Pharmaceuticals and Medical Devices Safety Information

No. 304 August 2013

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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) website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only available in Japanese language).

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Pharmaceuticals and Medical Devices Safety Information
No. 304 August 2013

Pharmaceutical and Food Safety Bureau,
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[Outline of Information]

D: Distribution of Dear Healthcare Professional Letters *P*: Revision of Precautions *C*: Case Reports

PMDA medi-navi (Pharmaceuticals and Medical Devices Information E-mail Alert Service)

The PMDA is providing the "PMDA medi-navi" a Pharmaceuticals and Medical Devices Information E-mail Alert Service (only available in Japanese language), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of Precautions is issued. This e-mail service will enable you to obtain safety information faster and more efficiently, free of charge. Please feel free to use this service for your faster information collection.
See our website for details of the service. → http://www.info.pmda.go.jp/info/idx-push.html

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

ADRs	Adverse drug reactions
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
CRP	C-reactive protein
DI	Drug information
DM	Direct mail
DSU	Drug Safety Update
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
IU	International unit
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
MAH	Marketing authorization holder
MR	Medical representative
MS	Marketing specialist
PCP	Pneumocystis carinii pneumonia
PCR	Polymerase chain reaction
ST	Sulfamethoxazole plus trimethoprim
TEN	Toxic epidermal necrolysis
γ-GTP	gamma-glutamyl transpeptidase

1

Surveillance on Availability, Dissemination, and Utilization of Drug Safety Information in Medical Institutions and Pharmacies

1. Introduction

In order to ensure appropriate use of drugs and medical devices, MHLW and PMDA are jointly conducting safety measures such as revisions of the Precautions section of package inserts, based on evidence including reports of adverse drug reactions. The safety information on these measures is provided from the MHLW, PMDA, and pharmaceutical companies to medical institutions via various routes. It is essential that the most up-to-date information available be disseminated to, and utilized by, healthcare professionals at clinical settings in an appropriate manner.

PMDA, based on the Second Mid-term Plan,* has been conducting surveillance starting in fiscal year (FY) 2010 to grasp the status of the availability, dissemination, and utilization of safety information at medical institutions and pharmacies, to determine the most appropriate style and method for providing information for easy access at clinical settings. From the results of the surveillance, PMDA aims to propose ideal ways for receiving, distributing, and utilizing safety information, thereby to help promote the safe use of drugs, etc. at clinical settings. This section presents the results of the surveillance conducted by PMDA in FY 2012.

* The Second Mid-term Plan (excerpt)
PMDA will conduct, in a stepwise manner starting in FY 2010, surveillance to check how companies conduct safety measures, including whether information is properly disseminated to medical institutions, and to check how the information provided by companies is disseminated and utilized within each medical institution.

2. Results of surveillance in FY 2012

(1) Surveillance method

The surveillance period was from January 7 to February 28, 2013, the surveillance was conducted at 8541 hospitals (all existing hospitals) and 26915 community pharmacies (half of all existing pharmacies) nationwide.

Self-administered questionnaire sheets were sent to the drug safety management supervisors at the institutions and filled out by them or the pharmacists involved in drug safety management. The respondents were asked to fill out the questionnaire sheet on the website in principle; however, the paper-based questionnaire sheet could be filled out and returned by postal mail (**Figure 1**).

Figure 1. Overview of surveillance

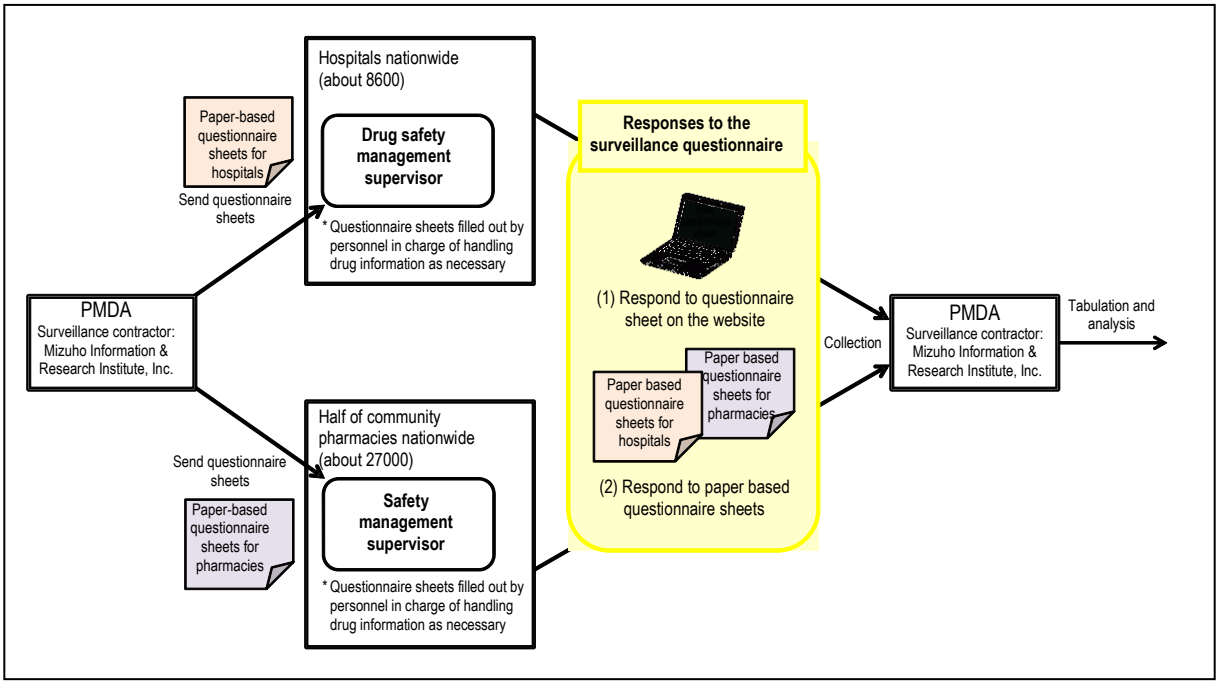


Figure 2. Outline of surveillance items

Surveyed institution	Outline of surveillance items	
Hospital	Basic information	☐ Type of institution, calculation of community medical fee, respondent information
	General safety information	☐ Internet use at the hospital pharmacy or pharmacy department ☐ Availability, dissemination, and utilization of drug safety information ☐ Bring-in drugs ☐ Management of safety information for drugs prescribed in community pharmacies ☐ Cooperation with nearby hospitals, clinics, and community pharmacies
	Individual case of drug safety information	☐ Denosumab (genetical recombination) ☐ Aliskiren fumarate
Community pharmacy	Basic information	☐ Type of information, drug safety management supervisor information
	General safety information	☐ Internet use at the pharmacy ☐ Availability, dissemination, and utilization of drug safety information ☐ Drug dispensing (checking prescription) ☐ Cooperation with nearby hospitals, clinics, and other pharmacies
	Individual case of drug safety information	☐ Aliskiren fumarate ☐ Ibuprofen

Surveillance items were prepared for hospitals and community pharmacies separately to ask questions about handling of drug safety information as shown in **Figure 2**.

(2) Surveillance results

The questionnaire sheets were collected from 4556 hospitals (53.4%) and 17276 community pharmacies (64.6%).

Results of the surveillance were reviewed by the "Review Committee on the Status of the Dissemination and Utilization of Safety Information on Drugs, etc., in Medical Institutions" consisting

of experts on medical safety and pharmaceutical practices established in PMDA, and summarized based on the opinions of the committee members.

This section describes, among the surveillance results, "common source of safety information," "Internet use to collect drug safety information," "enhancement of safety information management of bring-in drugs/prevention of medical accidents related to management of bring-in drugs," "enhancement of safety information management of drugs prescribed exclusively for extramural dispensing," and "enhancement of cooperation between hospital pharmacies and community pharmacies."

