/> Clinical study]) EPPV will be conducted for 6 months, and additional post-marketing vigilance activities will be considered if the specified number of reports is exceeded.	Jan. 1, 2016
Children (< 15 years old)	Will PMS be conducted?	Jan. 1, 2016

(important missing information)	(<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes [<input checked="" type="checkbox"/> Surveillance study <input type="checkbox"/> Clinical study]) Information about the risks of children developing adverse reactions will be collected to check whether or not there are any major differences compared to the prescribed population overall.	
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Appended Form 2

1. Drug use surveillance protocol
(If multiple surveillance studies with different designs are going to be conducted, then the protocols should be prepared for each design.)
 - (1) Surveillance study design title/name
(Examples: Cohort study, case control study, self-controlled design)
 - (2) Surveillance study objectives
 - A. Hypothesis for confirmation/verification
 - B. Outcome measures
 - (3) Background for formulation of surveillance study design
 - A. Results of surveillance studies conducted overseas and associated published reports and missing information
 - B. Level of urgency until surveillance study results are obtained
 - C. Feasibility (including, for example, the burden place on the health care setting and the ethical difficulties of therapeutic intervention)
 - (4) Data source (e.g., primary data newly obtained by the surveillance study, medical database)
 - (5) Definition of target patient population
 - A. Primary target patient population (e.g., patients treated with the drug product)
 - B. Comparative controls (not needed if the surveillance study is not going to include control group)
 - (6) Number of subjects to be studied, observation period, and rationales
 - A. Primary target population
 - B. Comparative control group
 - C. Observation period (for a self-controlled design, the relationship to the treatment period should be clearly noted)
 - (7) Number of sites expected to conduct the surveillance study
(and, if a medical database is going to be used secondarily, then the scale of the medical database)
 - (8) Expected surveillance study timeline
 - (9) Outcome identification method
(including whether or not existing medical data will be used, and the establishment of an event review committee)
 - (10) Analysis
 - A. Overview of analysis methods
 - B. If a sensitivity analysis is going to be conducted and, if so, the details thereof
 - (11) Surveillance study limitations
(e.g., potential discrepancies between the information that is truly desired and the information that can be obtained by conducting the surveillance study)
 - (12) Organizational structure for conducting the surveillance study
(If a part of the surveillance study activities are going to be outsourced, then the name and address of the party to which activities are going to be outsourced, and the scope of the activities being outsourced)
 - (13) Assurance of transparency/scientific appropriateness (e.g., advance protocol registration/involvement of third parties)
 - (14) Ethical considerations
 - A. Whether or not an ethics review is going to be conducted
 - B. Whether or not informed consent is going to be obtained
 - (15) Other considerations
- Attachments
 - A. Contract documents (draft)
 - B. Synopsis of drug use surveillance (draft)

- C. Drug use surveillance screening form (draft)
- D. Drug use surveillance case report form (draft)

2. Post-marketing clinical study protocol

- (1) Name and address of the party sponsoring the post-marketing clinical study
- (2) If a portion of the study activities is going to be outsourced, then the name and address of the party to which said activities are going to be outsourced, and the scope of the activities in question
- (3) Names and addresses of study sites (numbers of sites by the department planning to conduct the study)
- (4) Names and job titles of persons expected to serve as post-marketing clinical study principal investigators
- (5) Study objectives (if, for example, conducting the study is a post-approval commitment, then this should be noted)
- (6) Overview of the investigational drug
- (7) Study method
- (8) Information pertaining to subject selection (study patient population)
- (9) Number of patients to be enrolled in the study, and the rationale therefor
- (10) Parameters to be investigated in the study, such as observations and assessments
- (11) Planned term of the study
- (12) Parameters to be analyzed, and analysis methods
- (13) Information about access to source documents
- (14) Information about the storage of records (including data)
- (15) If a post-marketing clinical study coordinating investigator is going to be appointed, then the name and job title thereof
- (16) If a post-marketing clinical study coordinating committee is going to be established, then the names and job titles of the investigators comprising said committee
- (17) If an efficacy and safety review committee is going to be established, then this should be noted
- (18) If it is expected that the party sponsoring the post-marketing clinical study is including in the eligible patient population persons for whom the post-marketing clinical study drug is not effective or persons to whom it will be difficult to provide a written explanation of participation in the post-marketing clinical study and from whom it will therefore be difficult to obtain written informed consent in advance, then those facts should be noted, and the following explanations should be provided.
 - A. An explanation of the fact that the post-marketing clinical study in question must be conducted in patients to whom it is expected that it will be difficult to provide a written explanation and obtain written informed consent to study participation in advance
 - B. An explanation of the fact that the expected disadvantages for subjects of the post-marketing clinical study will be the minimum necessary
- (19) If the party sponsoring the post-marketing clinical study is planning on including in the study population persons for whom it is expected that it will be difficult to provide a written explanation and obtain written informed consent to study participation in advance, then those facts should be noted, and the following explanations should be provided.
 - A. An explanation of the fact that current treatment methods cannot be expected to be sufficiently effective in the persons who comprise the intended study population
 - B. An explanation of the fact that there is a good possibility that the use of the investigational drug will make it possible for the persons who comprise the intended study population to avoid life-threatening risks.
 - C. The fact that an efficacy and safety review committee is being established
- (20) The organizational structure for conducting the study (if the organizational structure is the same as that noted in the PMS master plan, then this should be noted)
- (21) Other necessary information

- Attachments
- A. Contract documents (draft)
- B. Explanation sheet (draft) and informed consent form (draft) for subjects
- C. Post-marketing clinical study screening form (draft)
- D. Case report form (draft)