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Effectiveness of drug postmarketing all-case surveillance as a safety measure in Japan

Hideyuki Kondo and Ken Masamune

Abstract

Introduction: The drug pharmacovigilance system in Japan is similar to those in the European Union (EU) and the United States. As a unique Japanese pharmacovigilance program, postmarketing all-case surveillance (PMACS) is required. PMACS plays a key role for postmarketing activities, but there are challenges that place much burden on PMACS conduct. This study investigates the impact of PMACS on postmarketing activities in Japan and proposes its potential improvement. This study also seeks the possibility to expand PMACS beyond Japan.

Materials and Methods: Reexamination reports issued from 2017 to 2019 were identified in September 2020 by searching 'reexamination report' and '201701' to '201912' on the Pharmaceuticals and Medical Devices Agency website. The corresponding Package Insert (PI) change orders and premarketing review reports were also identified. Reviewing these regulatory documents allowed for investigation of the PMACS impact on postmarketing activities.

Results: More than half (57%) of the drugs with PMACS had 'Limited dosing experience in Japan' as a reason for the PMACS requirement. As a safety measure, no PI change orders were imposed on 33% and 28% of drugs with and without PMACS, respectively. The means of the number of PI change orders were 2.23 and 2.14 for drugs with and without PMACS, respectively. There were no reexamination reports mentioning any concerns related to efficacy.

Discussion and Conclusion: PMACS should not be imposed only because of limited dosing experience in Japan at the premarketing stage. Rather, PMACS should focus on (1) collection of safety data (not efficacy), (2) necessity of distribution control, and/or (3) collection of case details for drugs with a limited treated population. PMACS also has the potential to be utilized in the EU and the United States, as their regulatory frameworks are acceptable for PMACS. Naglazyme (galsulfase) is a case where the PMACS-like studies have been required in each region.

Correspondence to:
Ken Masamune
Cooperative Major in Advanced Biomedical Sciences, Joint Graduate School of Tokyo Women's Medical University and Waseda University, Tokyo, Japan
masamune.ken@twmu.ac.jp

Hideyuki Kondo
Cooperative Major in Advanced Biomedical Sciences, Joint Graduate School of Tokyo Women's Medical University and Waseda University, Tokyo, Japan

Plain Language Summary

Effectiveness of data collection for all patients who receive a new drug as a safety measure in Japan

Introduction: In Japan, a drug company is obligated to conduct data collection after a new drug launch as an approval condition. The obligation is a unique Japanese requirement where a company must collect data from all patients receiving the drug in Japan in cooperation with hospitals. This is expected to contribute to intensive data collection and better drug distribution control and could potentially be useful in countries beyond Japan. However, no clear criteria have been established for decision making, despite the significant burden for companies and hospitals. Therefore, this study aimed to investigate

the impact of the obligation on safety measures and efficacy data collection and propose a potentially improved drug scope to impose the obligation.
Materials and Methods: Reexamination of reports issued by the Pharmaceuticals and Medical Devices Agency between 2017–2019.
Results: More than half (57%) of the included drugs had 'Limited dosing experience in Japan' as a reason for the obligation being required. However, regulatory order to change drug label, an action based on safety signal identification, was imposed on 33% and 28% of drugs with and without the obligation, respectively. The means of the number of the label change orders were 2.23 and 2.14 for drugs with and without obligation, respectively. Meanwhile, some drugs were highlighted as potential factors for better application of the obligation.
Conclusion: According to these results, the obligation should be imposed on a limited number of drugs by focusing not on dosing experience in Japan but on safety (not efficacy) data collection, necessity of distribution control, and/or collection of case details for drugs with a limited treated population. The obligation also has the potential to be utilized in the EU and the United States, as their regulatory frameworks are acceptable for the obligation.

Keywords: Japan, MHLW, package insert, PMDA, postmarketing all-case surveillance, reexamination

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Introduction

The drug pharmacovigilance system in Japan has three key components: (A) adverse reaction reporting system, (B) reexamination system with a Periodic Safety Update Report (PSUR), and (C) postmarketing study/surveillance.[1] Figure 1 shows an overview of the pharmacovigilance system in Japan.

The pharmacovigilance system in Japan is similar to those in the European Union (EU) and the United States:

A. Adverse reaction reporting system: The Japanese regulators, the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA), monitor and assess safety signals, and take regulatory measures as needed. Similar systems for adverse reaction reporting have been implemented in the EU (pharmacovigilance system)[2] and the United States (FDA adverse event reporting system).[3]
B. Reexamination system with PSUR: The reexamination system in Japan requires a Marketing Authorization Holder (MAH) to collect data for drugs and prepare PSURs for a certain period in their postmarketing stage. At the end of the reexamination period, the Japanese regulators assess the benefit/risk balance of these drugs. Systems to collect postmarketing data, prepare PSURs and assess the benefit/risk balance of an approved drug have been implemented in the EU (PSURs)[4] and the United States (Periodic adverse drug experience reports)[5] as well.
C. Postmarketing study/surveillance: A postmarketing study/surveillance requirement/commitment is imposed on an MAH upon drug approval in Japan. The EU and the United States have similar regulatory systems, Post-Authorisation Safety Studies (PASS)[6] and Postmarketing Requirements and Commitments,[7] respectively.

However, as a unique Japanese pharmacovigilance requirement, the MHLW is authorized to compel an MAH to conduct a postmarketing all-case surveillance (PMACS) as a drug approval condition. PMACS is a type of postmarketing study/surveillance requirement/commitment mentioned above. PMACS is an observational single-arm postmarketing study where an MAH must work with medical institutes to collect data from all the patients received its drug in Japan. PMACS has been implemented for more than 20 years in Japan,[8] and the number of approved drugs with PMACS as an approval condition have increased since 2003.[9]

The MHLW explains in the PMACS notification that PMACS is obligatory in the cases where the

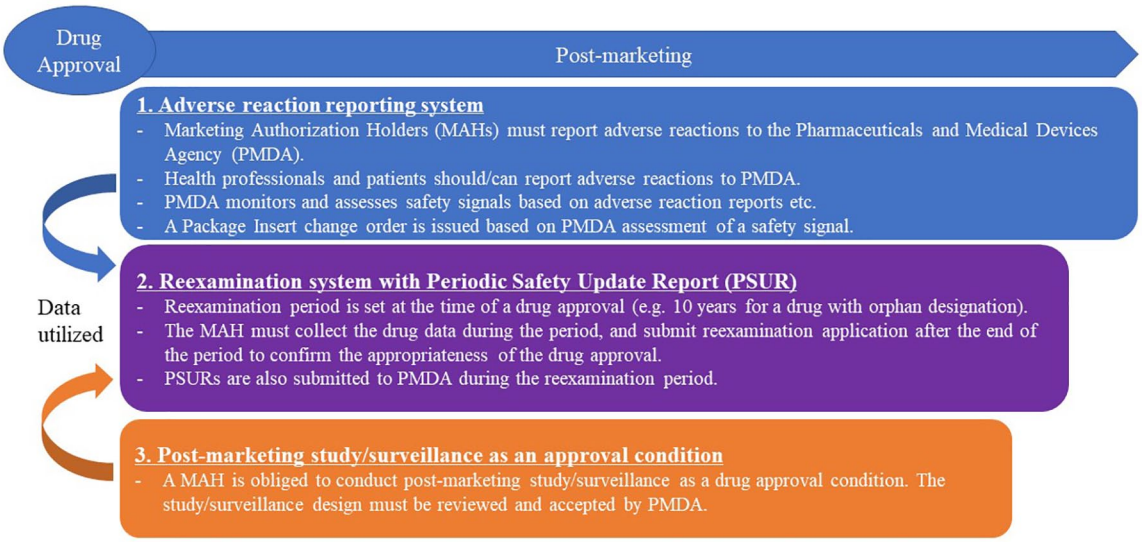

Figure 1. Pharmacovigilance system for Drugs in Japan. Adverse reaction reporting system, reexamination system and postmarketing study/surveillance are a key driver for drug pharmacovigilance system in Japan.

number of subjects in Japan is low or none in clinical studies for a drug at the premarketing phase or where the drug is likely to cause serious adverse effects.[10] The MHLW expects that PMACS contributes to collecting demographic information on patients in Japan and information on safety and efficacy quickly and without any biases.

