Pharmaceuticals and Medical Devices Safety Information

No. 355 August 2018

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* publication is issued reflective of safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) Medical Product Information web page (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only in Japanese).

Available information is listed here

Access to the latest safety information is available via the PMDA Medi-navi.

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Published by:
Ministry of Health, Labour and Welfare

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This English version of the PMDSI is intended to serve as a reference material for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the former shall prevail. PMDA shall not be responsible for any consequence resulting from use of this English version.

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No. 355 August 2018

Ministry of Health, Labour and Welfare & Pharmaceutical Safety and Environmental Health Bureau, Japan

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Review of Contraindications for Immunosuppressants in Pregnant Women, etc.**		The Ministry of Health, Labour and Welfare (MHLW) established the Japan Drug Information Institute in Pregnancy (JDIIP) in the National Center for Child Health and Development in October 2005 to provide consultations and to conduct investigations. Since 2016 particularly, we have been engaged in a project to promote the reflection of information on drug use in pregnant women, etc. in package inserts by organizing and assessing the information accumulated so far by the JDIIP. On July 10, 2018, precautions for 3 immunosuppressants were revised based on the discussions at the working group composed of experts from the JDIIP and PMDA. This section will introduce the details of the revision.	4
2	**List of Products Subject to Early Post-marketing Phase Vigilance**		List of products subject to Early Post-marketing Phase Vigilance as of June 30, 2018.	8
3	**(Reference) Revision of the Ministerial Ordinance on Good Post-marketing Study Practice (GPSP Ordinance)**		In the context that MID-NET, which was constructed with the engagement of MHLW and PMDA, starts full-scale operation in fiscal year 2018, the GPSP Ministerial Ordinance was revised in advance to ensure the reliability of the materials related to reexamination applications in case medical safety information databases are utilized to prepare such materials. This section will introduce the details of the revision.	10

E: Distribution of Dear Healthcare Professional Letters of Emergency Communication *R*: Distribution of Dear Healthcare Professional Letters of Rapid Communications *P*: Revision of Precautions *C*: Case Summaries

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of providers of medical care and pharmaceutical products.

If providers of medical care and pharmaceutical products such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As providers of medical care and pharmaceutical products, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse drug reaction
BP	Blood pressure
EPPV	Early post-marketing phase vigilance
FY	Fiscal year
GPSP	Good post-marketing study practice
JDIIP	Japan Drug Information Institute in Pregnancy
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MID-NET	Medical Information Database NETwork
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
WG	Working group

1

Review of Contraindications for Immunosuppressants in Pregnant Women, etc.

1. Introduction

When drugs are used during pregnancy, due attention must be paid to the effects on the fetus as well as on the mother. On the other hand, due to excessive concern about the risks associated with the use of drugs, the physician refrains from prescribing required medication or the patient quits taking a drug at her own discretion in some cases, which may worsen her condition and even affect the fetus. In other cases, the patient gives up becoming pregnant from the beginning because she is using a drug for the treatment of a chronic disease.

