Significance of data mining in routine signal detection: Analysis based on the safety signals identified by the FDA

Chisato Fukazawa

Department of Clinical Medicine (Pharmaceutical Medicine)

Graduate School of Pharmaceutical Sciences

Kitasato University

5-9-1 Shirokane, Minato-ku, Tokyo, 108-8641, Japan

Abstract

Pharmaceutical products are approved based on information on the products' safety and efficacy gathered in the premarketing phase. However, safety information from the premarketing phase is very limited, and we can't predict all the risks that will occur in the post marketing phase from it. Therefore, during the post marketing phase, it is essential to identify unknown risks and also to follow up risks for which the causality is uncertain at the premarketing phase.

Spontaneous reports are the most valuable information for identifying post marketing safety issues. In the first step of risk evaluation, spontaneous reports provide familiar information for detecting a sign of risk, which is often called a signal. Signals are detected by combining traditional methods based on the evaluation of individual case safety reports and statistical methods such as data mining. A signal does not always show a relationship between drugs and AEs, so we need to examine whether a signal truly indicates a risk. Based on the further examinations, we make a decision to take safety regulatory actions in response to the signals. The workflow from signal detection to decisions regarding safety regulatory actions is called "signal management."

While implementation of signal management has been established in European Medicines Agency (EMA), the United States Food and Drug Administration (FDA), and World Health Organization (WHO), it has not in Japan. Review of individual case safety reports has been conducted to evaluate spontaneous reports in Japan; however, use of data mining has not been practiced actively. To understand the significance of data mining in routine signal detection, in the present study, we tackled two questions (Part 1,2) encountering in the implementation of signal management using data mining by analyzing the safety signals identified from the FDA Adverse Reporting System (FAERS)

and related information

Purpose of the research Part 1 was to investigate appropriate situations in which data mining is effective in routine signal detection activities. Among the signals that the FDA identified from the FAERS between 2008 1Q and 2014 4Q, we selected 233 signals to evaluate in this study. We conducted a disproportionality analysis and classified these signals into two groups according to the presence or absence of statistical significance in the reporting odds ratio (ROR). Then, we compared the two groups based on the characteristics of the suspected drugs and adverse events (AEs). Safety signals were most frequently identified for new drugs that had been on the market for less than 5 years, but some signals were still identified for old drugs (≥20 years), and most of them were statistically significant. The proportion of the signals for "serious" events was significantly higher in the group of the signals without statistical significance by ROR [Fisher's exact test, p=0.032]. The result of the research Part 1 showed that data mining was effective in the following situations: 1) early detection of safety issues for newly marketed drugs, 2) continuous monitoring of safety issues for old drugs, and 3) signal detection of nonserious AEs to which little attention is usually given.

Purpose of the research Part 2 was to identify factors that influence the decision to take regulatory actions in routine signal management based on spontaneous reports. From the signals that the FDA identified in the FAERS between 2008 1Q and 2014 4Q, we selected 216 signals for which regulatory action was or was not taken. The characteristics of the signals were extracted from the FAERS database and its relevant public information. Univariate and multivariate logistic regression analysis was used to assess the relationship between each signal characteristic and the decision of regulatory action. As a result of the univariate logistic regression analysis, we selected 3 factors

(temporal relationship, previous awareness, risk for special populations) to include in the multivariate logistic regression analysis ($p<0.2$). The multivariate logistic regression analysis showed that previous awareness was associated with the decision of safety action ($p<0.05$). The result of the research Part 2 suggested that previous awareness of the risk during the pre- and post-marketing phases was a strong evidence for the decision to take regulatory actions in routine signal management.

Many pairs of drugs and AEs are reported daily through spontaneous case reports. Selecting a suitable method according to the characteristics of drugs and AEs would lead to the efficient evaluation of spontaneous reports. Although spontaneous reports are a valuable source for detecting safety signals in routine pharmacovigilance practice, they are often inadequate to assess whether a signal is truly a risk. To strengthen the evidence level of signals from spontaneous reports, we should review the accumulated safety results from the pre- and post-marketing stages and also verify the signals using other data sources.

