Pharmaceuticals and Medical Devices Safety Information

No. 351 March 2018

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on 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 available in Japanese language).

Available information is listed here

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Pharmaceuticals and Medical Devices Safety Information

No. 351 March 2018

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

[Outline of Information]

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 Reports

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

If medical and pharmaceutical providers 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 medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse drug reaction
AMED	Japan Agency for Medical Research and Development
CT	Computed tomography
DPC	Diagnosis Procedure Combination
EPPV	Early Post-marketing Phase Vigilance
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FY	Fiscal year
GPSP	Good Post-marketing Study Practice
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
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
SD	Safety Division

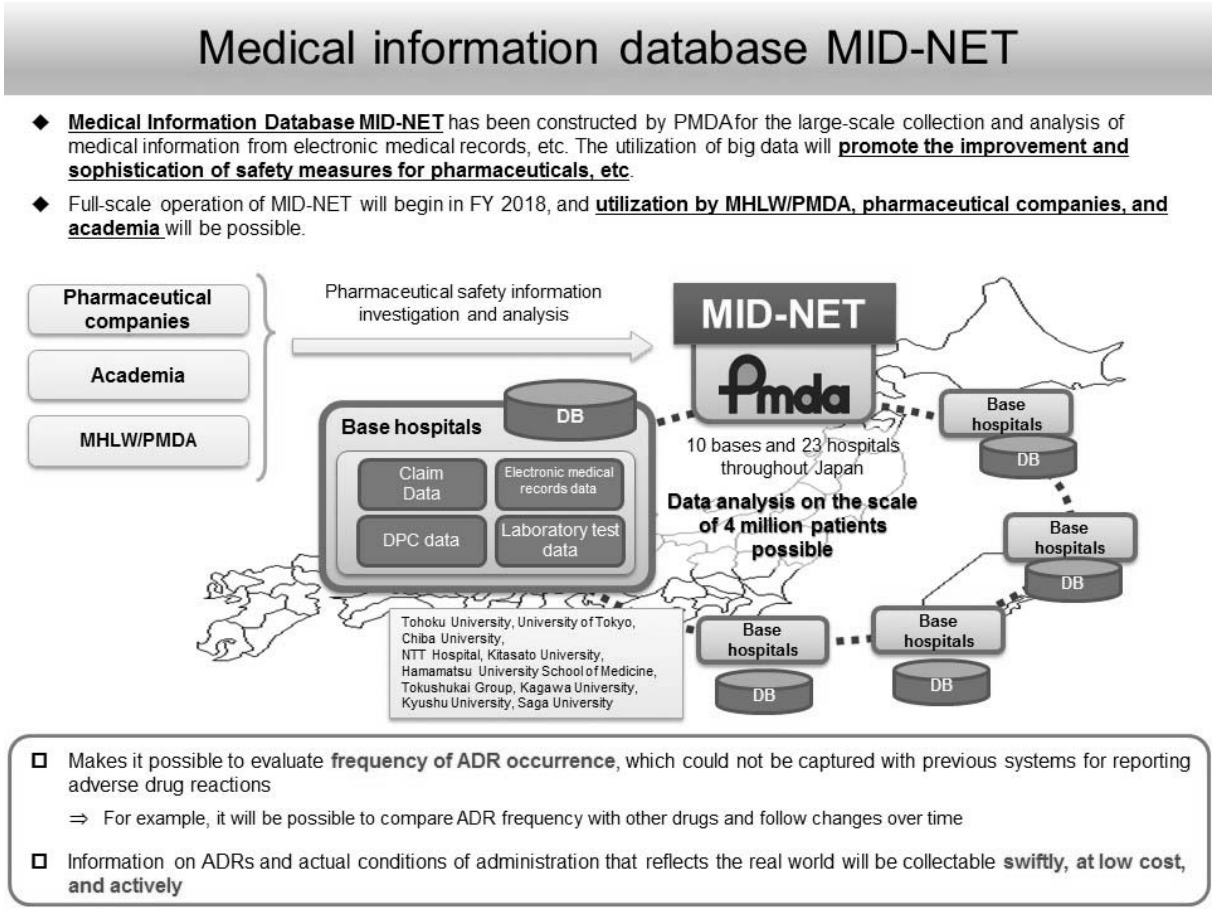
1

Medical Information Database MID-NET (Medical Information Database NETwork)

1. Introduction

The Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA) have been moving forward with the construction of a medical information database, Medical Information Database Network known as MID-NET. Through collaboration with 10 cooperating medical institutions nationwide, MID-NET is capable of collecting and analyzing medical information (electronic medical records, claim data, etc.) on a scale exceeding 4 million people, and we plan to make extensive use of it in drug safety measures, such as analysis of adverse drug reactions. This report introduces MID-NET, which will begin full-scale operations on April 1, 2018 (Fig. 1).

Fig. 1



2. Background of the MID-NET project

The basics of drug safety measures are to collect and evaluate information, such as on the actual conditions of drug use and the status of adverse drug reaction (ADR) occurrence, and then take appropriate action. Accordingly, the collection of information is central to safety measures, but at present the mainstream in information collection is ADR reports from pharmaceutical companies and medical institutions, together with drug use results surveys. The following problems exist with information obtained through these methods: [1] it is not possible to assess the frequency of ADR occurrence because the number of users of the drug (population parameter) is unknown, [2] it is not possible to compare the frequency of ADR occurrence with other drugs, [3] it is difficult to differentiate between ADRs and the symptoms of the underlying disease.