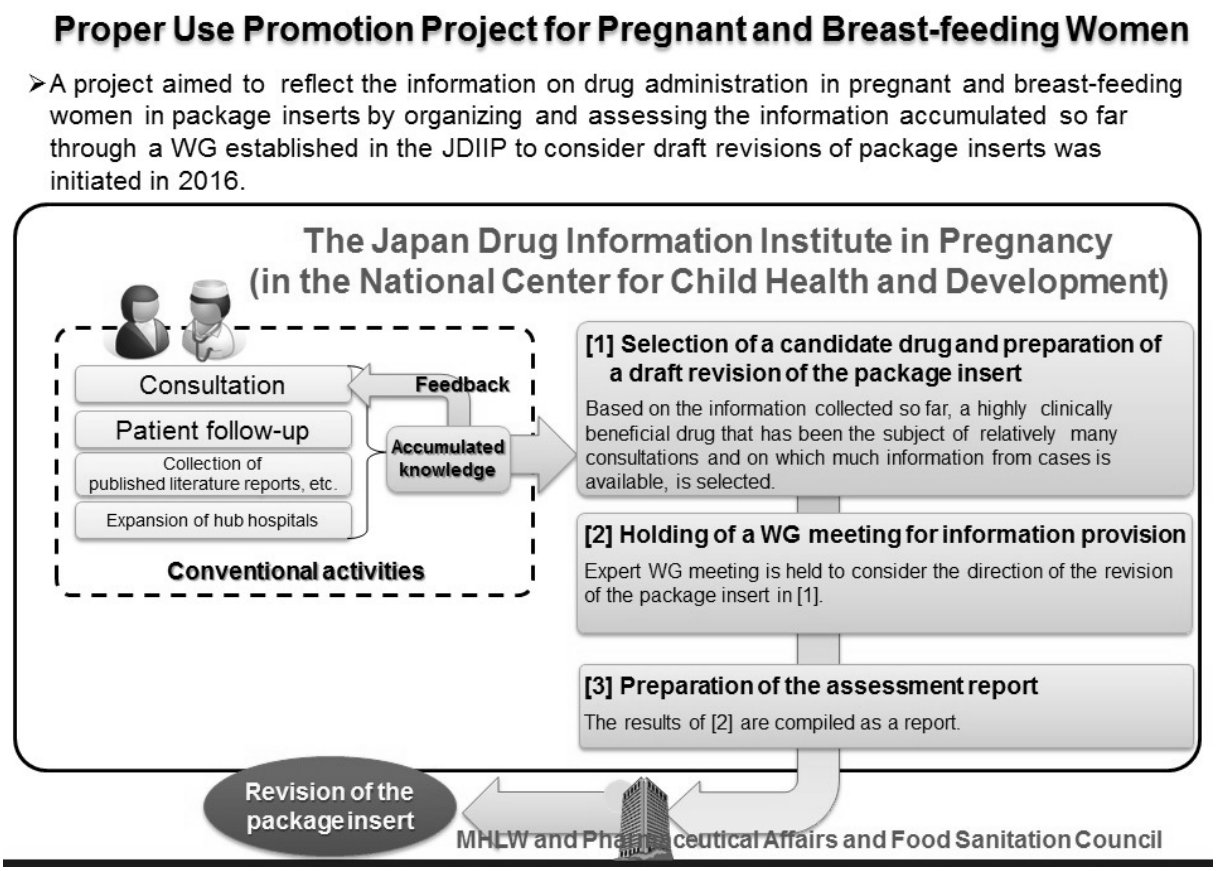
The package insert of each drug does not always provide adequate information on the effects of the drug when used during pregnancy on the fetus. To address this issue, the Japan Drug Information Institute in Pregnancy (JDIIP) was established in the National Center for Child Health and Development in October 2005 under the Proper Use Promotion Project for Pregnant and Breast-feeding Women by the Ministry of Health, Labour and Welfare (MHLW).

The JDIIP collects and assesses the latest evidence such as the effects of drugs on the fetus, and uses the information to provide consultation services to pregnant women and women who wish to become pregnant. The JDIIP also investigates pregnancy outcomes in consulters to establish new evidence.

Since 2016, we have been engaged in a project to promote the reflection of information on drug use in pregnant women, etc. in package inserts by organizing and assessing the information accumulated so far by the JDIIP. In this project, a working group (WG) composed of experts from the JDIIP has been established to consider draft revisions of package inserts, and the WG selects a candidate drug, organizes and evaluates the information accumulated so far, and compiles the draft revision of the package insert for the drug as a report (Figure 1).

Recently, we revised the package inserts of 3 immunosuppressants based on the results of the investigation by the WG. Details of the revision are introduced below.