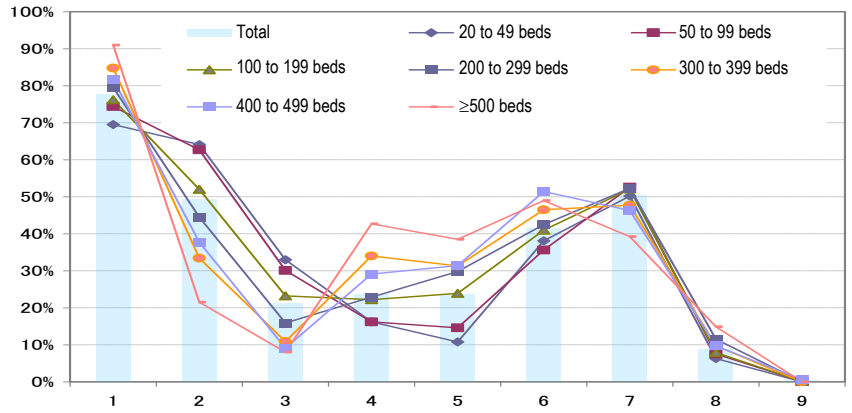
a. Common sources of safety information

The sources for obtaining drug safety information that are routinely and actively used at the hospitals were, in the order of decreasing use frequency, "pharmaceutical company medical representatives (MRs)," "direct mails (DMs) from pharmaceutical companies," "Drug Safety Updates (DSUs)," "PMDA medi-navi," "Pharmaceuticals and Medical Devices Safety Information," and "PMDA website." The larger the institutions, the more they use PMDA medi-navi, and PMDA website while small-scale institutions tend to use DMs. Compared with the results of a similar surveillance conducted in FY2010, obtaining information from MRs or Pharmaceuticals and Medical Devices Safety Information in FY2013 is on a decreasing trend, whereas obtaining information from PMDA medi-navi is on an increasing trend (**Figure 3**).

At the community pharmacies, the newly added surveillance subjects, the sources for obtaining drug safety information that are routinely used were mainly "MRs," "DMs," "drug wholesaler marketing specialists (MSs)," "DSUs," and "Pharmaceuticals and Medical Devices Safety Information." The larger the pharmacies, the more they use MRs while the smaller the pharmacies, the more they use DMs. Compared with the hospitals, less community pharmacies are obtaining information from PMDA medi-navi or PMDA website and more pharmacies are obtaining information from DMs (**Figure 4**).

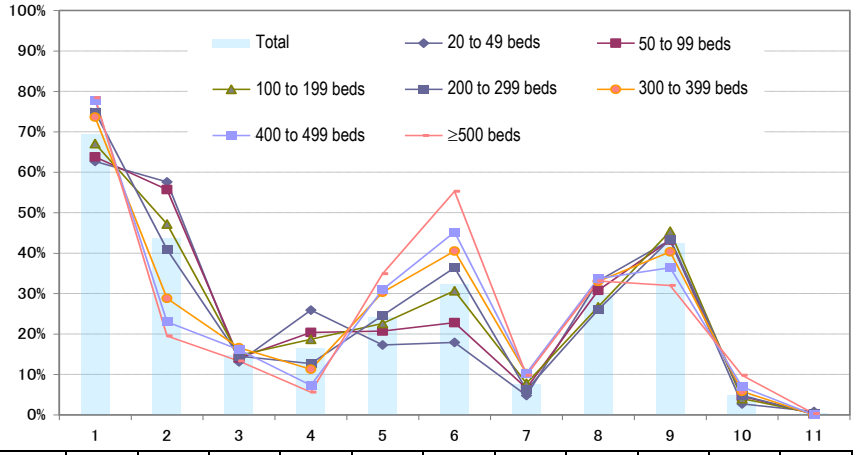
Figure 3. Routinely and actively used drug safety information sources at the hospitals; FY 2010 surveillance (Figure 3-1) and FY 2012 surveillance (Figure 3-2)

Figure 3-1. FY 2010 surveillance



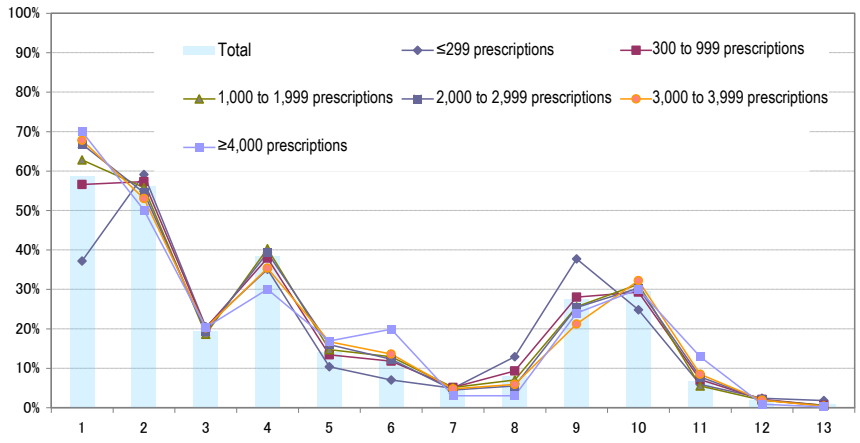
	Number of institutions surveyed	Pharmaceutical company MR	Pharmaceutical company DM	Drug wholesaler MS	PMDA website	PMDA medi-navi	Pharmaceuticals and Medical Devices Safety Information (published by MHLW)	DSU (published by the Federation of Pharmaceutical Manufacturers' Associations of Japan)	Others	No response
Total	3574	77.8%	49.3%	21.3%	23.7%	23.7%	41.4%	50.3%	8.9%	0.3%
20 to 49 beds	315	69.5%	64.1%	33.0%	16.2%	10.8%	38.1%	50.2%	6.3%	0.0%
50 to 99 beds	772	74.4%	62.7%	30.1%	16.2%	14.6%	35.6%	52.6%	7.5%	0.1%
100 to 199 beds	1119	76.2%	52.0%	23.2%	22.2%	23.9%	41.0%	52.1%	7.9%	0.1%
200 to 299 beds	497	79.5%	44.5%	15.9%	22.9%	29.8%	42.5%	52.3%	11.5%	0.0%
300 to 399 beds	329	84.8%	33.4%	10.9%	34.0%	31.3%	46.5%	47.7%	9.7%	0.0%
400 to 499 beds	175	81.7%	37.7%	9.1%	29.1%	31.4%	51.4%	46.3%	9.7%	0.6%
≥500 beds	288	91.0%	21.5%	8.0%	42.7%	38.5%	49.0%	39.2%	14.9%	0.0%

Figure 3-2. FY 2012 surveillance



	Number of institutions surveyed	Pharmaceutical company MR	Pharmaceutical company DM	Pharmaceutical company website	Drug wholesaler MS	PMDA website	PMDA medi-navi	Website other than pharmaceutical company or PMDA	Pharmaceuticals and Medical Devices Safety Information	DSU (published by the Federation of Pharmaceutical Manufacturers' Associations of Japan)	Others	No response
Overall	4,556	69.3%	43.7%	14.6%	16.5%	24.2%	32.3%	7.5%	29.6%	42.3%	4.9%	0.3%
20 to 49 beds	375	62.7%	57.6%	13.1%	25.9%	17.3%	17.9%	4.8%	33.1%	43.2%	2.7%	0.8%
50 to 99 beds	984	63.8%	55.7%	14.1%	20.4%	20.7%	22.8%	6.6%	30.8%	43.2%	4.6%	0.2%
100 to 199 beds	1,391	67.1%	47.2%	14.7%	18.7%	22.6%	30.7%	7.8%	26.7%	45.4%	4.0%	0.4%
200 to 299 beds	662	74.9%	40.9%	14.5%	12.7%	24.6%	36.4%	6.2%	26.0%	43.4%	4.8%	0.3%
300 to 399 beds	469	73.6%	28.8%	16.6%	11.3%	30.3%	40.5%	10.2%	33.0%	40.3%	5.8%	0.0%
400 to 499 beds	261	77.8%	23.0%	16.1%	7.3%	31.0%	45.2%	10.3%	33.7%	36.4%	6.9%	0.0%
≥500 beds	338	78.4%	19.5%	13.3%	5.6%	34.9%	55.3%	9.8%	33.1%	32.0%	9.8%	0.3%