Table of Contents

Abstract i

Table of Contents iv

List of Tables vi

List of Figures vii

Abbreviations viii

1 Introduction 1

2 Part 1: Significance of data mining in routine signal detection: Analysis based on the safety signals identified by the FDA 4

2.1 Part 1: Objective 4

2.2 Part 1: Methods 5

2.2.1 Data collection 5

2.2.2 Signal detection using data mining 6

2.2.3 Comparison of signals with or without statistical significance based on the characteristics of the suspected drugs 7

2.2.4 Comparison of signals with or without statistical significance based on the characteristics of the AEs 7

2.3 Part 1: Results 8

2.4 Part 1: Discussion 16

2.5 Part 1: Conclusion 20

3 Part 2: Factors influencing regulatory decision-making in signal management: Analysis based on the signals identified from the FAERS 21

3.1 Part 2: Objectives 21

3.2 Part 2: Methods 21

3.2.1 Selecting signals for this study 21

3.2.2 Factors that are recommended for consideration in signal management 22

3.2.3 Data analysis 27

3.3 Part 2: Results 27

3.4 Part 2: Discussion 38

3.5 Part 2: Conclusion 43

4 Overall Discussion 43

5 References 45

6 Acknowledgement 52

Appendix 1 53

Appendix 2 66

Appendix 3 67

List of Tables

Table 1 Characteristics of signals (N=233) identified from FAERS by FDA

Table 2 Safety actions in response to the 165 signals from the FAERS

Table 3 Reasons for no-action judgments in response to 51 signals

Table 4 Results of univariate logistic regression analysis

Table 5 Result of multivariate logistic regression analysis

List of Figures

Figure 1 Flowchart of selecting the signals to be evaluated in the present study

Figure 2 Classification of the signals according to therapeutic effects of the suspected drugs (ATC code)

Figure 3 Classification of the signals according to time since the marketing authorization of the suspected drugs

Figure 4 Classification of the signals according to time to onset of the AEs

Figure 5 Flowchart of selecting the signals for the evaluation in this study

Figure 6 Comparison of the signals' characteristics between the groups with and without the regulatory actions by Mann-Whitney U test

Figure 7 Number of the relevant information by section of the label described in the previous labels of the suspected drugs

Abbreviations

AE Adverse Events

ATC Anatomical Therapeutic Chemical

BLA Biologic License Application

CIOMS Council for International Organizations of Medical Sciences

DME Designated Medical Event

DRESS Drug Rash with Eosinophilia and Systemic Symptoms

EMA European Medicines Agency

EU European Union

FAERS FDA Adverse Event Reporting System

FDA the United States Food and Drug Administration

HLGT High-Level Group Terms

JAPIC Japan Pharmaceutical Information Center

JADER Japanese Adverse Drug Event Report database

MedDRA Medical Dictionary for Regulatory Activities

MGPS Multi-item Gamma Poisson Shrinker

NDA New-Drug Application

ORs odds ratios

PMDA Pharmaceuticals and Medical Devices Agency

PML progressive multifocal leukoencephalopathy

PMR post marketing requirement

PT preferred terms

ROR reporting odds ratio

PRAC Pharmacovigilance Risk Assessment Committee

REMS Risk Evaluation and Mitigation Strategies

SMQ Standardized MedDRA Queries

SOC system organ class

TSI tracked safety issues

US United States of America

95%CIs 95% confidence intervals

1 Introduction

Because the patient populations included in clinical trials are small and uniform, safety information gained from the premarketing phase is limited. It is impossible to fully describe the safety profile of a drug during the premarketing phase. Some drugs have been withdrawn from the market because of serious adverse reactions that were unknown during premarketing clinical trials; for example, valdecoxib was associated with Stevens-Johnson syndrome, and troglitazone was associated with hepatotoxicity [1]. Therefore, during the post marketing phase, to compensate for the lack of safety information obtained during the premarketing phase, it is essential to identify unknown risks and also to follow up risks for which the causality is uncertain at the premarketing phase. [1-2].

As one of the pharmacovigilance methods provided in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2E guideline [3], a spontaneous report is an important source in identifying potential risks. Signal detection from spontaneous reports is carried out by various regulatory authorities and companies in their routine pharmacovigilance practice. The report of the Council for International Organizations of Medical Sciences (CIOMS) working group VIII, which proposes practical methods of signal detection in pharmacovigilance, recommends two fundamental methods for signal detection: (1) review of individual case safety reports (review) and (2) statistical analyses in large databases (data mining) [4].

Signals identified by the combination of “review” and “data mining” are then validated and prioritized based on various factors, such as the strength of evidence for a causal effect and the public health impact. After further assessment, a decision is made whether any safety action is necessary. This workflow, called “signal management,” forms the basis of activities evaluating safety issues from spontaneous reporting systems

in the European Medicines Agency (EMA), the United States Food and Drug Administration (FDA), and the World Health Organization (WHO) [5-8].