Out of a recognition of these situations, the 2010 Review on the Pharmaceutical Administration to Prevent Recurrence of Yakugai (Drug-induced suffering) (final proposal) and the resulting Proposal on drug safety and security through utilization of an electronic medical information database (Japan Sentinel Project) indicated a need to promote safety measures that utilize a large-scale medical information database that makes up for the limitations of conventional safety measures that are centered on spontaneous reports of ADRs, etc., and drug use results surveys.

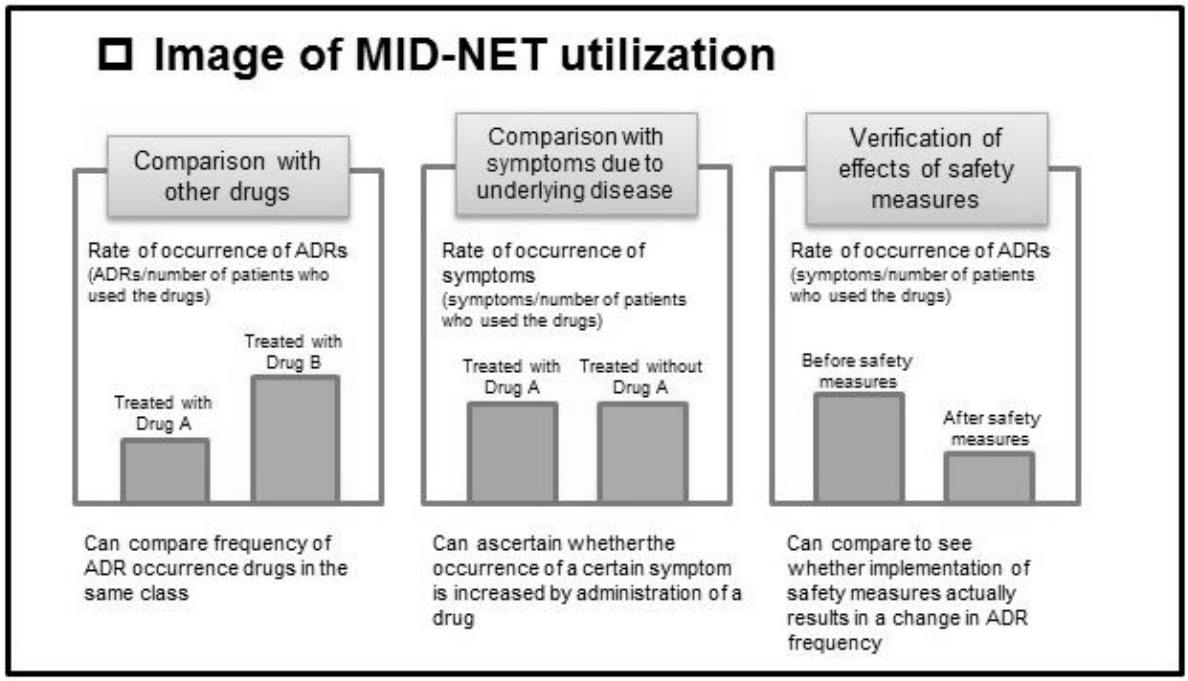
Well then, what specifically will be possible with the medical information database (Fig. 2)? Firstly, since it will be possible to calculate the frequency of occurrence for adverse drug reactions (number of ADR occurrences/number of people using the drug), it will become possible to compare ADR frequencies among drugs in the same class. Moreover, by making a comparison of adverse event frequencies between a group of patients treated with a certain drug and another group that is not so treated, it will be possible to examine whether that an event is an ADR caused by the drug or is instead caused by the underlying disease. By tracking the status of ADR occurrence over time, we can also expect to be able to verify whether the implementation of a safety measure has been effective or not in preventing ADRs.

These are not the only merits of the medical information database. Because eligible patients are usually strictly predefined in clinical trials including trials for marketing authorization, it is difficult to obtain data on patients with a past medical history, as well as pediatric or elderly patients, but since the database collects information without differentiating patients, it can more accurately reflect the actual situation (real world data). Up until now, pharmaceutical companies have had to spend a long time to perform large-scale drug use results surveys at enormous cost, but using database analysis instead is expected to lead to large-scale reductions in personnel and financial costs in pharmaceutical companies and medical institutions.

Looking overseas, we find that the United States began construction of a proactive pharmacovigilance system using a medical information database based on the Food and Drug Administration Amendments Act (FDAAA) of 2007. This project is called the Sentinel Initiative, and it has now reached the point where it can analyze information from claim data for approximately 200 million people. Construction of platforms for the utilization of medical information is proceeding apace in other Western countries as well.

In response to this, Japan launched the Medical Information Database Infrastructure Project in the fiscal year (FY) 2011 and has proceeded to construct medical information database MID-NET while involving 10 bases (cooperating medical institutions) throughout the country in the planning.