Figure 4. Routinely and actively used drug safety information sources at the community pharmacies (FY 2012)



	Number of surveillance	Pharmaceutical company MR	Pharmaceutical company DM	Pharmaceutical company website	Drug wholesaler MS	PMDA website	PMDA medi-navi	Website other than pharmaceutical company or PMDA	Receipt computer system	Pharmaceuticals and Medical Devices Safety Information (published by MHLW)	DSU (published by the Federation of Pharmaceutical Manufacturers' Associations of Japan)	External management division (main wholesaler to franchised pharmacies, e-mail)	Others	No response
Total	17,276	58.8%	56.1%	19.5%	38.4%	14.0%	11.9%	4.9%	8.1%	27.5%	29.6%	6.7%	2.0%	0.8%
≤299 prescriptions	1,936	37.2%	59.1%	20.5%	35.1%	10.4%	7.0%	4.9%	12.9%	37.7%	24.8%	5.9%	2.4%	1.8%
300 to 999 prescriptions	5,258	56.6%	57.3%	20.2%	37.9%	13.4%	11.8%	5.1%	9.3%	28.0%	29.3%	7.1%	2.1%	0.6%
1,000 to 1,999 prescriptions	6,574	62.8%	55.8%	18.6%	40.3%	14.7%	12.9%	5.1%	7.0%	25.6%	31.3%	5.5%	1.9%	0.6%
2,000 to 2,999 prescriptions	2,131	66.8%	54.5%	19.3%	39.3%	16.0%	12.3%	4.5%	5.5%	25.4%	30.3%	7.8%	2.0%	0.4%
3,000 to 3,999 prescriptions	693	67.8%	53.0%	20.2%	35.4%	16.7%	13.6%	4.8%	5.9%	21.2%	32.2%	8.5%	1.9%	0.4%
≥4,000 prescriptions	433	70.0%	50.1%	20.3%	30.0%	16.9%	19.9%	3.0%	3.0%	24.0%	30.0%	12.9%	0.9%	0.2%

b. Internet use to collect drug safety information

Responses to the questions on using frequency of the Internet to collect drug safety information show that the larger the hospitals or community pharmacies, the more they use the Internet to obtain the information. Compared with the hospitals, community pharmacies tend to use the Internet less frequently (**Figure 5**).

Use of the Internet to collect safety information is encouraged regardless of institution size. Effective use of information provided by PMDA (ex. PMDA website and PMDA medi-navi) will help promote the safe use of medical products.

Figure 5. Internet use to collect drug safety information; hospitals (Figure 5-1) and community pharmacies (Figure 5-2)

Figure 5-1. Hospitals

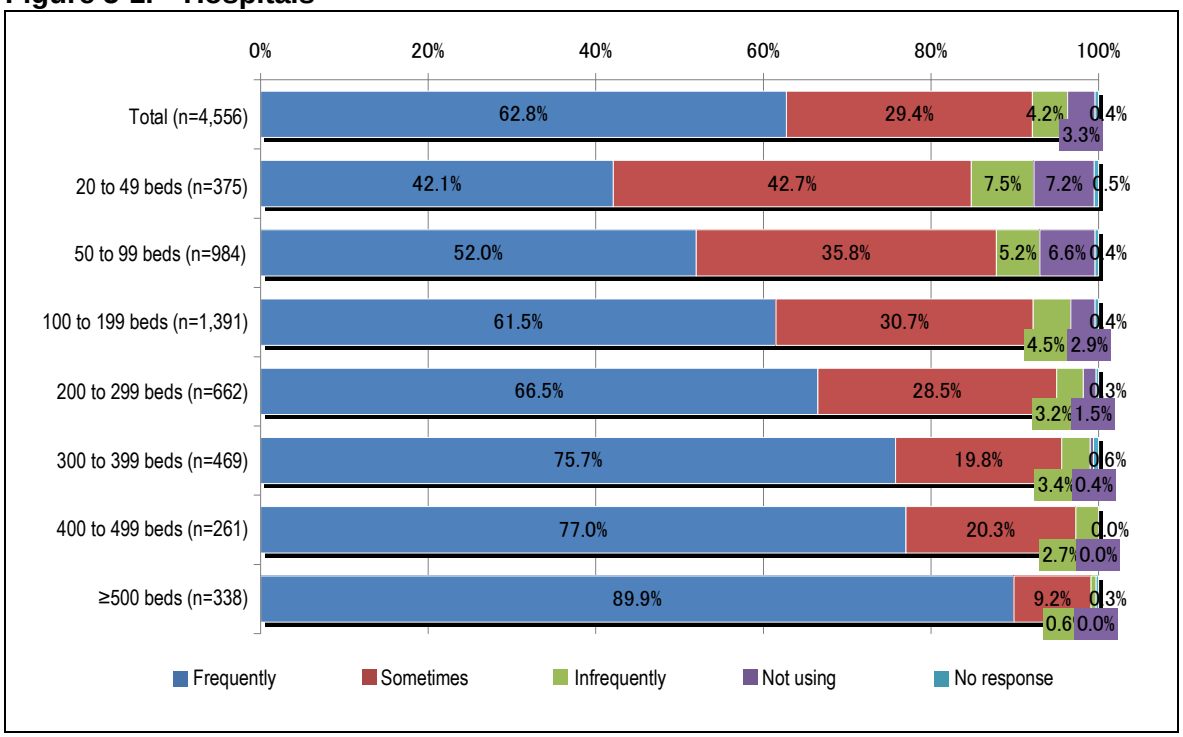
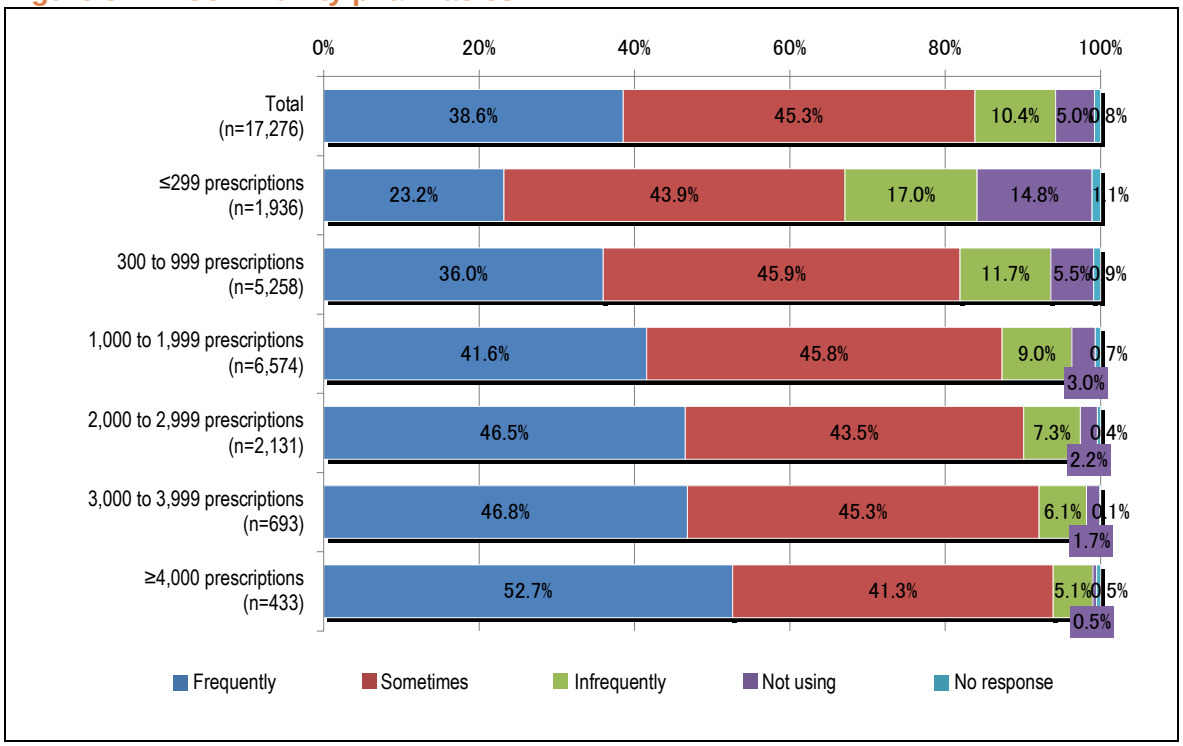