MAHs with PMACS experience indicated that PMACS had been useful mainly because (a) case details had been collected even in a limited population, (b) information on off-label use had been obtained, and (c) eligibility of medical institutes, physicians, and patients had been confirmed.[11] Meanwhile, it has been reported that the resource burden for MAH to conduct PMACS was more than 1.5 times (more than 5.0 times in some surveillances) compared with general postmarketing activities, including postmarketing studies.[11] Moreover, PMACS was burdensome for medical institutes due to excessive data collection and entity in a specified form, complicated survey form use, cumbersome contract procedures, and long-term patient follow-up.

Therefore, whether to impose PMACS or not as an approval condition should be carefully decided, taken into account the balance between expected achievement and necessary burden. However, there exist no specific criteria for the decision. Approximately 90% of drugs with PMACS have the reason for its obligation that the number of Japanese patients in the premarketing phase was too small.[11]

In summary, PMACS has played a key role in the pharmacovigilance system for drugs in Japan, while the decision whether PMACS is required or not was mainly made by limited dosing experience in Japan, in spite of the high burden of its conduct on MAH and medical institute. This study aimed to investigate the impact of PMACS on safety measures and efficacy data collection in Japan. According to the investigation, we propose a possible improvement of the product scope to impose PMACS as a drug approval condition. The proposal contributes to better pharmacovigilance activities in Japan. This study also considers the potential to introduce PMACS beyond Japan based on the pharmacovigilance systems in Japan, the EU, and the United States.

Materials and methods

Data material sources

There are three types of Japanese regulatory documents used in this study; (A) drug reexamination reports, (B) drug premarketing review reports, and (C) Package Insert (PI) change orders.

A. Drug reexamination report: It is prepared and published by the PMDA once the reexamination period has ended. The report summarizes the information related to

safety and efficacy data collected during the specified reexamination period. This includes PMACS data, if applicable.

B. Drug premarketing review report: It is prepared and published by the PMDA once the drug is approved. The report includes information on the approval conditions, including PMACS requirements.

C. PI change order: It is a regulatory notification issued by the MHLW as a safety measure at the postmarketing stage of a drug. PI is equivalent to Summary of Product Characteristics (SmPC) in EU and drug label in the United States. The MHLW issues the order if the PMDA identifies a safety signal for the drug and completes the assessment based on accumulated safety data via the adverse reaction reporting system, the PSUR, and postmarketing study/surveillance, including PMACS. An MAH must change the drug PI, according to the notification.

These documents can be found in the PMDA website to search for information on each drug in Japan.[12] In this study, the reexamination reports issued from 2017 to 2019 were identified in September 2020 by searching for 'reexamination report' and '201701' to '201912' on the PMDA website. The corresponding PI change orders and premarketing review reports were also identified on the same website.

The 3-year period is expected to present the trend of deciding whether to impose PMACS after the PMDA started conducting drug premarket reviews. The PMDA was established in April 2004,[13] and the standard duration of the premarketing priority review by the PMDA has been set at 9.0 months.[14] Therefore, new drugs reviewed by the PMDA were launched from 2005. The reexamination period of a drug is up to 10 years.[15] The median assessment duration for reexamination by the PMDA was 15.0 months in Fiscal Year 2018.[14] Hence, the reexamination reports from 2017 are expected to cover the majority of drugs reviewed by the PMDA.

Method to investigate the impact of PMACS

Listing and categorization of reexamination report. Reexamination reports issued from 2017 to 2019 were listed with issue date, nonproprietary name and brand name. Each report was flagged with the items below by checking premarketing review reports of these drugs:

A. Approval type: Identify whether the approval is for a new drug or label expansion (e.g. new indication).

B. PMACS: Identify whether PMACS was conducted.

C. Reason for PMACS: Categorized the reasons for PMACS with 'Limited dosing experience in Japan', 'Further data collection', 'Specific safety concern(s)', or 'Other'.

Then, the items below were added to the list by investigating PI change orders of each drug:

D. PI change order: Identify whether the MHLW issued order(s) for PI change during the reexamination period.

E. Number of PI change orders: Enter the number of PI change orders for each drug during the reexamination period.

Based on the list with these items above, the reexamination reports were categorized by (A) Approval type, (B) PMACS, and (D) PI change order. In addition, the number of reexamination reports were compared by (C) Reason for PMACS.

Assessment from viewpoint of drug safety measures. The number of PI change orders for each drug were checked. The number is considered a quantitative index for safety measures taken during their reexamination period, based on the description of PI change order in Part C of the section 'Data material sources'.

Then, drugs with five or more PI change orders issued during their reexamination periods were categorized by therapeutic area of the World Health Organization Anatomical Therapeutic Chemical and Defined Daily Dose (WHO ATC/DDD) index. Five or more PI change orders means that safety measures were taken every 2 years or more frequently on average during reexamination period.

Assessment from viewpoint of drug efficacy data collection. The efficacy information in each reexamination report was examined to identify any specific findings related to efficacy.

Identification of distinctive cases in term of PMACS impact. Each reexamination report was reviewed to identify any distinctive drugs/indications where decision with PMACS/no PMACS affected their postmarketing activities.

Results of investigation for the impact of PMACS

Listing and categorization of reexamination report

According to the search using the conditions outlined in the section 'Data material sources', 221 reexamination reports were identified in 2017–2019. Two reports for the egg-derived influenza A (H5 N1) vaccine were excluded from this study, because these vaccines had not been marketed during the reexamination period. In addition, a report on sitagliptin was excluded as two similar reports with two different brand names were published due to concurrent selling by two MAHs in Japan. Therefore, 218 reports were included in this study in total. The list of these reports is shown in Table 1.

Figure 2 shows the categorization of the 218 reexamination reports. Among them, 158 and 60 cases were for new drug and label expansion, respectively. PMACS was obligatory in 52 of the 158 cases with new drug approval. Among the 52 cases, one or more PI change orders were issued in 36 cases (69%) during the reexamination period. Meanwhile, there were 106 cases with new drug approvals where PMACS was not obligatory. Among the 106 cases, one or more PI change orders were issued in 73 cases (69%) during their reexamination periods.

PMACS was obligatory in 11 of the 60 cases with label expansion. One or more PI change orders were issued in 7 (64%) of the 11 cases during their reexamination periods. Meanwhile, there were 49 cases with label expansion where PMACS was not obligatory. Among the 49 cases, one or more PI change orders were issued in 37 cases (76%) during the reexamination period.

Figure 3 compares the number of reexamination reports by reason for PMACS. More than half (57%) of the cases with PMACS had 'Limited dosing experience in Japan' as a reason for PMACS obligation. PMACS was conducted voluntarily in four out of five cases with the reason 'Other'. The fifth case was Tracleer (bosentan hydrate) (Janssen Pharmaceutical K.K., Japan), for which PMACS was required because the indications approved were wider than those targeted in premarketing clinical studies.