Fig. 2

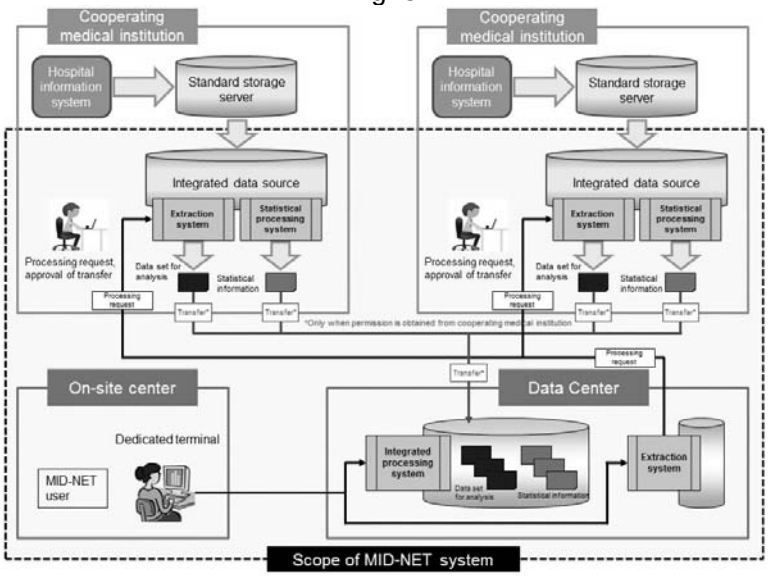


3. Overview and characteristics of MID-NET

We will now explain the overview of MID-NET. In MID-NET, databases are set up in 10 cooperating medical institutions (7 hospitals and 3 hospital groups), and they collect and accumulate data from Diagnosis Procedure Combination (DPC), electronic medical records, and laboratory test values. The databases at the cooperating medical institutions are linked to the PMDA Data Center through a network, and the data necessary for analysis is brought together at the Data Center from the various bases in a mechanism that allows for statistical analysis (Fig. 3). At the point in time where full-scale operation of MID-NET begins in FY 2018, we expect to be able to analyze data from a total of over 4 million people at the 10 bases.

A major characteristic of MID-NET is that it can analyze laboratory test data. Analyzing laboratory test data in addition to the diagnoses and prescribing information that can be collected from claim data, not only makes it possible to directly detect ADRs from changes in the test values, but also to combine multiple types of information thereby allowing to evaluate a greater diversity of ADRs.

Fig. 3



In line with the aims of the Medical Information Database Infrastructure Project, the objectives of utilizing MID-NET are [1] to operate around a main axis of safety measures of drugs, etc., including post-marketing surveillance and risk-benefit assessment, in addition to publicly funded research, and [2] conduct investigations and studies that are of high utility and serve the public interests (Fig. 4).

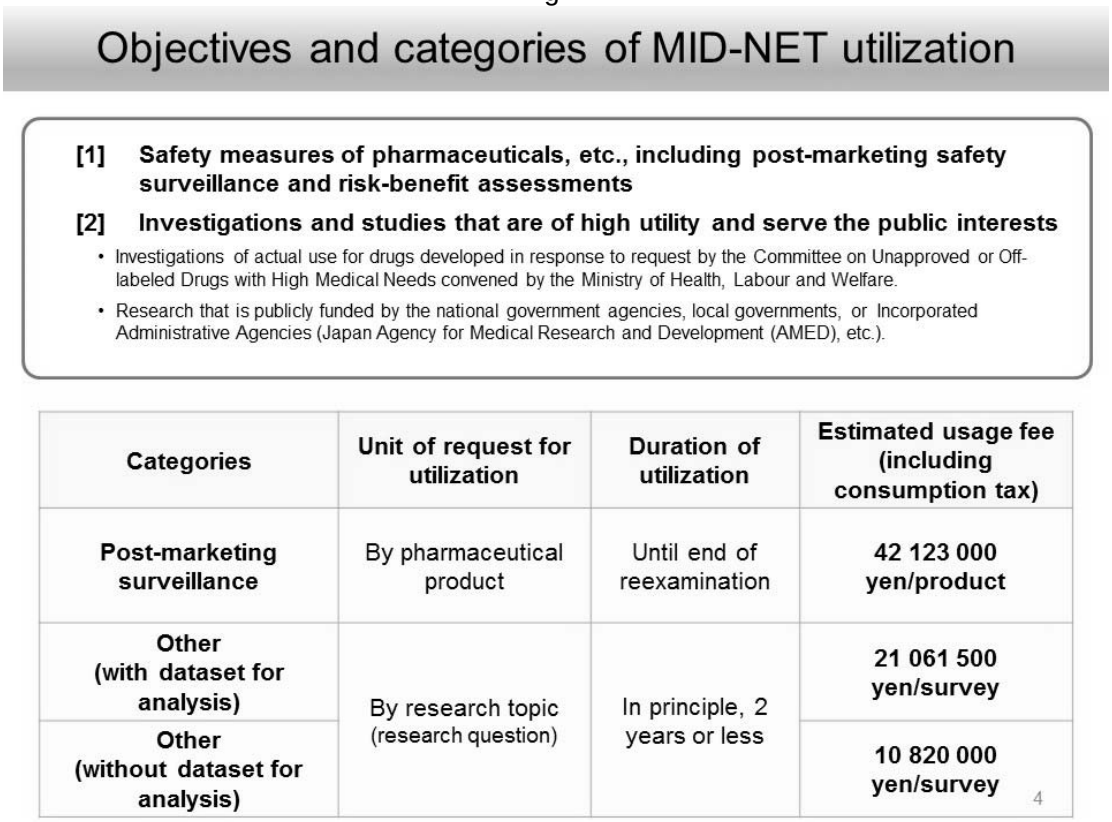
As previously stated, what we first envision as a specific use of MID-NET is post-marketing surveillance conducted by pharmaceutical marketing authorization holders (MAHs). The Good Post-marketing Study Practice (GPSP) Ordinance was amended in October 2017, and post-marketing database investigations were positioned by the ordinance as one type of post-marketing surveillance, etc., (to be enforced in April 2018) in addition to the use-results surveys and specific use-results surveys through which information has been collected directly from medical institutions thus far. Utilization of the database is expected to make it possible to conduct more advanced and efficient surveys based on epidemiological analyses. Moreover, PMDA plans to utilize MID-NET in the investigation of safety measures, and it can also be used by academia to conduct scientific research.