Figure 5-2. Community pharmacies



c. Enhancement of safety information management of bring-in drugs/prevention of medical accidents related to management of bring-in drugs

The hospital surveillance found many institutions are using drugs that patients bring with them when they are not available at the hospital pharmacy (See page 67, the Report on the surveillance results). The safety information concerning bring-in drugs is primarily collected and managed by pharmacists, specifically, by ward pharmacists or Drug Information (DI) pharmacists at large-scale hospitals (**Figure 6**). Ward pharmacists are expected to play an important role in managing a variety of bring-in drugs and in providing them with thorough and proper instructions for drug compliance. Use of the "medication record book" provided by pharmacies to provide information on drugs and/or patients is encouraged.

As regards management of safety information concerning bring-in drugs, 15 cases of medical accidents and 643 cases of medical near-miss incidents were reported in the surveillance (**Figure 7**). Frequently reported types of accidents/incidents included "mix-up of prescribed doses, strengths or drugs," "simultaneous use of a bring-in drug and other drugs with the same therapeutic effect," and "identification of prescription/dispensing error made at another institution (including cases where the prescription became inappropriate due to a change in the patient's condition)." Reported cases specific to bring-in drugs included "inconsistency between the bring-in drug and the drug information or the drug description provided on the drug bag, the medication record book or the referral letter," and "error in recording or hearsay for the result of identifying drugs." Typical cases are included in the Report on the surveillance results (page 88 and 89).

When identifying bring-in drugs, the patient leaflets on drug information and the drug bags provided by patients should be checked to see if the information is up to date. It should also be noted that the information might be based on an old prescription which has already changed or a prescription for other family members. When the patient brings drugs not available at the hospital pharmacy, caution should be exercised to avoid prescribing drugs with the same therapeutic effect, errors of instructions in the dosage and administration, or misidentification of strengths after switching to an alternative treatment. The safety information management of bring-in drugs should be ensured by confirming pre-admission drug use based on the referral letter, the patient leaflet on drug information, patient interview and other sources.

Figure 6. Hospital pharmacists in charge of collecting information on bring-in drugs

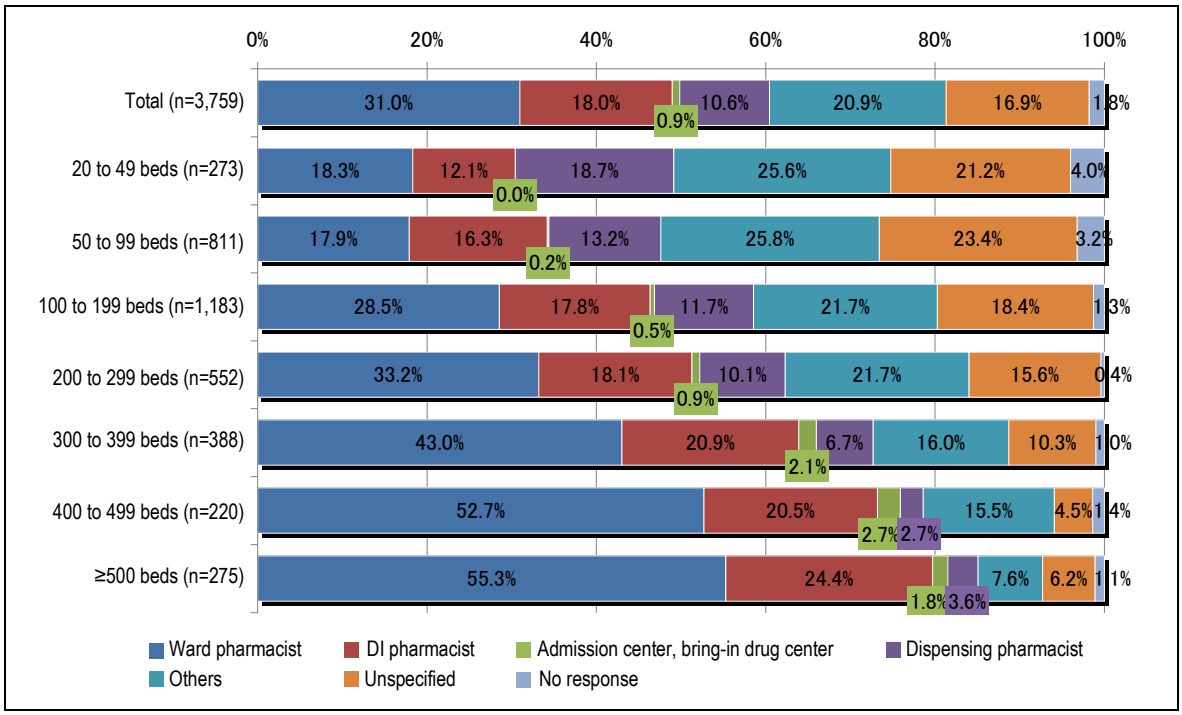
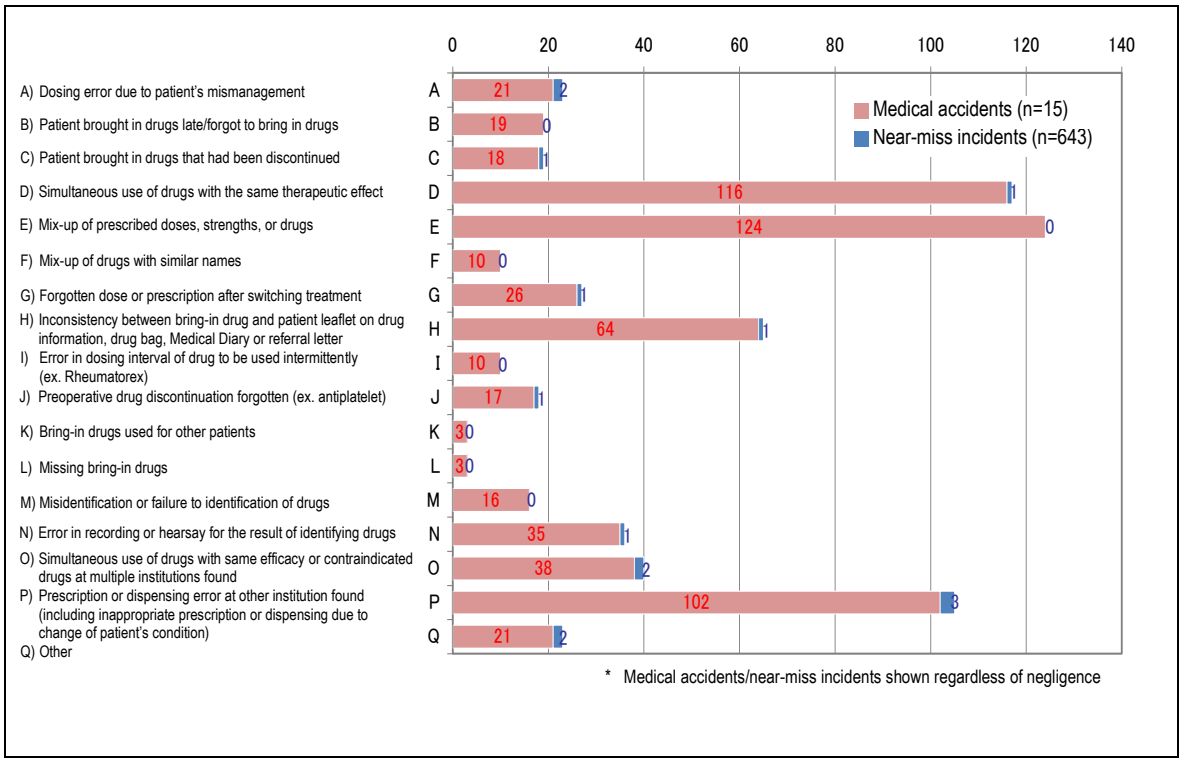