Assessment from viewpoint of drug safety measures

The number of PI change orders was identified for 198 drugs, as two reexamination reports were issued for 20 drugs, since these reports targeted different indications. As a PI change order is issued for the relevant drug, not for each indication, these 20 reports were excluded from the calculated number to avoid duplicate counting. Table 2 summarizes these results. No PI change orders were issued for 33% and 29% of drugs with and without PMACS, respectively, during their reexamination periods. The means of the number of PI change orders were 2.23 and 2.15 for drugs with PMACS and without PMACS, respectively.

Table 3 shows the number of drugs with five or more PI change orders issued during their reexamination periods by WHO ATC/DDD index. Totally, five or more PI change orders were issued in 10 out of 61 (16%) drugs with PMACS and 20 out of 137 (15%) drugs without PMACS. The highest number of the drugs fell into 'anti-infectives for systemic use' (11 drugs). However, the number was obtained due to the PI change order, not for a specific product, but for all the influenza related products in Japan with four influenza vaccines and Tamiflu (oseltamivir phosphate) (Chugai Pharmaceutical Co., Ltd., Japan). Once the order is excluded, 'anti-neoplastic and immunomodulating agents' have the highest number (eight drugs).

Assessment from viewpoint of drug efficacy data collection

There were no reexamination reports mentioning any outstanding findings related to drug efficacy.

Identification of distinctive cases in term of PMACS impact

Four drugs were identified by review of each reexamination report in terms of decision with and without PMACS which affected postmarketing activities; Nexavar (sorafenib tosilate) (Bayer

Table 1. List of reexamination reports issued from 2017 to 2019.

	Issue date	Nonproprietary name	Brand name	Approval type New product?	PMACS?	Reason for PMACS[a]	PI change order?	Number of PI change orders
1	29 March 2018	Adapalene	Differin Gel	Yes	No	NA	No	0
2	21 December 2017	Agalsidase Alfa (Genetical Recombination)	REPLAGAL	Yes	Yes	1	Yes	1
3	29 March 2018	Alendronate Sodium Hydrate	Bonalon Bag for I.V. Infusion	Yes	No	NA	Yes	1
4	29 March 2018	Alglucosidase Alfa (Genetical Recombination)	MYOZYME	Yes	Yes	1	Yes	1
5	11 September 2019	Aliskiren Fumarate	Rasilez Tablets	Yes	No	NA	Yes	4
6	11 September 2019	Alogliptin Benzoate	NESINA Tablets	Yes	No	NA	Yes	4
7	19 September 2019	Alogliptin Benzoate Pioglitazone Hydrochloride	LIOVEL Combination Tablets HD	Yes	No	NA	Yes	4
8	29 March 2018	Amiodarone Hydrochloride	Ancaron	Yes	Yes	1	Yes	3
9	29 March 2018	Ampicillin Sodium, Sulbactam Sodium	UNASYN-S for Intravenous Use	No	No	NA	Yes	1
10	11 September 2019	Amrubicin Hydrochloride	Calsed for Inj.	Yes	No	NA	Yes	2
11	20 December 2018	Aprepitant	EMEND Capsules	Yes	No	NA	No	0
12	29 March 2018	Aripiprazole	ABILIFY oral solution	Yes	No	NA	Yes	6
13	27 September 2018	Aripiprazole	ABILIFY oral solution	No	No	NA	Yes	6
14	29 June 2017	Aspirin, Lansoprazole	TAKELDA Combination Tablets	No	No	NA	No	0
15	29 March 2018	Atazanavir Sulfate	REYATAZ CAPSULES	Yes	Yes	2	Yes	5
16	5 September 2018	Atomoxetine Hydrochloride	Strattera Capsules	Yes	No	NA	Yes	3
17	5 September 2018	Azithromycin Hydrate	ZITHROMAC Intravenous use	Yes	No	NA	Yes	4
18	5 September 2018	Azithromycin Hydrate	ZITHROMAC Tablets	Yes	No	NA	Yes	6
19	29 March 2018	Baclofen	GABALON INTRATHECAL INJECTION	Yes	Yes	3	No	0
20	11 September 2019	Bazedoxifene Acetate	Viviant Tablets	Yes	No	NA	No	0

(Continued)

Table 1. (Continued)

	Issue date	Nonproprietary name	Brand name	Approval type New product?	PMACS?	Reason for PMACS[a]	PI change order?	Number of PI change orders
21	27 September 2018	Bevacizumab (Genetical Recombination)	AVASTIN for Intravenous Infusion	Yes	Yes	1	Yes	3
22	5 December 2018	Bimatoprost	LUMIGAN OPHTHALMIC SOLUTION	Yes	No	NA	No	0
23	5 June 2019	Blonanserin	LONASEN Tablets	Yes	No	NA	Yes	6
24	29 March 2018	Bortezomib	VELCADE Injection	Yes	Yes	1	Yes	3
25	19 December 2019	Bortezomib	VELCADE Injection	No	No	NA	Yes	3
26	28 September 2017	Bosentan Hydrate	Tracleer	Yes	Yes	4	Yes	3
27	28 September 2017	Budesonide	Pulmicort	No	No	NA	Yes	0
28	29 March 2018	Budesonide Formoterol Fumarate Hydrate	Symbicort Turbuhaler	No	No	NA	No	0
29	20 December 2018	Busulfan	Busulfex injection	Yes	Yes	1	No	0
30	29 March 2018	Calcium Folinate	LEUCOVORIN INJECTION	No	No	NA	Yes	1
31	30 March 2017	Candesartan Cilexetil Hydrochlorothiazide	ECARD Combination Tablets	Yes	No	NA	Yes	3
32	20 June 2019	Capecitabine	XELODA Tablets	Yes	No	NA	Yes	3
33	29 March 2018	Cetuximab (genetical recombination)	ERBITUX Injection	Yes	Yes	1	Yes	1
34	27 September 2018	Ciclesonide	Alvesco	Yes	No	NA	No	0
35	28 September 2017	Ciclosporin	Neoral	No	No	NA	Yes	4
36	29 June 2017	Ciclosporin	PAPILOCK Mini ophthalmic solution	Yes	Yes	1	No	0
37	29 March 2018	Cinacalcet Hydrochloride	REGPARA TABLETS	Yes	No	NA	Yes	1
38	20 June 2019	Cladribine	LEUSTATIN Injection	Yes	Yes	2	Yes	3
39	5 December 2018	Clopidogrel Sulfate	Plavix Tablets	No	No	NA	Yes	7
40	19 December 2019	Clozapine	CLOZARIL Tablets	Yes	Yes	1	Yes	5
41	21 December 2017	Darbepoetin Alfa (Genetical Recombination)	NESP INJECTION PLASTIC SYRINGE	No	No	NA	No	0

(Continued)

Table 1. (Continued)