Figure 1. Proper use promotion project for pregnant and breast-feeding women



2. Details of the Review by the WG

Table 1. List of target products

Active ingredient Brand name (name of company)	Active ingredient	Brand name (name of company)
	a. Tacrolimus hydrate b. Ciclosporin c. Azathioprine	a. Prograf Capsules 0.5 mg (Astellas Pharma Inc.) and the others b. Sandimmum for I.V. Infusion 250 mg (Novartis Pharma K.K.) and the others c. Imuran Tablets 50 mg (Aspen Japan K.K.) and the others
Therapeutic category	Miscellaneous metabolism agents	
Indications	Prophylaxis of rejection in organ transplants, etc.	

The 3 immunosuppressants (tacrolimus hydrate, ciclosporin, and azathioprine) are contraindicated in pregnant women or women who may be pregnant in their package inserts because these drugs have been shown to be teratogenic in animal studies.

On the other hand, with the improvement of the long-term prognosis of organ transplant patients with the use of immunosuppressants, and of the results of autoimmune disease treatment with co-administration of immunosuppressants, continuation of treatment in pregnant patients is regarded as an issue, and the medical need for continued treatment has been pointed out, as represented by the large number of 295 consultations on the 3 immunosuppressants with the JDIIP for (since October 2005), etc.

Taking these circumstances into consideration, the WG reviewed the precaution for pregnant women, etc. in the package inserts of these 3 immunosuppressants based on the evaluation and

analysis of safety information obtained in Japan and overseas, and compiled a report.

The evaluation and analysis by the WG led to the conclusion that it would be appropriate to remove “pregnant women or women who may be pregnant” from the contraindications of these 3 immunosuppressants, provided that it is specified as a precaution that this drug should only be administered to them if the potential therapeutic benefits are considered to outweigh the potential risks, for the reasons described below.

As for azathioprine, which has been shown to be teratogenic as well as genotoxic in non-clinical studies, it was determined necessary to take a precaution against pregnancy during treatment with this drug for women with reproductive potential or men having partners with reproductive potential.

(1) Although teratogenicity has previously been reported in animal studies, the results of overseas epidemiological studies that were comprehensively collected and evaluated by the JDIIP showed that there were no reports of a significant increase in the incidence of congenital anomalies in the fetuses of pregnant women treated with immunosuppressants.
(2) Japanese and overseas guidelines, etc. allow the use of immunosuppressants in pregnant women.
(3) In overseas package inserts, administration to pregnant women is basically not specified as a contraindication, and is allowed only if the potential therapeutic benefits outweigh the possible risks to the fetus because placental transfer has actually been observed, etc.
(4) Azathioprine has been shown to be genotoxic in non-clinical studies.

As for the Use during Pregnancy, Delivery, or Breastfeeding section, which currently provides data on teratogenicity, etc. observed in non-clinical studies, it was determined appropriate to additionally describe clinical data on pregnancy outcomes, effects on the fetus, etc. based on recent findings.

3. Review of Contraindications for Immunosuppressants in Pregnant Women, etc.

Recently, we discussed the revision of package inserts based on the results of consideration by the WG and the draft revisions of the package inserts proposed by the PMDA at the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 3rd meeting) on June 26, 2018.

Based on the discussion at the Subcommittee meeting, the MHLW issued a notification to instruct the revision of the package inserts of 3 immunosuppressants on July 10, 2018. Details of the revision are introduced below.

(1) Delete “pregnant women or women who may be pregnant” from the Contraindications section.
(2) Add a statement “this drug should only be administered if the potential therapeutic benefits are considered to outweigh the potential risks” in the Use during Pregnancy, Delivery, or Breastfeeding section.
(3) Add clinical data on pregnancy outcomes, effects on the fetus, etc. in the Use during Pregnancy, Delivery, or Breastfeeding section.
(4) (Only for azathioprine) Delete the language concerning contraception in the Important Precautions section, and add statements that women should be counseled to avoid pregnancy whenever possible while receiving this drug and that women with reproductive potential or men having partners with reproductive potential should be informed about the risks associated with this drug in the Use during Pregnancy, Delivery, or Breastfeeding section.