On the basis of discussion in the Committee on the Operation of Medical Information Databases, the general principle of having users bear the cost of the operation of MID-NET in the form of a usage fee has been established. The usage fee has been set at a level where annual operating costs and income from usage will balance out under conditions of stable operation. In the future, it will be necessary to make public announcements of income and expenditures and reset the usage fee as necessary to reflect actual operating conditions.

4. Examples of trial use of MID-NET

In advance of the full-scale start of operations in FY 2018, trial use of MID-NET is now being conducted by PMDA. The following are brief introductions of two of these examples of trial use that were announced by the Committee on the Operation of Medical Information Databases: (1) assessment of the actual prescribing practices of codeine-containing preparation and the risk for respiratory depression, and (2) investigation of the effects of safety measures on serious hypocalcaemia caused by Ranmark Subcutaneous Injection 120 mg.

Fig. 4



(1) Assessment of the actual prescribing practices of codeine-containing preparations and the risk for respiratory depression

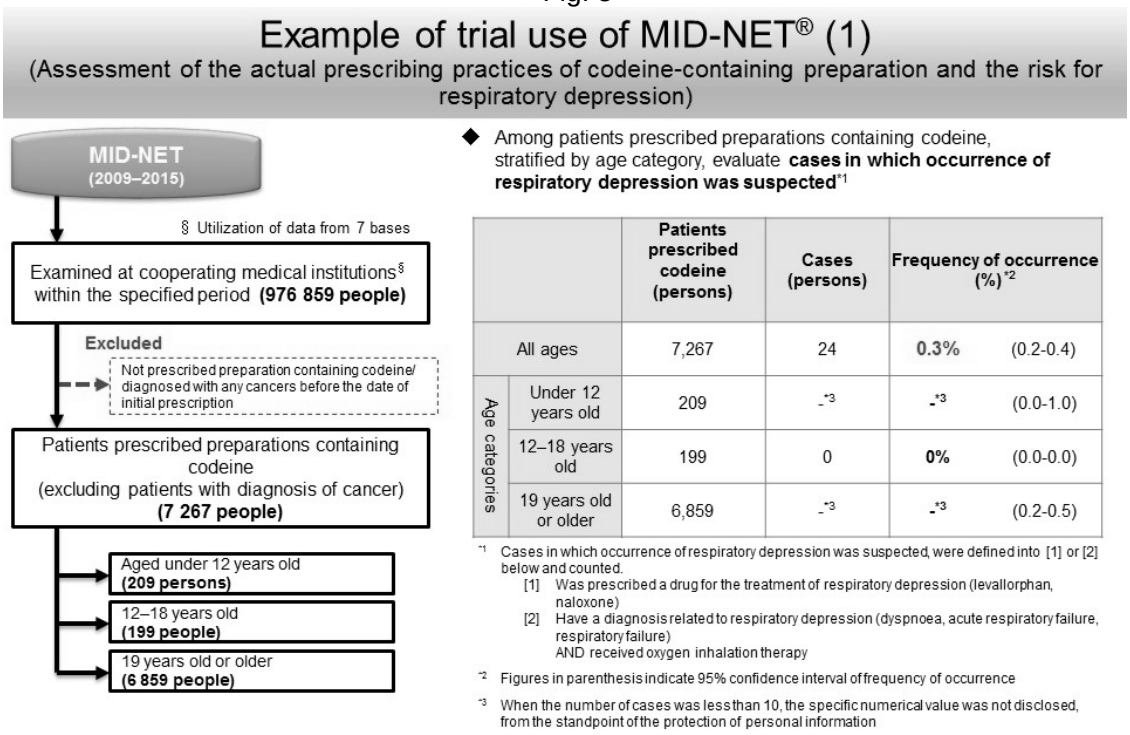
Drugs that contain the morphine-like ingredient codeine are used for antitussive and analgesic purposes, but in children there is a risk of very rare occurrences of the serious adverse reaction of respiratory depression, and prescribing is restricted overseas. In Japan, on the other hand, Revision of Precautions, which was issued in July of last year, states “the drug should not be used in children younger than 12 years old because serious respiratory depression may occur.”[1] In connection with this measure, an attempt was made to evaluate the risk of respiratory depression associated with codeine-containing preparations in MID-NET as well (Fig. 5).

The analysis first looked at the actual prescribing practices of codeine-containing preparations to non-cancer patients. The cases analyzed by MID-NET were the 7 267 cases remaining after patients diagnosed with cancer were eliminated from the patients prescribed codeine-containing preparations among all 976 856 patients examined at cooperating medical institutions. Among the cases analyzed, 209 were patients under the age of 12 and 199 were between the ages of 12 and 18, confirming that codeine-containing preparations were actually prescribed for children.

Moreover, in order to evaluate the risk for respiratory depression, cases in which the occurrence of respiratory depression was suspected were defined as those “prescribed therapeutic agents” or those with “a related diagnosis and implementation of oxygen inhalation therapy”, and the frequency of cases affected by the definitions was calculated. As a result, it was confirmed that respiratory depression was suspected in 24 of the 7 267 cases in the patient population, or in 0.3%. Thus, MID-NET is thought to be extremely useful as a tool for rapidly evaluating the frequency with which an adverse reaction occurs.

As shown in Fig. 5, cases in which the occurrence of respiratory depression was suspected in patients under the age of 12 are marked with “-” to indicate non-disclosure of information. This is because of the MID-NET rule that blocks the information where the number of cases is less than 10 from the standpoint of the protection of personal information. However, since disclosure is allowed if the total is 0 case, this shows that there may be 1 to 9 corresponding cases.