In Japan, a part of spontaneous reports collected by the Pharmaceuticals and Medical Devices Agency (PMDA) has been open to the public, which is named Japanese Adverse Drug Event Report database (JADER) [9]. However, information about what signals are detected from spontaneous reports including JADER, how does the PMDA evaluate signals, or what regulatory action are taken for signals is not shown clearly to the public. While the FDA and the EMA incorporate continuous surveillance of the data in the spontaneous reports databases and signal management including signal detection using statistical analysis into their regulation, the PMDA does not require it explicitly. With such a background, implementation of signal management and signal detection using data mining have not yet been established in Japan. Recently, globalization of developing pharmaceutical products has been promoted. Accordingly, it is also required to implement post-marketing safety measures in accordance with the global standards.

To understand the significance of data mining in routine signal detection, we tackled two questions encountering in the implementation of signal management including signal detection using data mining.

The first question is in which situations the data mining is effective in routine signal detection activities. Signal detection in spontaneous reporting systems may be performed based on review and data mining at the early stage of signal management; each of these methods has strengths and weaknesses [4]. Reviewers judge a signal with their medical expertise and information, but this judgment is dependent on their skills and experience. On the other hand, in data mining, a signal is judged based on statistics, but the process does not employ medical knowledge. We must identify a signal by properly

combining the two methods according to the situations; otherwise, we might overlook critical potential safety issues. In the research Part 1 of the present thesis, with the aim of investigating appropriate situations in which data mining is effective in routine signal detection activities, we conducted a signal detection with data mining approach for those potential signals that the FDA identified from the FAERS in the past and classified them into two groups: signals with statistical significance (detected signals by ROR) and those without (non-signals by ROR). Then, we compared the signals in the two groups based on the characteristics of the suspected drugs and AEs.

The second question is what factors influence decisions of whether a signal truly indicates a risk. Data mining gives only a result of calculation, so we cannot decide whether a signal truly indicates a risk only by a statistical result from data mining. Some guidelines and reports related to signal management recommend considering several factors during signal prioritization and assessment to rationally determine which actions to take [7-8]. Module IX of the Guideline on Good Pharmacovigilance Practices, a procedure manual for signal management created by European Medicines Agency (EMA), recommends considering such factors as strength of evidence, previous awareness, and clinical relevance/context [8]. Some European countries have introduced a method of prioritizing signals by scoring these factors, which is called impact analysis, in their signal management process [18-19]. However, it is unclear how strongly these factors contribute to decision-making regarding safety actions in response to signals. Some previous studies in the European Union (EU) investigated which factors play a role in the subjective process of signal selection or the decision to update product information (PI) [20-21]. In one study, presence of “serious reports”, AEs designated as a World Health Organization (WHO) “critical term”, AEs that were unlabeled, and presence of a disproportionate

association were shown to be independently associated with signal selection [20]. The other results showed that presence of evidence in multiple types of data sources, mechanistic plausibility of the drug-event association, seriousness of the event, and a drug age <5 years were associated with the decision to update PI [21]. The factors that influence decisions to take safety action in signal management have been presented in previous research; however, they were both based on the outcomes of signal management in the EU. It appears that the factors that mostly contribute to decisions regarding safety actions in signal management differ among countries and regions. To investigate different aspects of previous results, we focused on the outcomes of signal assessment in the United States (US). The research Part 2 aimed to identify the factors that influenced the decision to take safety actions in routine signal management based on the FDA adverse events reporting system (FAERS) by analyzing the safety signals identified from the FAERS and their relevant information.

We expect that the knowledge obtained from the present study will contribute to the improvement of post-marketing surveillance activities in Japan.

2 Part 1: Significance of data mining in routine signal detection: Analysis based on the safety signals identified by the FDA

2.1 Part 1: Objective

Data mining has been introduced as one of the most useful methods for signal

detection based on spontaneous reports, but data mining is not always effective in detecting all safety issues. To investigate appropriate situations in which data mining is effective in routine signal detection activities, we analyzed the characteristics of signals that the United States Food and Drug Administration (FDA) identified from the FDA Adverse Event Reporting System (FAERS).