	Issue date	Nonproprietary name	Brand name	Approval type New product?	PMACS?	Reason for PMACS[a]	PI change order?	Number of PI change orders
42	7 March 2019	Darbepoetin Alfa (Genetical Recombination)	NESP INJECTION PLASTIC SYRINGE	Yes	No	NA	No	0
43	11 December 2019	Darunavir Ethanolate	PREZISTANAIVE Tablets	Yes	Yes	2	Yes	6
44	5 June 2019	Deferasirox	Exjade	Yes	No	NA	No	0
45	20 December 2018	Dexamethasone cipecilate	Erizas Capsule for Nasal spray	Yes	No	NA	No	0
46	28 June 2018	Dexmedetomidine Hydrochloride	Precedex Injections	No	No	NA	No	0
47	5 June 2019	Diarsenic trioxide	Trisenox Injection	Yes	Yes	2	Yes	3
48	29 March 2018	Diazoxide	DIAZOXIDE Capsules	Yes	Yes	1	Yes	2
49	29 March 2018	Dienogest	DINAGEST Tablets	Yes	No	NA	Yes	2
50	11 September 2019	Diquafosol Sodium	DIQUAS ophthalmic solution	Yes	No	NA	No	0
51	21 December 2017	Doripenem Hydrate	FINIBAX	Yes	No	NA	Yes	4
52	21 December 2017	Doripenem Hydrate	FINIBAX	No	No	NA	Yes	4
53	21 December 2017	Dorzolamide Hydrochloride, Timolol Maleate	COSOPT ophthalmic solution	Yes	No	NA	No	0
54	27 September 2018	Doxorubicin Hydrochloride, Doxorubicin	DOXIL Injection	Yes	Yes	1	No	0
55	20 December 2018	Dutasteride	Avolve Capsules	Yes	No	NA	Yes	1
56	29 March 2018	Enoxaparin Sodium	Clexane S.C. Injection	Yes	No	NA	Yes	2
57	5 December 2018	Entacapone	Comtan Tablets	Yes	No	NA	Yes	1
58	29 March 2018	Entecavir Hydrate	Baraclude Tablets	Yes	No	NA	Yes	4
59	21 December 2017	Eplerenone	Selara Tablets	Yes	No	NA	No	0
60	14 March 2019	Erlotinib Hydrochloride	TARCEVA Tablets	Yes	Yes	2	Yes	3
61	29 March 2018	Estradiol	Julina tablets	Yes	No	NA	Yes	2
62	29 March 2018	Estradiol Levonorgestrel	Wellnara combination tablets	Yes	No	NA	Yes	1
63	30 March 2017	Etanercept (genetical recombination)	ENBREL 10 mg for S.C. Injection	No	Yes	3	Yes	5

(Continued)

Table 1. (Continued)

	Issue date	Nonproprietary name	Brand name	Approval type New product?	PMACS?	Reason for PMACS[a]	PI change order?	Number of PI change orders
64	28 September 2017	Etanercept (genetical recombination)	ENBREL 10 mg for S.C. Injection	Yes	Yes	3	Yes	5
65	14 March 2019	Everolimus	AFINITOR tablets	Yes	Yes	2	Yes	2
66	28 September 2017	Ezetimibe	Zetia	Yes	No	NA	Yes	1
67	21 December 2017	Famciclovir	Famvir Tablets	Yes	No	NA	Yes	3
68	29 March 2018	Famciclovir	Famvir Tablets	No	No	NA	Yes	3
69	29 June 2017	Fentanyl	OneDuro Patch	Yes	No	NA	Yes	1
70	14 March 2019	Fentanyl	OneDuro Patch	No	No	NA	Yes	1
71	20 December 2018	Fentanyl Citrate	Abstral Sublingual Tablets	Yes	No	NA	No	0
72	5 December 2018	Fentanyl Citrate	E-fen buccal tablet	Yes	No	NA	No	0
73	6 June 2018	Fentanyl Citrate	FENTOS Tapes	No	No	NA	No	0
74	11 September 2019	Fentanyl Citrate	FENTOS Tapes	No	No	NA	No	0
75	11 September 2019	Fexofenadine Hydrochloride	Allegra Dry Syrup	No	No	NA	No	0
76	7 March 2019	fibrinogen combined drug	TachoSil Tissue Sealing sheet	Yes	No	NA	No	0
77	7 March 2019	Fludarabine Phosphate	Fludara	Yes	Yes	2	Yes	3
78	5 December 2018	Fluticasone Furoate	Allermist 27.5 μg metered Nasal Spray	Yes	No	NA	Yes	1
79	11 September 2019	Fluticasone Furoate	Allermist 27.5 μg metered Nasal Spray	No	No	NA	Yes	1
80	30 March 2017	Follitropin alfa (genetical recombination)	Gonalef	No	No	NA	Yes	3
81	29 March 2018	Follitropin alfa (genetical recombination)	Gonalef	Yes	Yes	1	Yes	3
82	21 December 2017	Formoterol Fumarate Hydrate	Oxis	Yes	No	NA	Yes	0
83	30 March 2017	Gabapentin	GABAPEN Syrup	Yes	No	NA	Yes	4
84	30 March 2017	Gadoxetate Sodium	EOB・Primovist Inj. Syringe	Yes	No	NA	Yes	2
85	19 September 2019	Galsulfase (Genetical Recombination)	Naglazyme	Yes	Yes	1	Yes	1

(Continued)

Table 1. (Continued)

	Issue date	Nonproprietary name	Brand name	Approval type New product?	PMACS?	Reason for PMACS[a]	PI change order?	Number of PI change orders
86	21 December 2017	Ganirelix Acetate	GANIREST Subcutaneous	Yes	No	NA	Yes	1
87	30 March 2017	Garenoxacin Mesilate Hydrate	Geninax Tablets	Yes	No	NA	Yes	9
88	29 March 2018	Gemcitabine Hydrochloride	Gemzar Injection	No	Yes	2	Yes	3
89	6 June 2018	Gemtuzumab Ozogamicin (Genetical Recombination)	MYLOTARG Injection	No	Yes	1	No	0
90	29 March 2018	Human activated protein C, freeze-dried concentrated	Anact C	No	Yes	1	No	0
91	21 December 2017	Human Chorionic Gonadotrophin	GONATROPIN FOR INJECTION	No	Yes	1	Yes	2
92	20 June 2019	Ibritumomab Tiuxetan (genetical recombination)	ZEVALIN yttrium injection	Yes	Yes	1	Yes	1
93	14 March 2019	Idursulfase (Genetical Recombination)	ELAPRASE	Yes	Yes	1	No	0
94	11 December 2019	Imatinib Mesilate	Glivec Tablets	Yes	Yes	2	Yes	7
95	19 December 2019	Imatinib Mesilate	Glivec Tablets	No	Yes	2	Yes	7
96	30 March 2017	Imiquimod	BESELNA CREAM	Yes	No	NA	No	0
97	29 June 2017	Imiquimod	BESELNA CREAM	No	No	NA	No	0
98	21 December 2017	Infliximab (genetical recombination)	REMICADE for I.V. Infusion	No	No	NA	Yes	9
99	27 September 2018	Infliximab (genetical recombination)	REMICADE for I.V. Infusion	No	Yes	1	Yes	9
100	30 March 2017	Influenza HA vaccine	INFLUENZA HA VACCINE "BIKEN"	No	No	NA	Yes	5
101	30 March 2017	Influenza HA vaccine	INFLUENZA HA VACCINE "SEIKEN"	No	No	NA	Yes	5
102	30 March 2017	Influenza HA vaccine	INFLUENZA HA VACCINE "DAIICHI SANKYO"	No	No	NA	Yes	5
103	29 June 2017	Influenza HA vaccine	INFLUENZA HA VACCINE "KMB"	No	No	NA	Yes	5
104	21 December 2017	Insulin Detemir (Genetical Recombination)	Levemir InnoLet	Yes	No	NA	Yes	2

(Continued)

Table 1. (Continued)