4. Closing Comments

The present revision of the package insert is not intended to allow unconditionally the use of immunosuppressants in pregnant women or women who may be pregnant, which has previously been uniformly prohibited. Physicians prescribing immunosuppressants must carefully decide whether to administer the drug or not while closely monitoring the condition of the patient’s disease and weighing the expected therapeutic benefits against the possible risks associated with the treatment. Healthcare professionals are requested to understand the intention of the present

revision and the proper use of these drugs.

5. References

・ 2018 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (3rd meeting)
http://www.mhlw.go.jp/stf/shingi2/0000213222.html (only in Japanese)

・Revision of Precautions (Pharmaceutical Safety and Environmental Health Bureau [PSEHB]/Pharmaceutical Safety Division [PSD] Notification No. 0710-1, dated July 10, 2018)
http://www.mhlw.go.jp/content/11120000/000331161.pdf (only in Japanese)
http://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0006.html

2

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect ADR data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of June 30, 2018)
◎: Products for which EPPV was initiated after June 1, 2018

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Japanese cedar pollen extract Cedarcure Japanese Cedar Pollen Sublingual Tablets 2,000 JAU, 5,000 JAU	Torii Pharmaceutical Co., Ltd.	June 29 2018
◎	Ibuprofen L-lysine Ibulief I.V. Injection 20 mg	Senju Pharmaceutical Co., Ltd.	June 14, 2018
◎	Rasagiline mesilate Azilect Tablets 0.5 mg, 1 mg	Takeda Pharmaceutical Company Limited.	June 11, 2018
◎	Sirolimus Rapalimus Gel 0.2%	Nobelpharma Co., Ltd.	June 6, 2018
◎	Pemafibrate Parmodia Tab. 0.1 mg	Kowa Company, Ltd.	June 1, 2018
	Migalastat hydrochloride Galafold Capsules 123 mg	Amicus Therapeutics, Inc.	May 30, 2018
	Letermovir Prevymis Tablets 240 mg, Prevymis Intravenous Infusion 240 mg	MSD K.K.	May 28, 2018
	Mepolizumab (genetical recombination) [*1] Nucala for S.C. Injection 100 mg	GlaxoSmithKline K.K.	May 25, 2018
	Ipilimumab (genetical recombination) Yervoy Injection 50 mg	Bristol-Myers Squibb K.K.	May 25, 2018
	Nivolumab (genetical recombination) Opdivo I.V. Infusion 20 mg, 100 mg	Ono Pharmaceutical Co., Ltd.	May 25, 2018
	Botulinum toxin type A [*2] Botox for Injection 50 Units, 100 Units	GlaxoSmithKline K.K.	May 25, 2018
	Tofacitinib citrate [*3] Xeljanz Tablets 5 mg	Pfizer Japan Inc.	May 25, 2018
	Emicizumab (genetical recombination) Hemlibra Subcutaneous Injection 30 mg, 60mg, 90 mg, 105 mg, 150 mg	Chugai Pharmaceutical Co., Ltd.	May 22, 2018
	Guselkumab (genetical recombination) Tremfya Subcutaneous Injection 100 mg Syringe	Janssen Pharmaceutical K.K.	May 22, 2018