2.2 Part 1: Methods

2.2.1 Data collection

In accordance with Title IX, Section 921 of the FDA Amendments Act of 2007 (FDAAA) 7, the FDA conducts regular, biweekly screening of the FAERS database and posts a quarterly report called "Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Reporting System (FAERS)" on its website [14]. Quarterly reports contain the following information: 1) the drug that is suspected to be causing the safety signal, 2) AEs for the signal, and 3) FDA actions taken for the signal. From the quarterly reports posted on the FAERS website between 2008 1Q and 2014 4Q, we selected the signals for evaluation in this study as follows. Because of difficulties in its interpretation, we did not select the signals concerning quasi-drugs (N=1), combination products (N=1), drug-drug interactions (N=9), and comprehensive AEs for a specific population not definable by Medical Dictionary for Regulatory Activities (MedDRA) terms (e.g., safety during pregnancy) (N=14). All suspected drug names were standardized to active ingredient names. For class effects, we grouped active ingredient names with the same pharmacological effects. We selected the MedDRA terms that were suitable for the descriptions of the AE names in the quarterly reports from any of the system organ class (SOC), high-level group terms (HLGT), high-level terms (HLT), preferred terms (PT) or Standardized MedDRA Queries (SMQ). Two authors (CF and

YH) independently selected MedDRA terms that were suitable for descriptions of AE names in the FAERS quarterly reports. Then, they confirmed each other's results. Any disagreements between the two authors were resolved by consensus with another author (MN).

2.2.2 Signal detection using data mining

We utilized FAERS reports between 1997 4Q and 2014 4Q. As FAERS data were released to the public on its website from 2004 1Q, reports before 2004 1Q were purchased from the National Technical Information Service. Reports after 2004 1Q were downloaded from the FAERS website [15-16]. Any processes related to data cleaning, such as removal of duplicates, standardization of reported drug names, and coding of MedDRA terms (ver.18.0) to the reported AEs were conducted by the Japan Pharmaceutical Information Center (JAPIC). Duplicates were excluded by an automated multistep process aiming to check the overlap in the following fields: PRIMARYID (ISR, old version), CASEID (CASE, old version), EVENT_DT, MFR_NUM, AGE, SEX (GNDR_COD, old version), and WT.

To evaluate disproportionate reporting, we calculated the reporting odds ratio (ROR) with the 95% confidence interval (95% CI) for each drug and AE pair of the signals. The ROR is often employed as a measure of disproportionality in spontaneous reports databases [17-19]. For the calculation of ROR, we extracted the cases for each signal from FAERS reports between 1997 4Q and 2014 4Q with the following conditions: cases reported between 1997 4Q and the quarter in which the signal was posted, cases reported with both suspected drug names and AE names that we defined (mentioned above), and cases reported with a suspected drug name as a primary suspected drug

([ROLE_CODE] in DRUG file is “PS”). After the disproportionality analysis, we classified the signals into two groups (detected signals or non-signals by ROR) according to the published threshold criteria (case (N)≥2, lower bound for 95% CI (95% CIL)>1). Furthermore, to validate the quality of our disproportionality analysis, we evaluated disproportionate reporting by a different method and different thresholds (proportional reporting ratio (PRR), 95% CIL≥1, N≥3 or 5). We conducted our disproportionality analysis using Microsoft® Access and Excel version 14.0 (Microsoft Corporation, Washington, USA).

2.2.3 Comparison of signals with or without statistical significance based on the characteristics of the suspected drugs

We compared the signals with or without statistical significance in terms of therapeutic classification (Anatomical Therapeutic Chemical (ATC) classification code) and time since the marketing authorization of the suspected drug. If the suspected drug name was not found in the WHO ATC database (https://www.whocc.no/atc_ddd_index/), we assigned a suitable ATC code to the drug based on its indication and pharmacology. The time since the marketing authorization of the suspected drug was defined as the time interval between the approval date of the drug and the final date of the quarter that the signal was identified. We collected information on the approval date of the suspected drugs using the Drug@FDA database (https://www.accessdata.fda.gov/scripts/cder/daf/). For class effects, the approval date of the oldest substance was used as a representative value.