	Issue date	Nonproprietary name	Brand name	Approval type New product?	PMACS?	Reason for PMACS[a]	PI change order?	Number of PI change orders
105	28 June 2018	Insulin Glulisine (Genetical Recombination)	Apidra Cart S.C. Injection	Yes	No	NA	No	0
106	29 March 2018	Interferon Beta	FERON	No	No	NA	Yes	6
107	29 March 2018	Interferon Beta-1a (Genetical Recombination)	AVONEX IM Injection	Yes	Yes	1	Yes	2
108	29 March 2018	Irbesartan	AVAPRO Tablets	Yes	No	NA	Yes	1
109	29 March 2018	Irbesartan, Amlodipine Besilate	AIMIX	Yes	No	NA	Yes	2
110	29 June 2017	Itraconazole	ITRIZOLE Oral Solution	No	No	NA	Yes	4
111	27 September 2018	Japanese encephalitis vaccine	JEBIK V	Yes	No	NA	Yes	3
112	28 June 2018	Lamotrigine	Lamictal Tablets	Yes	No	NA	Yes	2
113	21 December 2017	Lanthanum Carbonate Hydrate	Fosrenol Chewable Tablets	Yes	Yes	1	Yes	2
114	19 December 2019	Lapatinib Tosilate Hydrate	Tykerb Tablets	Yes	Yes	1	No	0
115	21 December 2017	Laronidase (Genetical Recombination)	ALDURAZYME	Yes	Yes	1	No	0
116	21 December 2017	Latanoprost Timolol Maleate	Xalacom Combination Eye Drops	Yes	No	NA	No	0
117	29 March 2018	Levobupivacaine Hydrochloride, levobupivacaine	POPSCAINE 0.25% inj.	No	No	NA	No	0
118	29 March 2018	Levobupivacaine Hydrochloride, levobupivacaine	POPSCAINE 0.25% inj.	Yes	No	NA	No	0
119	21 December 2017	Levofloxacin Hydrate	CRAVIT FINE GRANULES	Yes	No	NA	Yes	3
120	29 March 2018	Levofloxacin Hydrate	CRAVIT INTRAVENOUS DRIP INFUSION	Yes	No	NA	Yes	2
121	5 September 2018	Lidocaine	Penles Tape	No	No	NA	No	0
122	20 June 2019	Liraglutide (Genetical Recombination)	Victoza Subcutaneous Injection	Yes	No	NA	Yes	3
123	7 March 2019	Meropenem Hydrate	Meropen	No	No	NA	Yes	2

(Continued)

Table 1. (Continued)

	Issue date	Nonproprietary name	Brand name	Approval type New product?	PMACS?	Reason for PMACS[a]	PI change order?	Number of PI change orders
124	11 December 2019	Methylphenidate Hydrochloride	Concerta Tablets	No	No	NA	Yes	3
125	29 March 2018	Miglitol	SEIBULE	Yes	No	NA	Yes	3
126	7 March 2019	Miriplatin Hydrate	MIRIPLA	Yes	No	NA	Yes	3
127	5 December 2018	Mirtazapine	REFLEX TABLETS	Yes	No	NA	Yes	4
128	6 June 2018	Modafinil	MODIODAL Tablets	Yes	Yes	1	Yes	2
129	11 September 2019	Modafinil	MODIODAL Tablets	No	No	NA	Yes	2
130	6 June 2018	Mometasone Furoate	ASMANEX Twisthaler	Yes	No	NA	No	0
131	29 March 2018	Mometasone Furoate Hydrate	NASONEX Nasal 50 μg 112sprays	Yes	No	NA	No	0
132	29 March 2018	Monteplase (genetical recombination)	Cleactor	No	Yes	2	Yes	1
133	21 December 2017	Moxifloxacin Hydrochloride	VEGAMOX Ophthalmic Solution	Yes	No	NA	No	0
134	29 March 2018	Moxifloxacin Hydrochloride	Avelox	Yes	No	NA	Yes	4
135	29 March 2018	Mozavaptan Hydrochloride	Physuline tablets	Yes	Yes	1	No	0
136	5 December 2018	Nalfurafine Hydrochloride	REMITCH CAPSULES	Yes	No	NA	Yes	1
137	29 June 2017	Naratriptan Hydrochloride	Amerge Tablets	Yes	No	NA	Yes	1
138	20 June 2019	Nelarabine	ARRANON G Injection	Yes	Yes	1	Yes	2
139	7 March 2019	Norethisterone Ethinylestradiol	LUNABELL tablets ULD	Yes	No	NA	Yes	2
140	11 December 2019	Olanzapine	Zyprexa tablets	Yes	No	NA	Yes	2
141	5 December 2018	Olanzapine	Zyprexa Zydis tablets	No	No	NA	Yes	7
142	30 March 2017	Olopatadine Hydrochloride	ALLELOCK Granules	No	No	NA	Yes	1
143	6 June 2018	Oseltamivir Phosphate	TAMIFLU Capsules	No	No	NA	Yes	6
144	29 March 2018	Oxaliplatin	ELPLAT I.V. INFUSION SOLUTION	Yes	Yes	2	Yes	4

(Continued)

Table 1. (Continued)

	Issue date	Nonproprietary name	Brand name	Approval type New product?	PMACS?	Reason for PMACS[a]	PI change order?	Number of PI change orders
145	20 December 2018	Oxycodone Hydrochloride Hydrate	OXIFAST	Yes	No	NA	No	0
146	5 December 2018	Paclitaxel	Abraxane I.V. Infusion	Yes	Yes	1	No	0
147	19 December 2019	Paliperidone	Invega Tablets	Yes	No	NA	Yes	4
148	11 December 2019	Palivizumab (Genetical Recombination)	Synagis Solution for intramuscular Administration	No	No	NA	Yes	1
149	30 March 2017	Pamidronate Disodium Hydrate	Aredia for I.V. infusion	No	No	NA	No	0
150	20 June 2019	Panitumumab (Genetical Recombination)	Vectibix	Yes	Yes	1	Yes	4
151	29 March 2018	Peginterferon Alfa-2a (Genetical Recombination)	PEGASYS for Subcutaneous Injection	No	No	NA	Yes	8
152	29 March 2018	Peginterferon Alfa-2a (Genetical Recombination)	PEGASYS for Subcutaneous Injection	No	No	NA	Yes	8
153	29 March 2018	Peginterferon Alfa-2b (Genetical Recombination)	PEGINTRON Powder for Injection	No	No	NA	Yes	4
154	21 December 2017	Pegvisomant (Genetical Recombination)	SOMAVERT for s.c. Injection	Yes	Yes	1	No	0
155	29 March 2018	Pemetrexed Sodium Hydrate	Alimta Injection	Yes	Yes	1	Yes	2
156	11 September 2019	Peramivir Hydrate	RAPIACTA for Intravenous Drip Infusion	Yes	No	NA	Yes	5
157	28 September 2017	Perflubutane	SONAZOID FOR INJECTION	No	No	NA	Yes	1
158	21 December 2017	Phenobarbital Sodium	NOBELBAR 250mg for Injection	No	No	NA	Yes	1
159	20 June 2019	Phenothrin	SUMITHRIN Lotion	Yes	No	NA	No	0
160	30 March 2017	Pioglitazone Hydrochloride Glimepiride	SONIAS Combination Tablets	Yes	No	NA	Yes	3
161	30 March 2017	Pioglitazone Hydrochloride Metformin Hydrochloride	METACT Combination Tablets	Yes	No	NA	Yes	4
162	19 December 2019	Pirfenidone	Pirespa	Yes	Yes	4	Yes	1
163	29 March 2018	Polaprezinc	Promac granules	Yes	No	NA	Yes	1

(Continued)

Table 1. (Continued)