Figure 7. Medical accidents and near-miss incidents involving bring-in drugs



d. Enhancement of safety information management of drugs prescribed exclusively for extramural dispensing

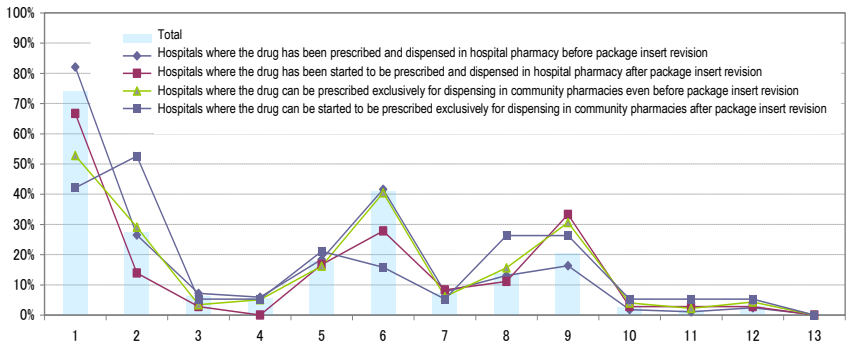
Of the surveyed hospitals using the drugs prescribed exclusively for extramural dispensing, 66% answered the drug safety information was not managed sufficiently. The main reason for insufficient safety information management was that they leave the management to community pharmacies.

According to the surveillance of Aliskiren (revision of Precautions instructed on June 5, 2012), the percentage of obtaining the drug information from MRs was lower in hospitals where the drug can be "prescribed exclusively for dispensing in community pharmacies" compared with the hospitals where the drug is "prescribed and dispensed in hospital pharmacy." The percentage of answers that they "did not know" about the details of relevant precautions was also high in hospitals where the drug can be "prescribed exclusively for dispensing in community pharmacies" (**Figure 8**).

It is indispensable for prescribing hospitals to collect the safety information concerning drugs dispensed in community pharmacies in an appropriate manner. Development of a system is advised to manage the safety information of drugs dispensed in community pharmacies in the same manner as the management of safety information of drugs dispensed in hospital pharmacies. Promotion of information sharing to ensure proper drug use is also encouraged so as to enable community pharmacies in charge of dispensing drugs to inspect the prescription more carefully.

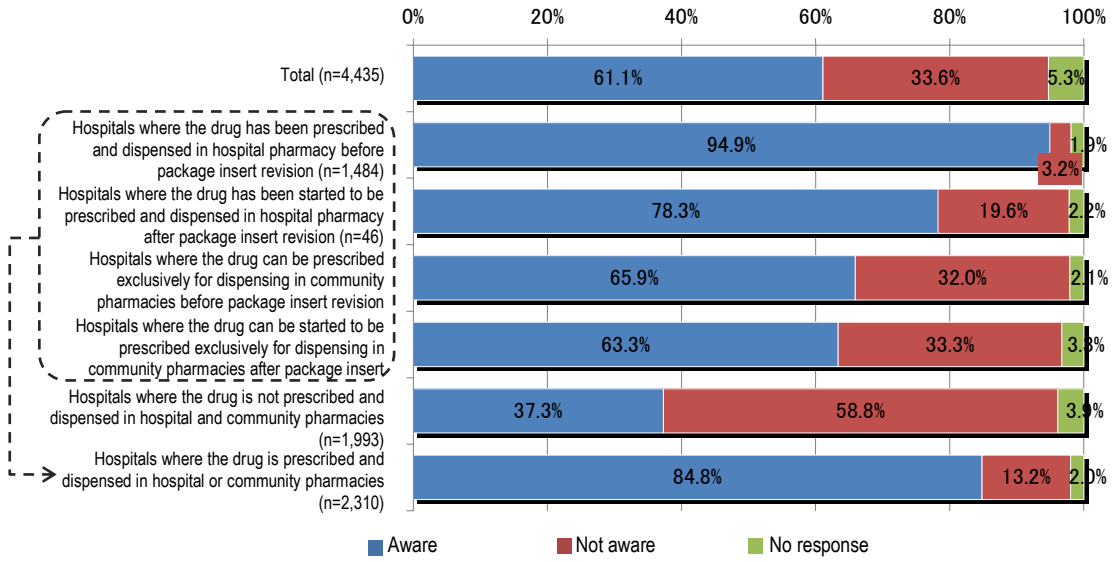
Figure 8. Access to safety information for aliskiren

Figure 8-1. Source of safety information by use status



	Number of institutions surveyed	Pharmaceutical company MR	Pharmaceutical company DM	Pharmaceutical company website	Drug wholesaler MS	PMDA website	PMDA medi-navi	Website other than manufacturer/PMDA	Pharmaceuticals and Medical Devices Safety Information (published by MHLW)	DSU (published by the Federation of Pharmaceutical Manufacturers' Associations of Japan)	Information exchange among pharmacists and physicians	Press release (newspaper and industrial newsletter)	Other	No response
Total	1,958	74.1%	27.2%	6.1%	5.6%	17.8%	40.8%	7.2%	13.8%	20.3%	2.4%	1.5%	2.9%	0.1%
Hospitals where the drug has been prescribed and dispensed in hospital pharmacy before package insert revision	1,409	82.1%	26.5%	7.2%	5.9%	18.4%	41.6%	7.6%	13.1%	16.3%	1.8%	1.1%	2.4%	0.1%
Hospitals where the drug has been started to be prescribed and dispensed in hospital pharmacy after package insert revision	36	66.7%	13.9%	2.8%	0.0%	16.7%	27.8%	8.3%	11.1%	33.3%	2.8%	2.8%	2.8%	0.0%
Hospitals where the drug can be prescribed exclusively for dispensing in community pharmacies even before package insert revision	494	52.8%	29.1%	3.4%	5.1%	16.2%	40.5%	6.1%	15.6%	30.6%	4.0%	2.2%	4.3%	0.0%
Hospitals where the drug can be started to be prescribed exclusively for dispensing in community pharmacies after package insert revision	19	42.1%	52.6%	5.3%	5.3%	21.1%	15.8%	5.3%	26.3%	26.3%	5.3%	5.3%	5.3%	0.0%