Fig. 5



[1] Notification No. 0704-1 by Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW dated July 4, 2017)

Moreover, since the causal relationship between codeine and the occurrence of respiratory depression is not rigorously evaluated in this analysis, it is possible that the frequency of occurrence may be overestimated because of the inclusion of cases due to the underlying disease. On the other hand, it has been pointed out that there is also potential for underestimation, because cases where respiratory depression has occurred but the patient was examined at a medical institution that was among the base facilities cooperating with MID-NET (e.g., at the clinic of a family doctor) cannot be included in the data. Thus, when using MID-NET, it is important to acknowledge its characteristics and limitations.

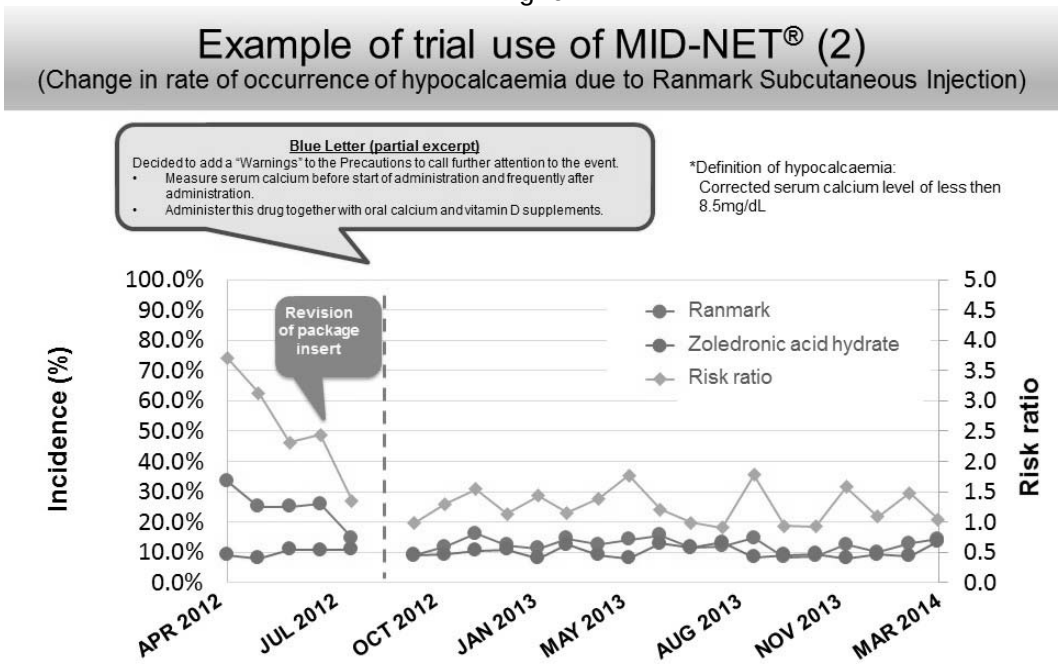
(2) Investigation of the effects of safety measures on serious hypocalcaemia caused by Ranmark Subcutaneous Injection 120 mg

In this second example, an attempt was made to evaluate the effects of safety measures through the use of MID-NET. Ranmark Subcutaneous Injection 120 mg (nonproprietary name: denosumab (genetic recombination), MAH: Daiichi Sankyo Company, Limited) is a drug for the treatment of bone lesions, which was launched in April of 2012. Following the market launch, the occurrence of serious hypocalcaemia, including some fatal cases, was reported, and further attention was called to the risks through the revision of the package insert in July of the same year and the issuance of rapid safety communications (Blue Letters) in September. In the Blue Letters, frequent measurement of serum calcium levels and oral supplements of calcium and vitamin D were added to the Warnings section of the package insert.

In order to evaluate these safety measures, the change over time in the rate of occurrence of hypocalcaemia (corrected serum calcium level under 8.5 mg/dL) in patients receiving Ranmark was analyzed in MID-NET. As a result, the rate of occurrence of hypocalcaemia in April, immediately after the market launch, was higher in the group receiving Ranmark, compared to the group receiving zoledronic acid hydrate, an existing similar drug (Fig. 6). However, a tendency for the rate of occurrence of hypocalcaemia to decrease over time was observed in the Ranmark group, and after the issuance of the Blue Letter, the risk ratio was approximately 1.0 generally.

Although the effect of the Blue Letter has not been elucidated in this analysis, the continuous safety measures taken after the market launch (revision of the package insert, provision of information by corporations, etc.) are thought to have contributed to the decrease in the risk of occurrence of hypocalcaemia and its maintenance.

Fig. 6



5. Handing of medical information in MID-NET

Privacy protection is addressed in the operation of MID-NET in various ways in light of the fact that medical information from electronic medical records, etc., is very sensitive personal information for the patients. All names, addresses, and patient numbers, etc., are removed from information that is sent from the databases of each cooperating medical institution to the data center managed by PMDA, and dates of birth and dates of examination, etc., are subjected to random number processing to permute date information while retaining contextual information.

Moreover, data cannot be taken out of the PMDA data center (from users' PCs, etc.) on an individual patient basis, and the information that can be bring outside by users is limited to statistical information after aggregated and analyzed. The Guidelines for the Security Management of the Medical Information Systems (Ministry of Health, Labour and Welfare) also require appropriate measures to be taken with regard to the environment within which users handle statistical information.

In addition, cooperating medical institutions must post a notice of the fact that medical information is utilized in MID-NET, and the website of the PMDA must also release names of individual users and utilization themes. Persons who are examined at cooperating medical institutions can refuse to allow such use of their medical information by requesting the medical institution as such. .

Individual issues regarding the use of MID-NET will undergo preliminary review by a council of experts to confirm that not only the method of managing information but also the purpose of use, scope of used information, and method of making public the results are all appropriate. This council of experts is composed of third-party experts independent of PMDA, and its purpose is to protect the privacy and other rights and interests of the patients while promoting the appropriate use of MID-NET.