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Evocalcet Orkedia Tablets 1 mg, 2 mg	Kyowa Hakko Kirin Co., Ltd.	May 22, 2018
Hydromorphone hydrochloride Naruvein Injection 2 mg, 20 mg	Daiichi Sankyo Propharma Co., Ltd.	May 16, 2018
Bedaquiline fumarate Sirturo Tablets 100 mg	Janssen Pharmaceutical K.K.	May 8, 2018
Ezetimibe/atorvastatin calcium hydrate Atozet Combination Tablets LD, HD	MSD K.K.	April 23, 2018
Dupilumab (genetical recombination) Dupixent S.C. Injection 300 mg Syringe	Sanofi K.K.	April 23, 2018
Elobixibat hydrate Goofice Tablets 5 mg	EA Pharma Co., Ltd.	April 19, 2018
Olaparib Lynparza Tablets 100 mg, 150 mg	AstraZeneca K.K.	April 18, 2018
Inotuzumab ozogamicin (genetical recombination) Besponsa Injection 1mg	Pfizer Japan Inc.	April 18, 2018
Benralizumab (genetical recombination) Fasenra Subcutaneous Injection 30 mg Syringe	AstraZeneca K.K.	April 18, 2018
Brexpiprazole Rexulti Tablets 1 mg, 2 mg	Otsuka Pharmaceutical Co., Ltd.	April 18, 2018
Atezolizumab (genetical recombination) Tecentriq I.V. Infusion 1200 mg	Chugai Pharmaceutical Co., Ltd.	April 18, 2018
Romidepsin Istodax Injection 10 mg	Celgene Corporation	April 18, 2018
Baloxavir marboxil Xofluza Tablets 10 mg, 20mg	Shionogi & Co., Ltd.	March 14, 2018
Abatacept (genetical recombination)*4 Orencia for I.V. Infusion 250 mg	Bristol-Myers Squibb K.K.	February 23, 2018
Sarilumab (genetical recombination) Kevzara 150 mg, 200 mg Syringe for SC Injection	Sanofi K.K.	February 5, 2018
Sildenafil citrate Revatio Dry Syrup for Suspension 900 mg,	Pfizer Japan Inc.	January 29, 2018
Esomeprazole magnesium hydrate Nexium Capsules 10 mg, 20 mg, Nexium Granules for Suspension 10 mg, 20 mg	AstraZeneca K.K.	January 19, 2018

*1 Eosinophilic granulomatosis with polyangiitis that does not adequately respond to existing treatments

*2 Spasmodic dysphonia

*3 Remission induction or maintenance therapy for moderate to severe ulcerative colitis (for use only in patients who were not sufficiently responsive to conventional treatments)

*4 Polyarticular juvenile idiopathic arthritis that does not adequately respond to existing treatments

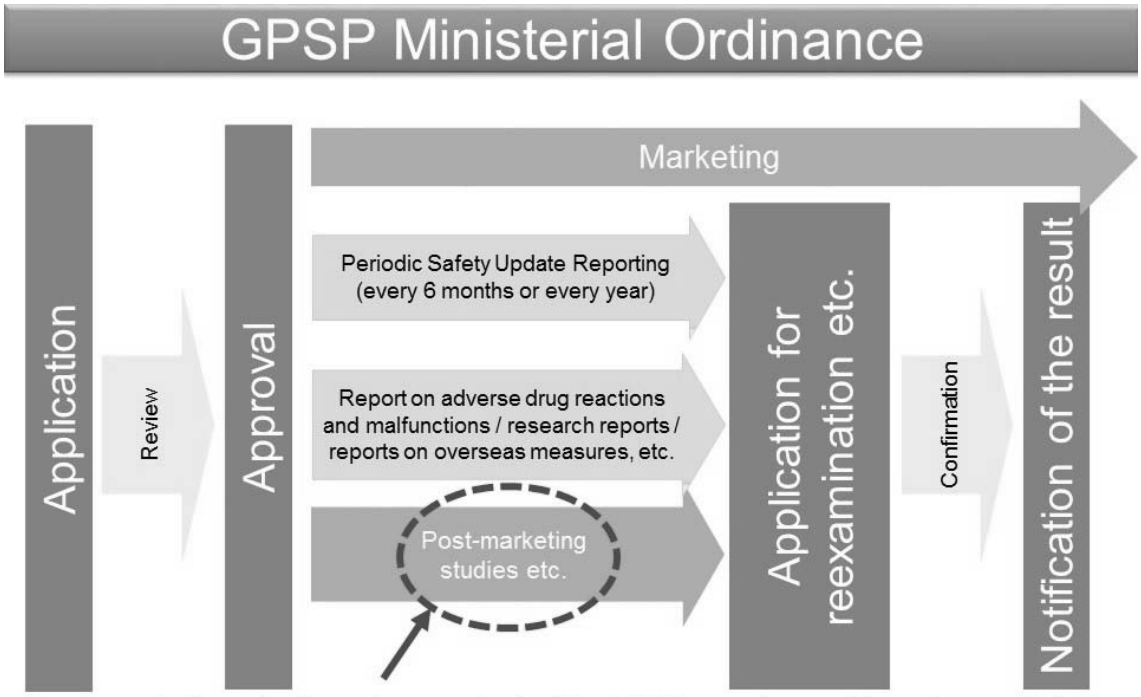
(Reference)