Figure 8-2. Awareness of alerts at hospitals by use status

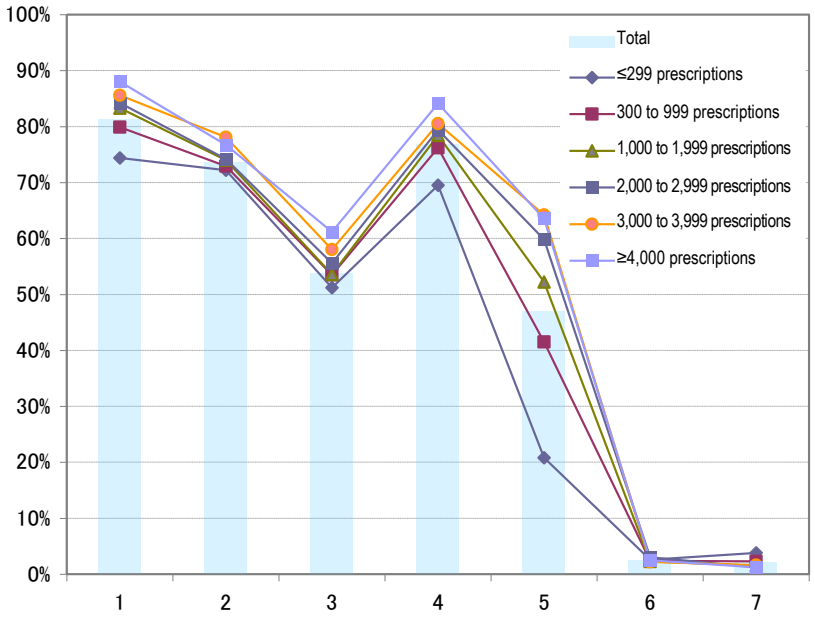


e. Enhancement of hospital-pharmacy cooperation

While the hospital surveillance showed prescribing physicians and community pharmacies were often responsible to check external prescriptions, many of the respondents in the community pharmacy surveillance said access to the patient's laboratory test results and the name of disorder would be required for community pharmacies in charge of dispensing drugs to perform better checking prescription (**Figure 9**).

Patient information such as laboratory test results and names of disorders is provided to community pharmacies in charge of dispensing drugs by 7% of responding hospitals. 17% of pharmacies had access to patient information from the prescribing hospitals/clinics. (page 115 and 258 of the Report on the surveillance results). Some institutions share medical chart information with community pharmacies or provide clinical test results and names of disorders in the prescriptions or medication record book (**Figure 10**). More institutions are encouraged to do so while ensuring careful handling of personal information.

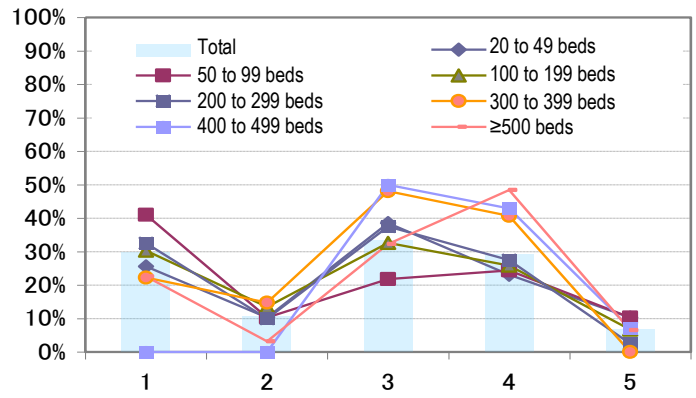
Figure 9. Necessary items for better checking prescriptions (community pharmacies' ideas)



	Number of surveillance	Grasp of latest drug safety information	Name of patient's disorder	Patient's laboratory tests	Patient's past drug use (including drug use record upon admission)	Securing adequate staff	Other	No response
Total	17,276	81.3%	73.6%	53.8%	76.8%	47.0%	2.4%	2.1%
≤299 prescriptions	1,936	74.4%	72.2%	51.2%	69.5%	20.8%	2.6%	3.8%
300 to 999 prescriptions	5,258	79.9%	72.9%	53.5%	76.2%	41.5%	2.4%	2.3%
1,000 to 1,999 prescriptions	6,574	83.3%	74.0%	53.6%	78.4%	52.2%	2.3%	1.5%
2,000 to 2,999 prescriptions	2,131	84.2%	74.2%	55.6%	79.4%	59.8%	3.0%	1.2%
3,000 to 3,999 prescriptions	693	85.6%	78.1%	58.0%	80.5%	64.2%	2.2%	1.6%
≥4,000 prescriptions	433	88.0%	76.7%	61.2%	84.1%	63.5%	2.5%	1.2%

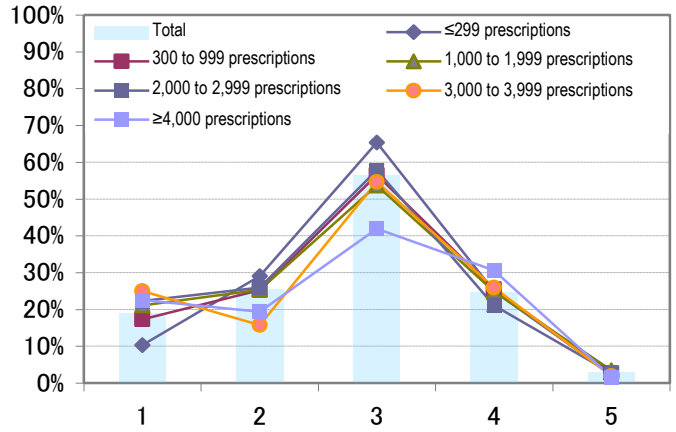
Figure 10. Cooperation with community pharmacies/hospital pharmacies or clinics

Figure 10-1. Provision of patient information to community pharmacies in charge of dispensing drugs



	Number of surveillance	Sharing of medical chart information	Including laboratory test results and name of disorder in the prescription	Including laboratory test results and name of disorder in the medication record book	Other	No response
Total	321	29.9%	10.6%	33.3%	29.3%	6.9%
20 to 49 beds	39	25.6%	10.3%	38.5%	23.1%	10.3%
50 to 99 beds	78	41.0%	10.3%	21.8%	24.4%	10.3%
100 to 199 beds	89	30.3%	13.5%	32.6%	25.8%	6.7%
200 to 299 beds	40	32.5%	10.0%	37.5%	27.5%	2.5%
300 to 399 beds	27	22.2%	14.8%	48.1%	40.7%	0.0%
400 to 499 beds	14	0.0%	0.0%	50.0%	42.9%	7.1%
≥500 beds	31	22.6%	3.2%	32.3%	48.4%	6.5%

Figure 10-2. Community pharmacies' access to patient information available at prescribing hospitals/clinics



	Number of surveillance	Sharing medical chart information	Checking laboratory test results and name of disorder included in the prescription	Checking laboratory test results and name of disorder in the medication record book	Other	No response
Total	2,943	18.9%	25.3%	56.4%	24.7%	2.9%
≤299 prescriptions	300	10.3%	29.0%	65.3%	25.0%	2.3%
300 to 999 prescriptions	968	17.3%	25.2%	56.5%	25.5%	2.7%
1,000 to 1,999 prescriptions	1,122	21.1%	25.3%	53.7%	24.9%	3.5%
2,000 to 2,999 prescriptions	332	22.3%	25.9%	57.8%	21.1%	2.7%
3,000 to 3,999 prescriptions	108	25.0%	15.7%	54.6%	25.9%	1.9%
≥4,000 prescriptions	62	22.6%	19.4%	41.9%	30.6%	1.6%

3. Conclusion

Appropriate dissemination and utilization of the most current drug safety information in clinical practice is important to secure appropriate use of medical products including drugs. The PMDA website and PMDA medi-navi are useful information sources to ensure access to drug safety information in a prompter manner. My Drug List for Safety Update, which is an additional service for the PMDA medi-navi subscribers, can be a powerful tool for information management of drugs prescribed exclusively for extramural dispensing and bring-in drugs which are not dispensed in the hospital. Use of these information source provided by the PMDA is strongly recommended.