2.2.4 Comparison of signals with or without statistical significance based on the

characteristics of the AEs

We compared the signals between the groups with or without statistical significance in terms of seriousness and time to onset of the AEs. The seriousness of the AEs was judged based on the report of CIOMS Working Group V [20]. If the AE name was listed as an AE/reaction to be always considered “serious” in the CIOMS Working Group V (the list of CIOMS Working Group V), it was judged as “serious”, and if the AE name was not listed, it was judged as “nonserious”. In addition, we hypothesized that signals of “serious” events can be detected easily by other methods regardless of the statistical significance in a disproportionality analysis. To test this hypothesis, we conducted a Fisher's exact test for the combination of the presence of the statistical significance in our disproportionality analysis and the seriousness of the AEs for the signals. For this purpose, we used StatsDirect version 2.7.9 (StatsDirect Ltd., Altrincham, Cheshire, UK).

To calculate the time to onset of AEs, we extracted the information about the date when the AE occurred ([EVENT_DT] in DEMO file) and the date when the administration of the suspected drug started ([START_DT] in THER file) from the FAERS data. Then, we calculated the range between [START_DT] and [EVENT_DT] for each case and calculated the median to be used as a representative value for the drug and AE pair. If multiple administrations of suspected drugs existed in the same case, we used the date of the first administration for this calculation.

2.3 Part 1: Results

Between 2008 1Q and 2014 4Q, the FDA identified 258 potential signals (count based on drug and AE pair) from the FAERS. From these 258 potential signals, we selected 233 signals for evaluation in this study. The number of total FAERS reports

utilized in this study was 5,885,015, and the total number of cases for the 233 signals was 53,561. As a result of our disproportionality analysis (ROR, 95% CIL>1, N≥2), 156 signals were statistically significant (detected signals by ROR), and 77 signals were not (non-signals by ROR) (Fig. 1). There was no large difference in the number of signals in the two groups by PRR (95% CIL≥1, N≥3 or 5).

The characteristics of the signals (N=233) are summarized in Table 1. When we classified the 233 signals according to the therapeutic effect (ATC code) of the suspected drugs, the major therapeutic groups frequently observed in suspected drugs were antipsychotics (N) [N=52 (22.3%)], antineoplastic and immunomodulating agents (L) [N=44 (18.9%)], and anti-infectives for systemic use (J) [N=32 (13.7%)]. This tendency was observed regardless of the presence or absence of statistical significance (Fig. 2).