Rules for the utilization of MID-NET have been formulated by the Committee on the Operation of Medical Information Databases and are presently posted on the website of PMDA. The usage guideline includes measures to be taken when the established rules are violated, such as suspension of use, destruction of used data, and making public the name and address of the violating user, etc., on the basis of the contract concluded between the user and PMDA.

6 In conclusion

MID-NET has been constructed to serve as a platform for large-scale pharmacoepidemiological analysis of medical information by corporations, academia, and the government. The GPSP Ordinance is being revised, and regulations and systems are being readied for the full-scale start of MID-NET's operations on April 1, 2018. Use of MID-NET is expected to make it possible to actively collect and evaluate information on the frequency with which adverse drug reactions occur and the actual conditions of pharmaceutical use in a rapid and low cost manner and also promote the improvement and sophistication of safety measures.

<Website for MID-NET–related information (PMDA)>
https://www.pmda.go.jp/safety/mid-net/0001.html
(Only available in Japanese language)

<Website of Committee on the Operation of Medical Information Databases (MHLW) >
http://www.mhlw.go.jp/stf/shingi/other-iyaku.html?tid=324393
(Only available in Japanese language)

2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated February 13, 2018, the contents of important revisions and a case summary that served as the basis for these revisions are provided in this section.

1 Gardenia fruit

Brand name (name of company)	Tsumura Herbal Medicine Gardenia Fruit (Tsumura & Co.) and the others
Therapeutic category	Herbal medicine
Indications	Used for formulation of Kampo medicines (Japanese traditional medicines)

PRECAUTIONS (underlined parts are revised)

Important Precautions	When using Kampo medicine (Japanese traditional medicine) containing gardenia fruit, patient's predisposition and symptoms (so-called "Sho" in Japanese in Kampo medicine), and the indication for Kampo medicine should be considered. Patients should be carefully observed and continuation of treatment should be avoided if symptoms/signs are not ameliorated. Long-term use of Kampo medicine containing gardenia fruit may result in mesenteric phlebosclerosis accompanied by abnormal colour, oedema, erosion, ulcer, and stenosis of the colon (most reported cases occurred after more than 5 years of treatment). Periodic examinations including computed tomography and large bowel endoscopy are recommended when long-term use is needed. When taken concomitantly with Kampo products etc., caution should be exercised regarding duplicative doses of the herbal medicines contained.
Adverse reactions (clinically significant adverse reactions)	**Mesenteric phlebosclerosis:** Mesenteric phlebosclerosis may occur with long-term use of Kampo medicine containing gardenia fruit. If abdominal pain, diarrhoea, constipation, abdominal distension, and other signs and symptoms repeatedly occur, or if the patient tests positive for faecal occult blood, administration should be discontinued. At the same time, examinations such as computed tomography and large bowel endoscopy should be performed, and appropriate measures should be taken. Intestinal resection has been reported in some cases.
Reference information	The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 7 months (April 2014 to November 2017) 4 cases (no fatal cases) The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 10 000 Launched in Japan: April 1986

Case summary

No.	Patient		Daily dose Treatment duration	Adverse reactions	
	Gender/ Age	Reason for use (Comorbid disease)		Clinical course and therapeutic measures	
1	Female 20s	Atopic dermatitis	3.0 g 10 years 309 days	Mesenteric phlebosclerosis	
				10 years and 309 days before discontinuation: Administration of gardenia fruit started.	
				(Day of onset): The patient visited the hospital with pain in the right lower abdomen.	
				Day of discontinuation: Characteristic findings for mesenteric vein (calcification, thickening of bowel wall) were observed on CT. All herbal medicines were discontinued on the same day. The patient was fasted and given fluid replacement.	
				2 days after discontinuation: Alleviation of the symptoms of right lower abdominal pain was observed.	
				4 days after discontinuation: Lower GI endoscopy was performed. Bronze coloration was observed inside intestinal canal. Findings were not inconsistent histologically.	
				5 days after discontinuation: Blood tests showed a tendency toward improvement in the inflammatory reaction, so meals were resumed.	
				8 days after discontinuation: The patient was discharged from the hospital because the course showed no subsequent appearance of evident abdominal symptoms. Course to be monitored through outpatient visits.	
				112 days after discontinuation: Final examination	
	Concomitant medications:		Forsythia fruit, akebia stem, platycodon root, safflower, smilax glabra, glycyrrhiza, schizonepeta spike, lonicera flower, saposhnikovia root and rhizome coptis rhizome, peach kernel, asinus gelatin		

3

Revision of Precautions (No. 292)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs in accordance with the Notifications dated February 13, 2018

1 Herbal medicine
Gardenia fruit

Brand name	Tsumura Herbal Medicine Gardenia Fruit (Tsumura & Co.) and the others
Important Precautions	When using Kampo medicine (Japanese traditional medicine) containing gardenia fruit, patient's predisposition and symptoms (so-called "Sho" in Japanese in Kampo medicine), and the indication for Kampo medicine should be considered. Patients should be carefully observed and continuation of treatment should be avoided if symptoms/signs are not ameliorated. Long-term use of Kampo medicine containing gardenia fruit may result in mesenteric phlebosclerosis accompanied by abnormal colour, oedema, erosion, ulcer, and stenosis of the colon (most reported cases occurred after more than 5 years of treatment). Periodic examinations including computed tomography and large bowel endoscopy are recommended when long-term use is needed. When taken concomitantly with Kampo products etc., caution should be exercised regarding duplicative doses of the herbal medicines contained.
Adverse reactions (clinically significant adverse reactions)	**Mesenteric phlebosclerosis:** Mesenteric phlebosclerosis may occur with long-term use of Kampo medicine containing gardenia fruit. If abdominal pain, diarrhoea, constipation, abdominal distension, and other signs and symptoms repeatedly occur, or if the patient tests positive for faecal occult blood, administration should be discontinued. At the same time, examinations such as computed tomography and large bowel endoscopy should be performed, and appropriate measures should be taken. Intestinal resection has been reported in some cases.