Revision of the Ministerial Ordinance on Good Post-marketing Study Practice (GPSP Ordinance)

1. Introduction

As introduced in Pharmaceuticals and Medical Devices Safety Information No. 351, the MHLW and PMDA had been moving forward with the construction of a medical information database, Medical Information Database NETwork (MID-NET), which started its full-scale operation in FY2018. Prior to this, in order to ensure the reliability of materials attached to the application for reexamination and reevaluation when medical information databases are used for post-marketing studies of drugs as a basis for such materials, the Ministerial Ordinance for Partial Revision of the Ministerial Ordinance on Good Post-marketing Study Practice (MHLW Notification No. 116, 2017; hereinafter referred to as Revised GPSP Ordinance) was issued on October 26, 2017, and enforced on April 1, 2018. In the Revised GPSP Ordinance, the definition of "post-marketing database studies" was additionally provided, and regulations were organized to clarify that "Post-marketing observational studies with primary data collection (drug use-results surveys) " are studies conducted using information collected from medical institutions.

This report introduces such post-marketing studies under the Revised GPSP Ordinance.



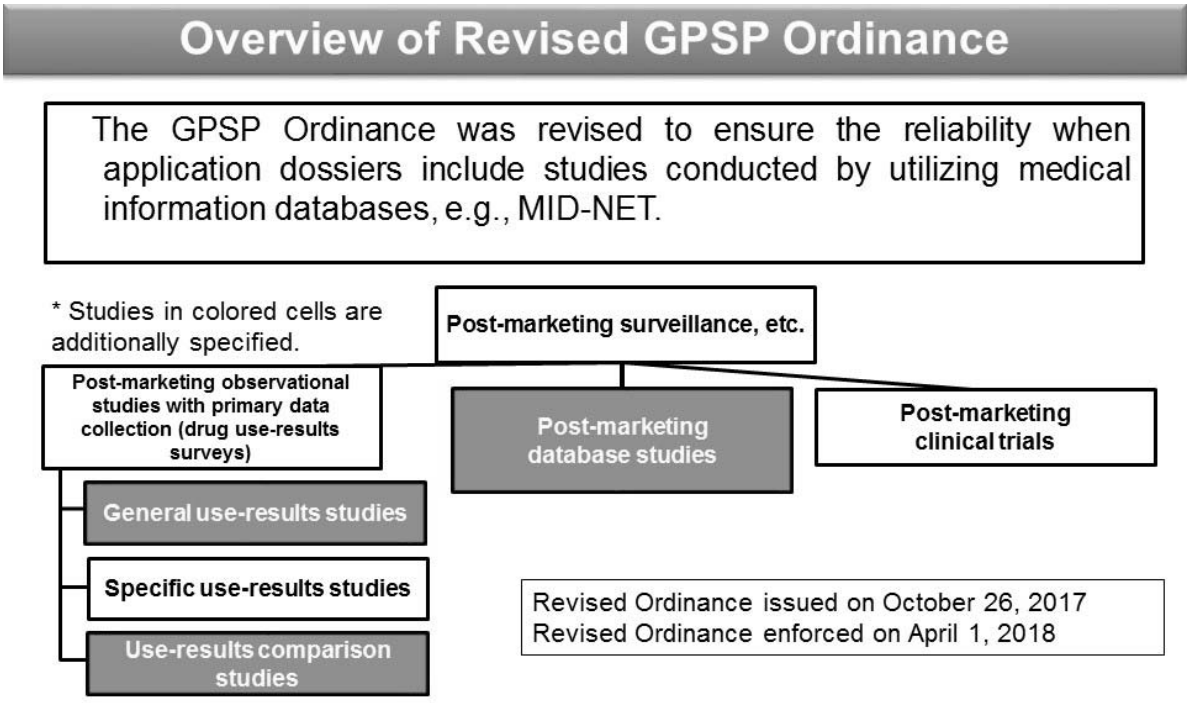
Post-marketing studies etc. conducted by MAHs must meet the given reliability criteria (GPSP Ordinance: Good Post-marketing Study Practice Ministerial Ordinance).