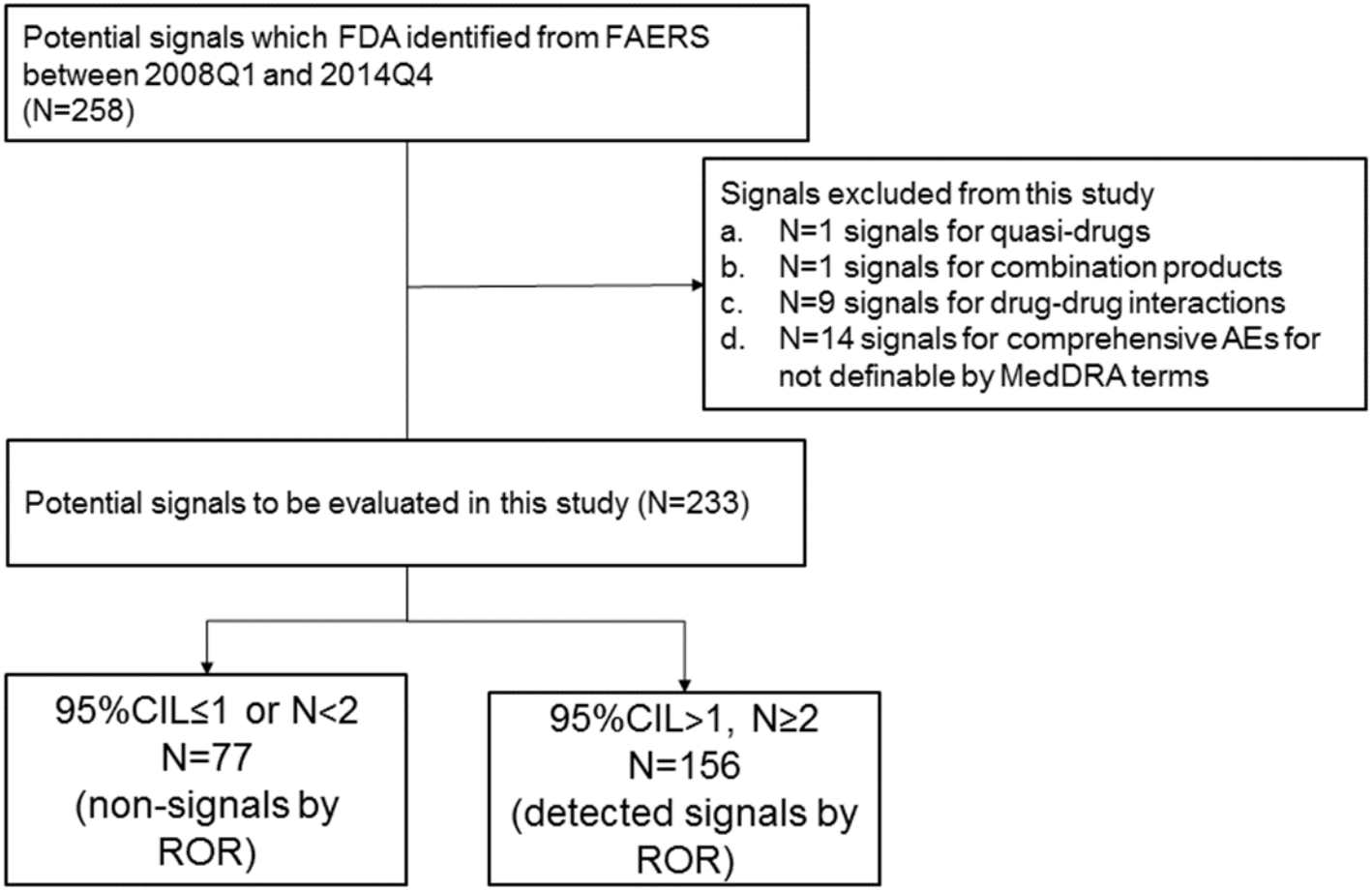

Fig. 1 Flowchart of selecting the signals to be evaluated in the present study

Table 1 Characteristics of signals (N=233) identified from FAERS by FDA

	ALL (%)	Detected signals by ROR [a] (%)	Non-signals by ROR [b] (%)
Signal, n (%)	233 (100)	156 (100)	77 (100)
Therapeutic effects of the suspected drugs (ATC code)			
Antipsychotic (N)	52 (22.3)	32 (20.5)	20 (26.0)
Antineoplastic and immunomodulating agents (L)	44 (18.9)	26 (16.7)	18 (23.4)
Anti-infectives for systemic use (J)	32 (13.7)	26 (16.7)	6 (7.8)
Other	105 (45.1)	72 (46.2)	33 (42.9)
Time since the marketing authorization of the suspected drugs			
<5 years	76 (32.6)	53 (34.0)	23 (29.9)
≥5 and <10 years	47 (20.2)	24 (15.4)	23 (29.9)
≥10 and <20 years	47 (20.2)	32 (20.5)	15 (19.5)
≥20 years	63 (27.0)	47 (30.1)	16 (20.8)
Seriousness of the event [c]			
Serious	143 (61.4)	88 (56.4)	55 (71.4)
Nonserious	90 (38.6)	68 (43.6)	22 (28.5)
Time to onset of the event [d]			
Less than 30 days	129 (60.3)	93 (63.3)	36 (53.7)
Equal to or more than 30 days	85 (39.7)	54 (36.7)	31 (46.3)

a detected signals by ROR: signals with statistical significance (cases≥2, lower bound for 95% confidence interval >1) by ROR. b non-signals by ROR: signals without statistical significance by ROR. c Serious AEs described in the list of the CIOMS Working Group V; Nonserious: AEs that are not considered “serious”, [p=0.032, Fisher’s exact test]

d The total number of signals for the classification according to the time to onset is 214. Due to missing data, we could not calculate the time to onset for 19 signals.