2

Kampo products

[1] Inchinkoto
[2] Orengedokuto
[3] Kamishoyosan
[4] Shiniseihaito

Brand name	[1] Tsumura Inchinkoto Extract Granules for Ethical Use (Tsumura & Co) and the others [2] Tsumura Orengedokuto Extract Granules for Ethical Use (Tsumura & Co) and the others [3] Tsumura Kamishoyosan Extract Granules for Ethical Use (Tsumura & Co) and the others [4] Tsumura Shiniseihaito Extract Granules for Ethical Use (Tsumura & Co) and the others
Important Precautions	Long-term use of Kampo medicine (Japanese traditional medicine) containing gardenia fruit may result in mesenteric phlebosclerosis accompanied by abnormal colour, oedema, erosion, ulcer, and stenosis of the colon (most reported cases occurred after more than 5 years of treatment). Periodic examinations including computed tomography and large bowel endoscopy are recommended when long-term use is needed.

3 **Kampo products**

[5] Unseiin
[6] Kamikihito
[7] Keigairengyoto
[8] Gorinsan
[9] Saikoseikanto
[10] Shishihakuhito
[11] Seijobofuto
[12] Seihaito
[13] Bofutsushosan
[14] Ryutanshakanto

Brand name

[5] Tsumura Unseiin Extract Granules for Ethical Use (Tsumura & Co) and the others
[6] Tsumura Kamikihito Extract Granules for Ethical Use (Tsumura & Co) and the others
[7] Tsumura Keigairengyoto Extract Granules for Ethical Use (Tsumura & Co)
[8] Tsumura Gorinsan Extract Granules for Ethical Use (Tsumura & Co)
[9] Tsumura Saikoseikanto Extract Granules for Ethical Use (Tsumura & Co)
[10] Kotaro Shishihakuhito Extract Fine Granules (Kotaro pharmaceutical Co., Ltd)
[11] Tsumura Seijobofuto Extract Granules for Ethical Use (Tsumura & Co)
[12] Tsumura Seihaito Extract Granules for Ethical Use (Tsumura & Co)
[13] Tsumura Bofutsushosan Extract Granules for Ethical Use (Tsumura & Co) and the others
[14] Tsumura Ryutanshakanto Extract Granules for Ethical Use (Tsumura & Co) and the others

Important Precautions

Long-term use of Kampo medicine (Japanese traditional medicine) containing gardenia fruit may result in mesenteric phlebosclerosis accompanied by abnormal colour, oedema, erosion, ulcer, and stenosis of the colon (most reported cases occurred after more than 5 years of treatment). Periodic examinations including computed tomography and large bowel endoscopy are recommended when long-term use is needed.

Adverse reactions (clinically significant adverse reactions)

Mesenteric phlebosclerosis: Mesenteric phlebosclerosis may occur with long-term administration. If abdominal pain, diarrhoea, constipation, abdominal distension, and other signs and symptoms repeatedly occur, or if the patient tests positive for faecal occult blood, administration should be discontinued. At the same time, examinations such as computed tomography and large bowel endoscopy should be performed, and appropriate measures should be taken. Intestinal resection has been reported in some cases.

4 **Antivirals**

Efavirenz

Brand name

Stocrin Tablets 200 mg, 600 mg (MSD K. K.)

Adverse reactions (clinically significant adverse reactions)

Prolonged QT: Prolonged QT may occur. Patients should be carefully monitored through methods such as periodic examinations.

5 **X-ray contrast agents**

Iohexol (for urinary tract, blood vessel, CT)

Brand name	Omnipaque 140 Injection 50 mL, 220 mL, Omnipaque 240 Injection 20 mL, 50 mL, 100mL, Omnipaque 300 Injection 20 mL, 50 mL, 100 mL, 150 mL, Omnipaque 350 Injection 20 mL, 50 mL, 100 mL, Omnipaque 240 Injection Syringe 100 mL, Omnipaque 300 Injection Syringe 50 mL, 80 mL, 100 mL, 110 mL, 125 mL, 150 mL, Omnipaque 350 Injection Syringe 45 mL, 70 mL, 100 mL (Daiich Sankyo Co., Ltd.), and the others
Adverse reactions (clinically significant adverse reactions)	**Skin disorders:** Oculomucocutaneous syndrome (Stevens-Johnson syndrome), and acute generalized exanthematous pustulosis may occur. Patients should be carefully monitored and appropriate measures should be taken if pyrexia, erythema, small pustules, itchy sensation, ocular hyperaemia, stomatitis, or other abnormalities are observed.

6 **X-ray contrast agents**

Iomeprol

Brand name	Iomeron 300 Injection 20 mL, 50 mL, 100 mL, Iomeron 350 Injection 20 mL, 50 mL, 100 mL, Iomeron 400 Injection 20 mL, 50 mL, 100 mL, Iomeron 300 Injection Syringe 50 mL, 75 mL, 100 mL, Iomeron 350 Injection Syringe 50 mL, 75 mL, 100 mL, 135 mL (Bracco-Esai Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	**Skin disorders:** Oculomucocutaneous syndrome (Stevens-Johnson syndrome), and acute generalized exanthematous pustulosis may occur. Patients should be carefully monitored and appropriate measures should be taken immediately if pyrexia, erythema, small pustules, itchy sensation, ocular hyperaemia, stomatitis, or other symptoms are observed.