	Issue date	Nonproprietary name	Brand name	Approval type New product?	PMACS?	Reason for PMACS[a]	PI change order?	Number of PI change orders
164	29 June 2017	Pranlukast Hydrate	ONON drysyrup	No	No	NA	Yes	1
165	20 June 2019	Pregabalin	LYRICA Capsules	Yes	No	NA	Yes	2
166	19 December 2019	Raltegravir potassium	ISENTRESS Tablets	Yes	Yes	2	Yes	3
167	20 June 2019	Ramelteon	Rozerem Tablets	Yes	No	NA	No	0
168	7 March 2019	Rasburicase (Genetical Recombination)	RASURITEK	Yes	No	NA	No	0
169	7 March 2019	Rebamipide	Mucosta tablets	Yes	No	NA	Yes	1
170	29 March 2018	Rifabutin	MYCOBUTIN Capsules	No	Yes	2	No	0
171	29 March 2018	Risperidone	RISPERDAL Consta Intramuscular Injection	Yes	No	NA	Yes	5
172	29 March 2018	Rocuronium Bromide	ESLAX Intravenous	Yes	No	NA	Yes	2
173	21 December 2017	Ropinirole Hydrochloride	ReQuip CR Tablets	Yes	No	NA	Yes	4
174	29 June 2017	Rosuvastatin Calcium	CRESTOR Tablets	Yes	No	NA	Yes	4
175	19 December 2019	Sapropterin Hydrochloride	BIOPTEN GRANULES	No	Yes	1	No	0
176	11 September 2019	Sildenafil Citrate	Revatio Tablets	Yes	Yes	1	No	0
177	28 September 2017	Sitafloxacin Hydrate	GRACEVIT TABLETS	Yes	No	NA	Yes	5
178	14 March 2019	Sitagliptin Phosphate Hydrate	GLACTIV Tablets	Yes	No	NA	Yes	8
179	19 December 2019	Sodium Hyaluronate Crosslinked Polymer, Sodium Hyaluronate Crosslinked Polymer Crosslinked with vinylsulfone	SYNVISC	Yes	No	NA	No	1
180	28 June 2018	Sodium Risedronate Hydrate	Actonel Tablets	Yes	No	NA	Yes	5
181	14 March 2019	Sorafenib Tosilate	Nexavar tablets	Yes	Yes	2	Yes	8
182	27 September 2018	Strontium(^{89}Sr)chloride	METASTRON	Yes	Yes	1	No	0
183	7 March 2019	Sugammadex Sodium	BRIDION Intravenous	Yes	No	NA	Yes	3
184	21 December 2017	Sunitinib Malate	SUTENT Capsule	Yes	Yes	2	Yes	5

(Continued)

Table 1. (Continued)

	Issue date	Nonproprietary name	Brand name	Approval type New product?	PMACS?	Reason for PMACS[a]	PI change order?	Number of PI change orders
185	30 March 2017	Tacrolimus Hydrate	Prograf Capsules	No	No	NA	Yes	8
186	11 September 2019	Tacrolimus Hydrate	TALYMUS OPHTHALMIC SUSPENSION	Yes	Yes	1	Yes	1
187	19 December 2019	Tacrolimus Hydrate	Prograf Capsules	No	Yes	4	Yes	8
188	30 March 2017	Tadalafil	Cialis Tablets	Yes	No	NA	No	0
189	11 September 2019	Tadalafil	Zalutia Tablets	Yes	No	NA	No	0
190	29 March 2018	Tafluprost	TAPROS ophthalmic solution	Yes	No	NA	No	0
191	14 March 2019	Talaporfin Sodium	LASERPHYRIN 100 mg FOR INJECTION	Yes	Yes	2	No	0
192	21 December 2017	Tazobactam, Piperacillin Hydrate	ZOSYN	Yes	No	NA	Yes	1
193	5 September 2018	Tazobactam, Piperacillin Hydrate	ZOSYN	No	No	NA	Yes	1
194	5 December 2018	Tebipenem Pivoxil	ORAPENEM FINE GRANULES	Yes	No	NA	Yes	1
195	29 March 2018	Temozolomide	TEMODAL Capsules	Yes	Yes	1	Yes	4
196	19 September 2019	Temsirolimus	TORISEL Injection	Yes	Yes	2	Yes	1
197	20 December 2018	Teriparatide Acetate	Teribone Injection	Yes	No	NA	No	0
198	11 December 2019	Teriparatide (Genetical Recombination)	Forteo Subcutaneous injection kits	Yes	No	NA	Yes	2
199	21 December 2017	Thrombomodulin alfa (genetical recombination)	Recomodulin Inj.	Yes	Yes	4	No	0
200	21 December 2017	Tiotropium Bromide Hydrate, Tiotropium Bromide	Spiriva Inhalation Capsules	Yes	No	NA	Yes	3
201	19 September 2019	Tobramycin	TOBI Inhalation solution	Yes	Yes	1	No	0
202	21 December 2017	Topiramate	Topina Fine Granules	Yes	No	NA	Yes	1
203	14 March 2019	Topiramate	Topina Tablets	No	No	NA	Yes	1
204	30 March 2017	Tosufloxacin Tosilate Hydrate	OZEX	Yes	No	NA	Yes	2
205	29 March 2018	Tramadol Hydrochloride	Tramal OD Tablets	No	No	NA	Yes	3

(Continued)

Table 1. (Continued)

	Issue date	Nonproprietary name	Brand name	Approval type New product?	PMACS?	Reason for PMACS[a]	PI change order?	Number of PI change orders
206	5 September 2018	Tramadol Hydrochloride	Tramal OD Tablets	No	No	NA	Yes	3
207	27 September 2018	Tramadol Hydrochloride Acetaminophen	TRAMCET Combination Tablets	Yes	No	NA	Yes	4
208	6 June 2018	Trastuzumab (Genetical Recombination)	HERCEPTIN for Intravenous Infusion	Yes	Yes	4	No	0
209	21 December 2017	Travoprost	TRAVATANZ Ophthalmic Solution	Yes	No	NA	No	0
210	21 December 2017	Travoprost, Timolol Maleate	DUOTRAV Combination Ophthalmic Solution	Yes	No	NA	No	0
211	14 March 2019	Triamcinolone Acetonide	MaQaid OPHTHALMIC INJECTION	No	No	NA	No	0
212	14 March 2019	Triamcinolone Acetonide	MaQaid OPHTHALMIC INJECTION	Yes	No	NA	No	0
213	20 December 2018	Valsartan Amlodipine Besilate	EXFORGE Combination Tablets	Yes	No	NA	Yes	4
214	30 March 2017	Valsartan Hydrochlorothiazide	Co-DIO Combination Tablets	Yes	No	NA	Yes	5
215	11 September 2019	Valsartan, Cilnidipine	ATEDIO Combination Tab	Yes	No	NA	Yes	1
216	5 September 2018	Varenicline Tartrate	CHAMPIX Tablets	Yes	No	NA	Yes	5
217	30 March 2017	Voglibose	BASEN	Yes	No	NA	Yes	2
218	11 September 2019	Zoledronic Acid Hydrate	ZOMETA for I.V. infusion	Yes	Yes	3	Yes	8

NA, not applicable; PI, package insert; PMACS, postmarketing all-case surveillance.
[a]The numbers in this column mean 1: Limited dosing experience in Japan; 2: Further data collection; 3: Specific safety concerns; 4: Other.

Yakuhin, Ltd, Japan), Naglazyme (galsulfase) (BioMarin Pharmaceutical Japan K.K., Japan), Lamictal (lamotrigine) (GlaxoSmithKline K.K., Japan) and Concerta (methylphenidate hydrochloride) (Janssen Pharmaceutical K. K., Japan).

Discussion

Listing and categorization of reexamination report

As Figure 3 shows that PMACS was obligatory in more than half (57%) of the cases due to 'Limited dosing experience in Japan', the MHLW has made a decision of PMACS/no PMACS, taking much into account dosing experience in Japan. However, 'Limited dosing experience in Japan' is not a suitable decision criterion, as no difference of safety measures or efficacy data collection was observed between the cases with PMACS and no PMACS in this study.