The above information is only a part of the results of the surveillance conducted in FY 2012. The PMDA website presents the outline and detailed report of the surveillance results.

PMDA is very grateful for medical institutions and the community pharmacies that collaborated in this surveillance.

[PMDA's Medical Product Information web page]

http://www.info.pmda.go.jp/

(You can access the PMDA medi-navi [only available in Japanese language] and My Drug List for Safety Update [only available in Japanese language] from this website.)

[Outline of the FY 2012 surveillance and detailed report on the surveillance results]

http://www.info.pmda.go.jp/kyoten_iyaku/dentatsu_katsuyou.html (only available in Japanese language)

2

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated July 9, 2013, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Golimumab (Genetical Recombination)

Brand Name (name of company)	Simponi Subcutaneous Injection Syringe 50 mg (Janssen Pharmaceutical K.K.)
Therapeutic Category	Miscellaneous metabolism agents-Miscellaneous
Indications	Rheumatoid arthritis which is not adequately responsive to conventional therapies (including prevention of structural joint damage)

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Interstitial pneumonia: Interstitial pneumonia may occur. Patients should be carefully monitored for respiratory symptoms including pyrexia, cough, and dyspnoea. If any abnormalities are observed, examinations such as a chest X-ray, chest CT, blood gas testing should be immediately performed, administration of this drug should be discontinued, differential diagnosis from pneumocystis pneumonia (e.g. β-D glucan measurement) should be considered, and appropriate measures should be taken. In addition, when administering the drug to patients with a history of interstitial pneumonia, caution should be exercised by conducting periodic interviews, etc.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 1 year and 8 months (from initial marketing to May 2013)

- Interstitial pneumonia-associated cases: 8 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 13,700 (May 2012 to April 2013)

Launched in Japan: September 2011

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Rheumatoid arthritis (hypertension, dizziness, supraventricular extrasystoles, gastritis)	100 mg/ 4 weeks for 154 days	**Interstitial pneumonia** 12 years ago before the start of administration: The patient experienced rheumatoid arthritis. Day 1 of administration: The patient started receiving golimumab at 100 mg. Day 154 of administration: Final administration of golimumab at 100 mg was performed. Around Day 160 of administration: Exertional dyspnoea occurred.

				Day 167 of administration (day of onset): Cough and dyspnoea occurred. [Chest X-ray findings] Small granular shadows - interstitial opacities appeared. Pneumonia including pneumocystis pneumonia (PCP) was suspected and the patient was urgently admitted to hospital. The results in the sputum test and β-D-glucan were negative, but PCP was suspected and administration of sulfamethoxazole plus trimethoprim (ST) combination drug was started. In addition, administration of prednisolone 80 mg/day was started for interstitial pneumonia. Day 6 of onset: The dose of prednisolone was reduced to 40 mg/day. Day 10 of onset: The dose of prednisolone was reduced to 20 mg/day. Day 13 of onset: The dose of prednisolone was reduced to 10 mg/day. Day 17 of onset: Bronchoscopy was performed, but PCP-polymerase chain reaction (PCR) was negative. Lung symptoms and increased CRP were observed again. Day 18 of onset: The dose of prednisolone was increased to 30 mg/day. Day 32 of onset: The dose of prednisolone was reduced to 27 mg/day. Day 39 of onset: The patient recovered from interstitial pneumonia and was discharged from hospital. Golimumab was not re-administered to the patient.
	Concomitant medications: indapamide, valsartan, amlodipine besilate, pilsicainide hydrochloride hydrate, bisoprolol fumarate, aspirin/dialuminate, irsogladine maleate, mosapride citrate hydrate			

Laboratory Examination

	2 days before administration	Day 154 of administration	Day 167 of administration (day of onset)	Day 2 of onset	Day 4 of onset	Day 12 of onset	Day 15 of onset	Day 19 of onset	Day 26 of onset	Day 30 of onset
CRP (mg/dL)	0.0	0.5	3.1	2.9	0.5	0.2	0.7	0.1	0.0	0.0
KL-6 (U/mL)	-	374	-	1,280	-	-	-	-	-	1,280

3

Revision of Precautions (No. 248)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated July 9, 2013 (excluding those presented in "2. Important Safety Information" of the preceding Bulletin and this Bulletin).

1 Psychotropics

Paliperidone

Brand Name

Invega Tablets 3 mg, 6 mg, 9 mg (Janssen Pharmaceutical K.K.)

Adverse Reactions (clinically significant adverse reactions)

Paralytic ileus: Intestinal paralysis (e.g. inappetence, nausea/vomiting, severe constipation, abdominal distension or abdominal flaccidity, and stagnation of intestinal contents) may occur and some of the cases may result in paralytic ileus. If intestinal paralysis is observed, appropriate measures such as discontinuation of administration should be taken. Antiemetic action was observed in animal testing (dogs).. Caution should be exercised since this drug has the potential to make nausea/vomiting clinically inapparent.

2 Acting mainly on gram-positive and gram-negative bacteria

Sulbactam Sodium/Ampicillin Sodium

Brand Name

UNASYN-S for Intravenous Use 0.75 g, 1.5 g, 3 g, UNASYN-S KIT for Intravenous Use 1.5 g, 3 g (Pfizer Japan Inc.) and the others

Adverse Reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis: Toxic epidermal necrolysis, oculomucocutaneous syndrome, or acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

3 Synthetic antibacterials

Sitafloxacin Hydrate

Brand Name

GRACEVIT TABLETS 50 mg, GRACEVIT FINE GRANULES 10%
(Daiichi Sankyo Company, Limited)

Adverse Reactions (clinically significant adverse reactions)

Shock, anaphylaxis: Shock or anaphylaxis may occur. Patients should be carefully monitored, and if abnormalities such as decreased blood pressure, dyspnoea, skin eruption, angioedema are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Oculomucocutaneous syndrome (Stevens-Johnson syndrome): Oculomucocutaneous syndrome may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Pseudomembranous colitis: Pseudomembranous colitis may occur. If abdominal pain, frequent diarrhoea, etc. are observed, administration of this drug should be discontinued and appropriate measures should be taken.

4 **Antivirals**

Peramivir Hydrate

Brand Name	RAPIACTA Bag for Intravenous Drip Infusion 300 mg, RAPIACTA Vial for Intravenous Drip Infusion 150 mg (Shionogi & Co., Ltd.)
Important Precautions	Hepatic dysfunction or jaundice may occur in the early stage (e.g. the next day of administration of this drug). Patients should be carefully monitored through liver function tests from immediately after administration of this drug.
Adverse Reactions (clinically significant adverse reactions)	**Hepatic dysfunction, jaundice**: Hepatic dysfunction or jaundice with significant elevations of AST (GOT), ALT (GPT), γ-GTP, Al-P and/or other signs or symptoms may occur in the early stage (e.g. the next day of administration of this drug). Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

5 **Chemotherapeutics-Miscellaneous**

Itraconazole

Brand Name	ITRIZOLE Capsules 50, ITRIZOLE Oral Solution 1%, ITRIZOLE Injection 1% (Janssen Pharmaceutical K.K.) and the others
Adverse Reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis, exfoliative dermatitis, erythema multiforme**: Toxic epidermal necrolysis, oculomucocutaneous syndrome, acute generalised exanthematous pustulosis, exfoliative dermatitis (erythroderma), or erythema multiforme may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

6 **Anthelmintics**

Albendazole

Brand Name	Eskazole Tablets 200 mg (GlaxoSmithKline K.K.)
Important Precautions	Hepatic dysfunction or jaundice may occur. Periodic liver function tests should be performed during administration of this drug, and if any abnormalities are observed, appropriate measures such as dose reduction or drug suspension should be taken.
Adverse Reactions (clinically significant adverse reactions)	**Hepatic dysfunction, jaundice**: Hepatic dysfunction or jaundice with elevations of AST (GOT), ALT (GPT), bilirubin, Al-P, etc. may occur. Periodic liver function tests should be performed during administration of this drug, and If any abnormalities are observed, appropriate measures such as dose reduction or drug suspension should be taken.