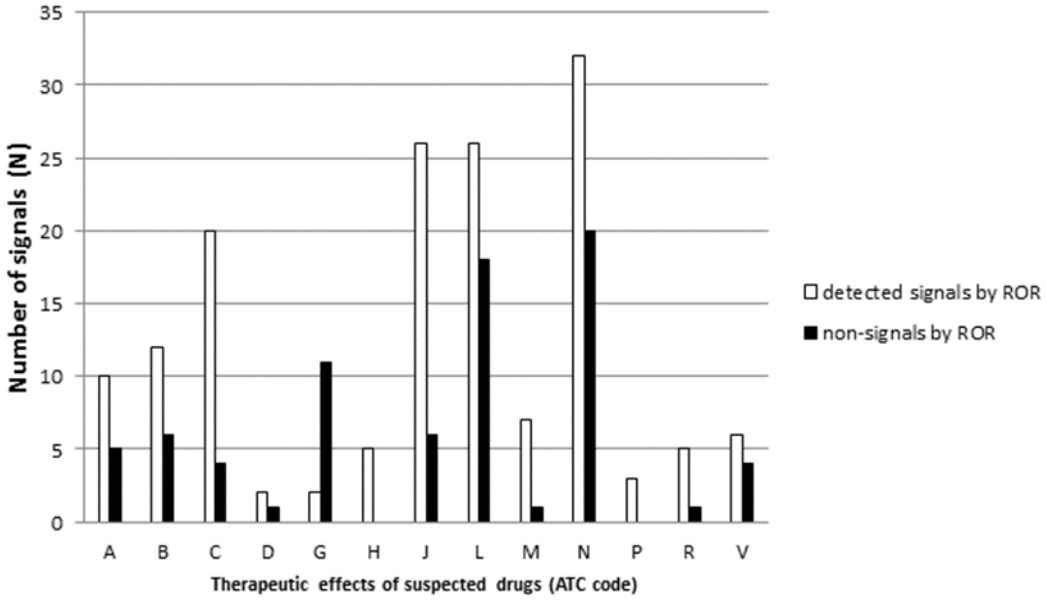

Fig. 2　Classification of the signals according to therapeutic effects of the suspected drugs (ATC code)

ATC：Anatomic Therapeutic Chemical classification, A: Alimentary tract and metabolism, B: Blood and blood forming organs, C: Cardiovascular system, D: Dermatologicals, G: Genito urinary system and sex hormones, H: Systemic hormonal preparations, J: Antiinfectives for systemic use, L: Antineoplastic and immunomodulating agents, M: Musculo-skeletal system, N: Nervous system, P: Antiparasitic products, R: Respiratory system, V: Various

From the result of the classification of the signals based on the time since the marketing authorization of the suspected drugs, we found that the signals identified by the FDA were generated from various aged drugs. The median time from approval to signal identification was 9 years [range 0.2-69]. Signals were identified most frequently for new drugs that had been on the market for less than 5 years [N=76 (32.6%)]. Some signals were identified from old drugs that had been on the market for more than 20 years [N=63 (27.0%)]. Most of these signals were statistically significant in our disproportionality analysis [N=53 (34.0%) for new drugs (<5 years), and N=47 (30.1%) for old drugs (≥20 years)] (Fig. 3).

Approximately 60% of the signals were for "serious" events described in the list of CIOMS Working Group V [N=143 (61.4%)]. Among 143 signals for "serious" events, 88 signals were statistically significant, while 55 signals were not. The proportion of the signals for "serious" events was significantly higher in the group of non-signals by ROR [Fisher's exact test, p=0.032].

From the 53,561 total eligible cases, 23,546 cases had the date information of both [EVENT_DT] and [START_DT]. Based on these cases, we calculated the time to onset of AEs for 214 signals. The time to onset for 129 AEs (60.3%) ranged from 0 to <30 days (Fig. 4). The number of signals for AEs with late time to onset (≥30 days) was drastically decreased. Among 85 signals for AEs with late time to onset, 54 signals were statistically significant in our disproportionality analysis.