Another finding is that dosing experience with different indications in Japan is considered when deciding on the PMACS obligation. PMACS was

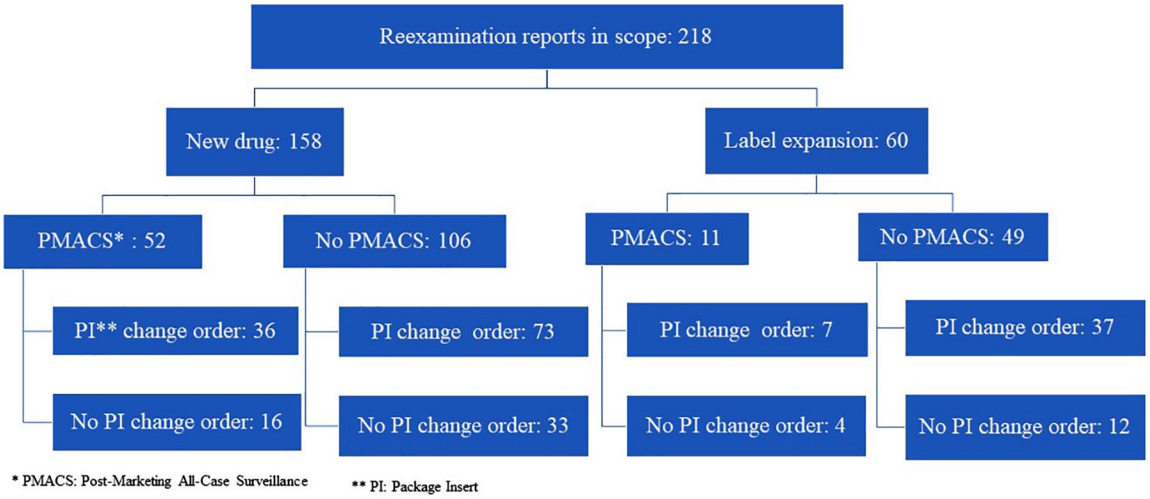

Figure 2. Reexamination report categorization. The identified 218 reexamination reports in 2017–2019 were categorized by PMACS requirement and PI change order, and the breakdown number of reexamination reports in each category is shown.

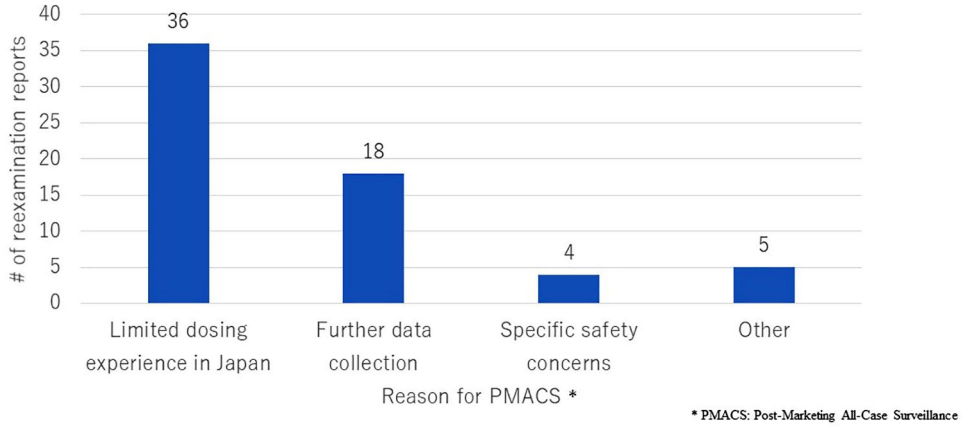

Figure 3. Number of reexamination reports by reason for PMACS. The number of reexamination reports issued from 2017 to 2019 was compared by reason for PMACS.

Table 2. Number of PI change orders.

	PMACS	No PMACS
Total number of drugs reported	61	137
Number of drugs with no PI change order	20 (33%)	40 (29%)
Mean of PI change orders	2.23	2.15
Maximum number of PI change orders	9	9

The number of PI change orders for drugs with reexamination reports issued from 2017 to 2019 was compared based on mandatory status of PMACS.
PI, package insert; PMACS, postmarketing all-case surveillance.

Table 3. Number of drugs with five or more PI change orders by WHO ATC/DDD index.

WHO ATC/DDD index	Number of drugs	
	PMACS	No PMACS
Antineoplastic and immunomodulating agents	6	2
Anti-infectives for systemic use	2	9
Nervous system	1	5
Musculo-skeletal system	1	1
Alimentary tract metabolism	0	1
Blood and blood forming organs	0	1
Cardiovascular system	0	1

Among drugs with reexamination reports issued from 2017 to 2019, those with five or more PI change orders during their reexamination period were accumulated, categorized by WHO ATC/DDD index and compared based on mandatory status of PMAC.
PMACS, postmarketing all-case surveillance; WHO ATC/DDD, World Health Organization anatomical therapeutic chemical and defined daily dose.

obligatory for 52/158 cases in new drugs *versus* 11/60 cases in label expansions.

Assessment from viewpoint of drug safety measures

As shown in Table 2, similar percentages of drugs with no PI change were observed (33% and 29% of drugs with and without PMACS, respectively). In addition, the mean number of PI change orders was similar between drugs with PMACS and no PMACS. These results indicate that postmarketing activities achieved safety measures to a similar degree between with and without PMACS. Therefore, the decision of PMACS/no PMACS based on mainly 'Limited dosing experience in Japan' contributed little to safety measures while the PMACS burden occurred.

Assessment from viewpoint of drug efficacy data collection

As mentioned in the section 'Assessment from viewpoint of drug efficacy data collection', no outstanding efficacy findings were observed in reexamination process, regardless of with and without PMACS. This means that decision of PMACS/no PMACS have little impact on efficacy data collection, even though the PMACS was required mainly for the purpose of 'Limited dosing experience in Japan' or 'Further data collection'. This point is also supported, considering that, as mentioned in the section 'Introduction', PMACS is usually a single-arm observational study where findings for efficacy are likely limited. In fact, postauthorization efficacy studies are separated from PASSs and clearly imposed, if needed, in the EU.[16]

Identification of distinctive cases in term of PMACS impact

No distinctive cases were identified from the viewpoint of drug efficacy data collection, as there were no findings in any reexamination reports as mentioned in the section 'Assessment from viewpoint of drug efficacy data collection'. The four drugs shown in the section 'Identification of distinctive cases in term of PMACS impact' were categorized as follows in terms of PMACS decision and safety measures taken:

A. Drug with PMACS, resulting in outstanding safety measures: Nexavar (sorafenib tosilate) (Bayer Yakuhin, Ltd, Japan) and Naglazyme (galsulfase) (BioMarin Pharmaceutical Japan K.K., Japan)
B. Drug without PMACS, resulting in outstanding safety measures: Lamictal (lamotrigine) (GlaxoSmithKline K.K., Japan)
C. Drug with PMACS, resulting in failed safety measures: None
D. Drug without PMACS, resulting in failed safety measures: Concerta (methylphenidate hydrochloride) (Janssen Pharmaceutical K. K., Japan)

Details of each case are explained below:

A. Nexavar (sorafenib tosilate) (Bayer Yakuhin, Ltd, Japan), an anticancer drug, could be considered one of the best examples where PMACS worked well. When it was approved, data from 171 Japanese patients had been accumulated in premarketing clinical studies.[15] The number of Japanese patients treated at premarketing stage was higher than the number of Japanese patients influencing the obligatory decision with PMACS (100 patients).[9] That is, the MAH would not have been obligated to conduct PMACS in term of limited dosing experience in Japan. However, PMACS was obligatory. This was because the drug was the first molecular-targeted drug in the field of urological malignancies in Japan and because a variety of adverse drug reactions were observed during premarketing clinical studies.[15] As a result, eight PI change orders were issued during the reexamination period, including two urgent safety information letters.[17] One of the letters was related to interstitial pneumonia, an unexpected adverse drug reaction that had not been observed in the premarketing phase. The other was related to liver failure and hepatic encephalopathy. Liver failure was one of the safety notes highlighted by PMACS, according to data from premarketing clinical studies. PMACS contributed to the detection of both known and unknown safety concerns for this drug, regardless of dosing experience in Japanese patients.