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 new drugs. It is imposed that its Marketing Authorization Holder is responsible for collecting the adverse drug reactions (ADRs) from all of the medical institutions where the drugs are used and for 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 adverse drug reactions. EPPV is specified as a condition of approval.

(As of August 1, 2013)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Tofacitinib Citrate XELJANZ Tablets 5 mg	Pfizer Japan Inc.	July 30, 2013
Metreleptin (Genetical Recombination) Metreleptin for Subcutaneous Injection 11.25 mg "SHIONOGI"	Shionogi & Co., Ltd.	July 25, 2013
Saxagliptin Hydrate ONGLYZA Tablets 2.5 mg, 5 mg	Kyowa Hakko Kirin Co., Ltd.	July 9, 2013
Oxybutynin Hydrochloride NEOXY TAPE 73.5 mg	Hisamitsu Pharmaceutical Co., Inc.	June 27, 2013
Clofarabine Evoltra 20 mg I.V. Infusion	Genzyme Japan K.K.	June 21, 2013
Lidocaine Penles Tape 18 mg*1	Nitto Denko Corporation	June 14, 2013
Tacrolimus Hydrate Prograf Capsules 0.5 mg, 1 mg*2	Astellas Pharma Inc.	June 14, 2013
Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL Intravenous Infusion, AVASTIN 400 mg/16 mL Intravenous Infusion*3	Chugai Pharmaceutical Co., Ltd.	June 14, 2013
Tramadol Hydrochloride Tramal Capsules 25 mg, 50 mg*4	Nippon Shinyaku Co., Ltd.	June 14, 2013
Aripiprazole ABILIFY tablets 3 mg, 6 mg, 12 mg, ABILIFY OD tablets 3 mg, 6 mg, 12 mg, ABILIFY powder 1%, ABILIFY oral solution 0.1%	Otsuka Pharmaceutical Co., Ltd.	June 14, 2013
Dexmedetomidine Hydrochloride (1) Precedex Intravenous Solution 200 μg "Hospira" (2) PRECEDEX Intravenous Solution 200 μg "Maruishi"	(1) Hospira Japan Co., Ltd. (2) Maruishi Pharmaceutical Co., Ltd.	June 14, 2013
Denosumab (Genetical Recombination) PRALIA SUBCUTANEOUS INJECTION 60 mg SYRINGE	Daiichi Sankyo Company, Limited	June 11, 2013

Acotiamide Hydrochloride Hydrate Acofide Tablets 100 mg	Zeria Pharmaceutical Co., Ltd.	June 6, 2013
Levetiracetam E Keppra Tablets 250 mg, 500 mg*[7]	UCB Japan Co. Ltd	May 31, 2013
Istradefylline NOURIAST Tablets 20 mg	Kyowa Hakko Kirin Co., Ltd.	May 30, 2013
Rufinamide Inovelon Tablets 100 mg, 200 mg	Eisai Co., Ltd.	May 29, 2013
Acamprosate Calcium Regtect Tablets 333 mg	Nippon Shinyaku Co., Ltd.	May 27, 2013
Ofatumumab (Genetical Recombination) Arzerra for I.V. infusion 100 mg, 1000 mg	GlaxoSmithKline K.K.	May 24, 2013
Tocilizumab (Genetical Recombination) ACTEMRA 162 mg Syringe for SC Injection, ACTEMRA 162 mg Auto-Injector for SC Injection	Chugai Pharmaceutical Co., Ltd.	May 24, 2013
Exenatide BYDUREON for Subcutaneous Injection 2 mg	Astra Zeneca K.K.	May 16, 2013
Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Stribild Combination Tab.	Japan Tobacco Inc.	May 14, 2013
Paromomycin Sulfate AMEPAROMO capsules 250 mg	Pfizer Japan Inc.	April 12, 2013
Botulinum Toxin Type B NerBloc for Intramuscular Injection 2500 Units	Eisai Co., Ltd.	March 27, 2013
Desmopressin Acetate Hydrate MINIRINMELT OD Tablet 60 μg*[8]	Ferring Pharmaceuticals Co., Ltd.	March 25, 2013
Regorafenib Hydrate Stivarga tablets 40 mg	Bayer Yakuhin, Ltd.	March 25, 2013
Methadone Hydrochloride METHAPAIN Tablets 5 mg, 10 mg	Teikoku Seiyaku Co., Ltd.	March 25, 2013
Fesoterodine Fumarate Toviaz Tablets 4 mg, 8 mg	Pfizer Japan Inc.	March 15, 2013
Certolizumab Pegol (Genetical Recombination) Cimzia 200 mg Syringe for S.C. Injection	UCB Japan Co. Ltd	March 8, 2013
Insulin Degludec (Genetical Recombination) TRESIBA Injection FlexTouch, TRESIBA Injection Penfill	Novo Nordisk Pharma Ltd.	March 7, 2013
Monobasic sodium phosphate monohydrate/Dibasic sodium phosphate anhydrous Phosribbon Combination Granules*[9]	Zeria Pharmaceutical Co., Ltd.	March 4, 2013
Fexofenadine Hydrochloride/Pseudoephedrine Hydrochloride dellegra Combination Tablets	Sanofi K.K.	February 28, 2013
Sodium Risedronate Hydrate BENET Tablets 75 mg.	Takeda Pharmaceutical Company Limited	February 28, 2013
Sodium Risedronate Hydrate Actonel Tab. 75 mg	Ajinomoto Pharmaceuticals Co., Ltd.	February 28, 2013
Rotigotine Neupro patch 2.25 mg, 4.5 mg, 9 mg, 13.5 mg	Otsuka Pharmaceutical Co., Ltd.	February 26, 2013

Levocarnitine L-Cartin FF oral solution 10%, L-Cartin FF injection 1000 mg	Otsuka Pharmaceutical Co., Ltd.	February 26, 2013
Apixaban Eliquis tablets 2.5 mg, 5 mg	Bristol-Myers K.K.	February 26, 2013
Atovaquone/Proguanil Hydrochloride Malarone Combination Tablets	GlaxoSmithKline K.K.	February 22, 2013
Tetrabenazine CHOREAZINE Tablets 12.5 mg	Alfresa Pharma Corporation	February 22, 2013
Famciclovir Famvir Tab. 250 mg*10	Asahi Kasei Pharma Corporation	February 21, 2013
Desmopressin Acetate Hydrate MINIRINMELT OD Tablet 120 μg, 240 μg*11	Ferring Pharmaceuticals Co., Ltd.	December 21, 2012

*1 An additional indication for “relief of pain in laser irradiation treatment of the skin”

*2 An additional indication for “treatment of patients with interstitial pneumonia associated with polymyositis/dermatomyositis”

*3 An additional indication for “treatment of patients with malignant glioma”

*4 An additional indication for “analgesia of chronic pain cannot be managed by treatments with non-opioid analgesics”

*5 An additional indication for “adjunctive therapy for depression/depressive state”

*6 An additional indication for “sedation in surgery or treatment without intubation under local anesthesia”

*7 An additional administration for “pediatrics”

*8 An additional indication for “treatment of patients with central diabetes insipidus”

*9 An additional indication for “treatment of patients with hypophosphataemia”

*10 An additional indication for “treatment of patients with herpes simplex”

*11 An additional indication for “treatment of patients with central diabetes insipidus”