2. Type of Post-marketing Studies

In the previous GPSP Ordinance, the following 3 types of studies had been defined as post-marketing studies: "Post-marketing observational studies with primary data collection (drug use-results surveys)," "post-marketing clinical trials" and as one type of Post-marketing observational studies with primary data collection (drug use-results surveys), "specific use-results studies." In the Revised GPSP Ordinance, on the other hand, "post-marketing database studies" are specified as post-marketing studies, in addition to "Post-marketing observational studies with primary data

collection (drug use-results surveys)." and "post-marketing clinical trials." Furthermore "post-marketing observational studies with primary data collection (drug use-results surveys)" are further categorized into "general use-results studies," "specific use-results studies," and "use-results comparison studies." Individual definitions are shown in the table. The Revised GPSP Ordinance explicitly specifies that "post-marketing database studies" are studies conducted using "medical information databases" (collection of information including medical records, which is structurally organized for search on a computer), whereas "post-marketing observational studies with primary data collection (drug use-results surveys)" are studies conducted using information collected directly from medical institutions.

"Use-results comparison studies" had conventionally been conducted as one type of "post-marketing observational studies with primary data collection (drug use-results surveys)" but are additionally listed under post-marketing observational studies with primary data collection (drug use-results surveys) to clarify that a study can be conducted under GPSP ordinance not only based on information of patients who are using a particular pharmaceutical product but also based on information of patients who are not using the relevant pharmaceutical product, both of which are collected from medical institutions for comparison. Post-marketing observational studies with primary data collection (drug use-results surveys) other than specific use-results studies and use-results comparison studies fall under the category of "general use-results studies."



Category	Subcategory	Definition
Post-marketing observational studies with primary data collection (drug use-results surveys)		Studies conducted using information collected from medical institutions to detect and confirm information on the incidence of adverse drug reactions by drug class, and information on the quality, efficacy, and safety of drugs in medical practice.
	General use-results studies	Studies conducted without specifying the condition of the patients using the drug in question (excluding drug use-results comparison studies).
	Specific use-results studies	Studies conducted while specifying the condition of the patients who use the drug in question, e.g., children, elderly people, pregnant and parturient women, or those with renal or hepatic impairment, long-term users, and other specified drug use conditions (excluding use-results comparison studies).
	Use-results comparison studies	Studies conducted by comparing the information of patients using the drug in question and patients not using the drug.
Post-marketing database studies		Studies conducted using medical information databases to detect and confirm information on the incidence of adverse drug reactions by drug class and information on the quality, efficacy, and safety of the drugs.
Post-marketing clinical trials		Trials conducted using approved dosages and administration, and indications to verify the inferences etc. drawn from assessment of the results of clinical trials for marketing authorization, post-marketing observational studies with primary data collection (drug use-results surveys), and post-marketing database studies, or to collect information that cannot be obtained in medical practice.

3. Closing Comments

Not only marketing authorization holders (MAHs), but also medical institutions constitute integrally the conduct of post-marketing studies. We sincerely appreciate their understanding of the contents of the Revised GPSP Ordinance and continued cooperation for the surveillance.