7

Preparations containing gardenia fruit (OTC drugs) (oral dosage form)

Brand name	Dasmoc (Kobayashi Pharmaceuticals Co., Ltd.), Tsumura Kampo Bofutsushosan Extract Granules (Tsumura & Co), Uchida Shishihakuhito (Uchida Wakanyaku Ltd.)
Consultation	If the following symptoms are observed after using this drug, these may be adverse reactions. So, immediately discontinue the use, and show this document to your physician, pharmacist, or registered distributor for a consultation. The following serious symptoms occur infrequently. Immediately seek medical aid if you experience any of these signs and symptoms. **Mesenteric phlebosclerosis:** Abdominal pain, diarrhoea, constipation, abdominal distension, and other signs and symptoms repeatedly occur with long-term administration. Contact a physician, pharmacist, or registered distributor for a consultation when long-term use of this drug is needed.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its Marketing Authorization Holder (MAH) is responsible for collecting ADR from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADR. EPPV is specified as a condition of approval.

(As of January 31, 2018)
◎: Products for which EPPV was initiated after January 1, 2018

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
◎	Sildenafil citrate Revatio Dry Syrup for Suspension 900 mg, Revatio OD Film 20 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
	Eculizumab (genetical recombination)[*1] Soliris for Intravenous Infusion 300 mg	Alexion Pharma G.K.	December 25, 2017
	Aminolevulinic acid hydrochloride[*2] Alaglio Divided Granules 1.5 g	SBI Pharmaceuticals Co., Ltd.	December 19, 2017
	Palbociclib Ibrance Capsules 25 mg, 125 mg	Pfizer Japan Inc.	December 15, 2017
	Belimumab (genetical recombination) Benlysta for I.V. Infusion 120 mg, 400 mg Benlysta for S.C. Injection 200 mg Autoinjector, 200 mg Syringe	GlaxoSmithKline K.K.	December 13, 2017
	Bezlotoxumab (genetical recombination) Zinplava for Intravenous Drip Infusion 625 mg	MSD K.K.	December 8, 2017
	Budesonide Rectabul 2 mg Rectal Foam 14 Doses	EA Pharma Co., Ltd.	December 7, 2017
	Lonoctocog alfa (genetical recombination) Afstyla I.V. Injection 250, 500, 1000, 1500, 2000, 2500, 3000	CSL Behring K.K.	December 1, 2017
	Glecaprevir hydrate/pibrentasvir Maviret Combination Tablets	AbbVie GK	November 27, 2017
	Rupatadine fumarate Rupafin Tablets 10 mg	Teikoku Seiyaku Co., Ltd.	November 27, 2017
	Avelumab (genetical recombination) Bavencio Intravenous Injection 200 mg	Merck Serono Co., Ltd.	November 22, 2017
	Daratumumab (genetical recombination) Darzalex Intravenous Infusion 100 mg, 400 mg	Janssen Pharmaceutical K.K.	November 22, 2017

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Flutemetamol (^{18}F) Vizamyl Intravenous Injectable	Nihon Medi-Physics Co., Ltd.	November 10, 2017
	Quetiapine fumarate*3 Bipresso Extended Release Tablets 50 mg, 150 mg	Astellas Pharma Inc.	October 27, 2017
	Sildenafil citrate Revatio Tablets 20 mg	Pfizer Japan Inc.	September 27, 2017
	Nusinersen sodium*4 Spinraza Intrathecal Injection 12 mg	Biogen Japan Ltd.	September 22, 2017
	Lyophilized human prothrombin complex concentrate Kcentra for I.V. Injection 500, 1000	CSL Behring K.K.	September 19, 2017
	Teneligliptin hydrobromide hydrate/ Canagliflozin hydrate Canalia Combination Tablets	Mitsubishi Tanabe Pharma Corporation	September 7, 2017
	Amenamevir Amenalief Tab. 200 mg	Maruho Co., Ltd.	September 7, 2017
	Baricitinib Olumiant Tablets 2 mg, 4 mg	Eli Lilly Japan K.K.	September 1, 2017
	Pralatrexate Difolta Injection 20 mg	Mundipharma K.K.	August 30, 2017
	Nusinersen sodium Spinraza Intrathecal injection 12 mg	Biogen Japan Ltd.	August 30, 2017
	Leuprorelin acetate*5 Leuplin SR for Injection Kit 11.25 mg	Takeda Pharmaceutical Company Limited	August 25, 2017
	Eltrombopag olamine*6 Revolade Tablets 12.5 mg, 25 mg	Novartis Pharma K.K.	August 25, 2017
	Lyophilized human antithrombin III concentrate*7 Kenketu Nonthron 500 for Injection, 1500 for Injection	Nihon Pharmaceutical Co., Ltd.	August 25, 2017
	Florbetapir (^{18}F) Amyvid Injection	Fujifilm RI Pharma Co., Ltd.	August 21, 2017

*1 Generalized myasthenia gravis (for use only in patients whose symptoms are difficult to control with high-dose intravenous immunoglobulin therapy or hemocatharsis)

*2 Visualization of tumor tissues of the non-muscle invasive bladder cancer in transurethral resection of bladder tumor

*3 Depressive symptoms in bipolar disorder

*4 Spinal muscular atrophy

*5 Suppression of progression of congenital bulbospinal muscular atrophy

*6 Aplastic anaemia

*7 Portal vein thrombosis associated with decreased antithrombin III