   Naglazyme (galsulfase) (BioMarin Pharmaceutical Japan K.K., Japan) is also considered appropriate to apply PMACS. Only seven patients were treated with this drug for more than a 10-year PMACS period.[18] No new important safety concerns were observed, and efficacy information was limited because of the low number of patients. However, data from all patients were intensively collected for a long period under PMACS. The data of each case could help the understanding of its use.

B. Lamictal (lamotrigine) (GlaxoSmithKline K.K., Japan) supports the idea that postmarketing activities without PMACS are effective. For this drug, the urgent safety signal regarding serious skin disorders and the underlying cause were identified without PMACS. Accordingly, some safety actions, including issuing an urgent safety information letter,[17] were taken to ensure dose compliance at the escalation phase and quick discontinuation of drug dosing if a skin disorder was observed. As a result, the number of cases of inappropriate use decreased.

C. There was no case identified in this category. In general, PMACS is a good tool to collect safety data comprehensively, as all patients treated with the targeted drug are captured.

D. Concerta (methylphenidate hydrochloride) (Janssen Pharmaceutical K.K., Japan) is considered a case where PMACS should have been required since its launch. The drug was not required to conduct PMACS as an approval condition, while supply restrictions, including prescribing physician registration, needed to be introduced. As a result, more than 500 prescriptions were issued by ineligible physicians during its reexamination period; the drug was dispensed based on 75 inappropriate prescriptions; and no serious adverse drug reactions due to the inappropriate prescriptions were observed.[19] Then, according to the reexamination assessment by the PMDA, further measures were required for its appropriate use, including the introduction of a system to register all patients to be prescribed.

Proposal on PMACS application

As discussed in sections 'Listing and categorization of reexamination report,' 'Assessment from viewpoint of drug safety measures', and 'Assessment from viewpoint of drug efficacy data collection', the decision of PMACS/no PMACS based on mainly 'Limited dosing experience in Japan' contributed little to safety measures or efficacy data collection, in spite of high PMACS burden. Meanwhile, the four distinctive cases are identified in terms of PMACS decision and safety measures taken. Based on these points, the proposed product scope to impose PMACS is as follows:

A. Drugs related to Designated Diseases in Article 67 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMDA Act)[20]: currently, cancer, sarcoma, and leukemia are specified as a designated disease according to the article referring to drugs '*for which use not under the guidance of physicians or dentists is highly likely to cause hazards*.'
   Nexavar (sorafenib tosilate) (Bayer Yakuhin, Ltd, Japan) supports this proposal. This case represents a successful application of mandatory PMACS, even though dosing experience in Japanese patients at the premarketing stage was available to some extent. In addition, as highlighted in Table 3, 'antineoplastic and immunomodulating agents' had the highest number (eight) of drugs with five or more PI change orders issued during their reexamination periods. This indicates that intensive safety information collection under PMACS contributed to advancing the appropriate use of drugs in the therapeutic area.
B. Drugs with special distribution restrictions: Concerta (methylphenidate hydrochloride) (Janssen Pharmaceutical K.K., Japan) supports this proposal. For example, the distribution of narcotics must be strictly managed in Japan to avoid drug abuse or dependence. For such a drug, PMACS would allow tracking appropriate drug use and collecting safety and efficacy data efficiently, because distribution restriction and data collection could be pursued simultaneously.
C. 'Ultra-orphan' drugs: There is no legal definition of 'Ultra-orphan' drugs in Japan and other countries/regions such as in the EU and the United States, but the Scottish Medicine Consortium has set a definition that considers the prevalence (1 in 50,000 or less) and conditions, including chronicity, severe disablement, and necessitating highly specialized management.[21] Naglazyme (galsulfase) (BioMarin Pharmaceutical Japan K.K., Japan) supports this proposal. For such a drug, PMACS could contribute to closely monitoring every patient and quickly collecting and sharing detailed information on each dosing experience for appropriate drug. Furthermore, the burden for MAHs and medical institutes to conduct PMACS could be reasonable because of the low number of patients to be followed up.

Finally, PMACS could be utilized not only in Japan but also in other regions/countries such as the EU and the United States. As described in the section 'Introduction', both regulators have a similar pharmacovigilance system similar to that in Japan with the authority to impose MAHs to conduct a postmarketing study. Thus, these systems already have the regulatory framework to introduce PMACS, enabling proposition by regulators and MAHs alike, if preferable.

For example, Naglazyme (galsulfase) (BioMarin Pharmaceutical Japan K.K., Japan) has been approved not only in Japan but also in the EU and the United States, and clinical surveillance programs have been conducted as a condition of its authorization/approval in the EU and the United States.[22,23] One of the objectives of the programs was to collect clinical data from as many treated patients as possible. In this case, the programs could be appropriately conducted as PMACS, similar to that in Japan.

In addition, Nexavar (sorafenib tosilate) (Bayer Yakuhin, Ltd, Japan), which had PMACS obligation and resulted in outstanding safety measures, indicated that PMACS can be effective not only in Japan but also other countries. The reasons to decide PMACS obligation were not Japan-specific ones (e.g. 'Limited dosing experience in Japan').

Conclusion

This study revealed that the appropriate safety action (issuing PI change order) was taken, regardless of the mandatory status of PMACS and the degree of dosing experience in Japanese patients at the premarketing stage. Meanwhile, it also identified some drugs where PMACS worked well or could be effective. Considering the significant burden PMACS exerts on MAHs and medical institutes, in addition to these study findings, the product scope to impose PMACS should be improved. Particularly, PMACS should not be imposed only because of limited dosing experience in Japan at the premarketing

stage. Rather, PMACS requirement should focus on (1) collection of safety data (not efficacy), (2) necessity of distribution control, and/or (3) collection of case details for drugs with a limited treated population. Finally, PMACS has the potential to be utilized not only in Japan but also in other countries/regions, such as the EU and the United States. Both regulators have similar pharmacovigilance systems to Japan, which means that they already have the regulatory framework to introduce PMACS. Both these regulators and MAHs could propose PMACS, if preferable. This study demonstrated Naglazyme (galsulfase) (BioMarin Pharmaceutical Japan K.K., Japan) as a case where PMACS or clinical surveillance programs like PMACS have been required in each region/country.

Limitations

This study targeted the reexamination reports issued in 2017–2019 to determine the implementation of PMACS after the PMDA was established, as mentioned in the 'Materials and Methods' section. The concept of safety measures has advanced in Japan since the establishment of the PMDA, including the introduction of the Risk Management Plan in 2013.[24] Therefore, the latest trends in the implementation of PMACS could be observed once further investigation is conducted after the relevant reexamination reports are published.

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Author contributions

Both the authors made substantial contributions to designing the study, collecting data, examining the relevant information, and drafting and reviewing this paper. Dr Masamune has taken the final responsibility to submit this paper in this journal.

Conflict of interest statement

Hideyuki Kondo is a employee of Novartis Pharma K.K.

Ethical approval/patient consent

Not applicable, as this study did not recruit any patients or provide intervention to them. The study was conducted based on public data.

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ORCID iD

Hideyuki Kondo https://orcid.org/0000-0002-8763-4262

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