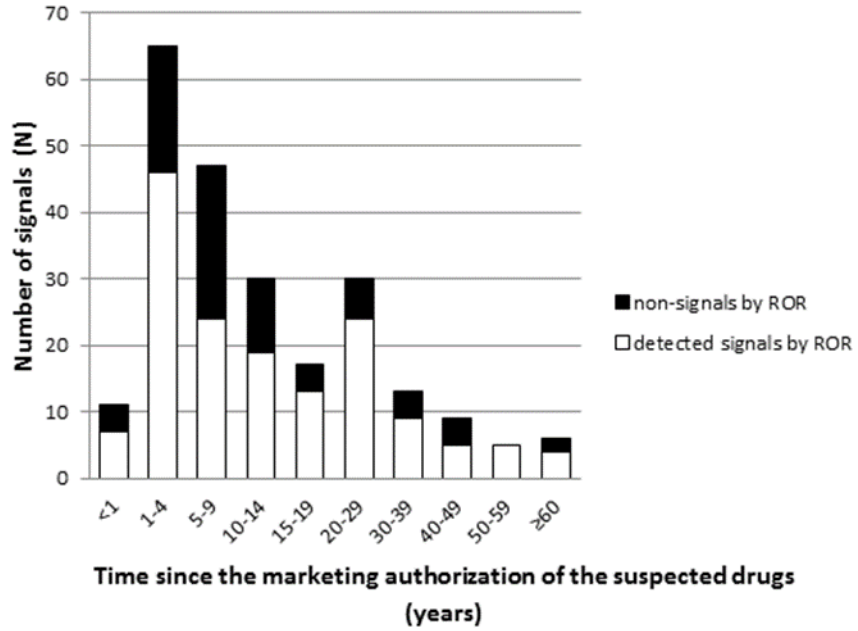

Fig. 3 Classification of the signals according to time since the marketing authorization of the suspected drugs

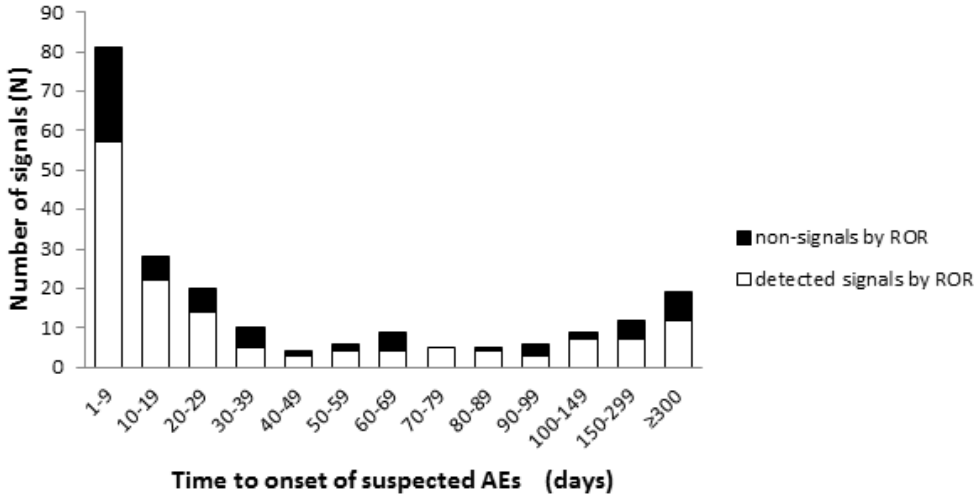

Fig. 4 Classification of the signals according to time to onset of the AEs

2.4 Part 1: Discussion

In this study, we conducted signal detection using data mining for signals that the FDA identified from the FAERS in the past, and we classified them into two groups according to the presence or absence of statistical significance in the ROR. Then, we compared the signals between the two groups based on the characteristics of the suspected drugs and the AEs.

From the classification result according to the therapeutic effect (ATC code) of the suspected drugs, signals were mostly related to antipsychotics (N), antineoplastics and immunomodulating agents (L), and anti-infectives for systemic use (J). It is generally said that adverse drug reactions caused by antipsychotics, antineoplastics, and anti-infective drugs tend to occur in their therapeutic windows. Therefore, it is necessary to use them carefully considering the risk-benefit balance for patients. The awareness of the safe use of these drugs might affect the number of signals identified from the FAERS.

We classified the signals according to the time since the marketing authorization of the suspected drugs. From the results of the analysis, the median time from the approval of the suspected drugs to the identification of the signals was 9 years. It seems that this time interval of 9 years is unexpectedly long, which implies that safety issues are not always identified immediately after approval. We should continue to monitor drug safety steadily throughout the entire life of a pharmaceutical product.

The median time from the identification of the signals to the date of the label change, if any, was 0.9 years in the present study (Appendix 1). Therefore, it was assumed that the time from the approval of the suspected drugs to the label change was approximately 10 years in the US. Some studies that analyzed safety-related label changes by the FDA showed that the median time from approval to safety-related label changes

was 11 years [21-22]. These studies also found that the major source of evidence contributing to safety actions was spontaneous reports. The 9-year median time from the approval of the suspected drugs to the identification of the signals is reasonable given the time in which the FDA further assessed the signals.

In addition, our results showed that the signals that the FDA identified from the FAERS appeared most frequently in new drugs with less than 5 years on the market. In general, it is considered that the number of signals increases immediately after launch due to the increasing number of reports associated with the expansion of the exposed patients and the attention of clinicians towards novel drugs (called the Weber effect) [19]. Candore et al. showed that the proportion of signals of disproportionate reporting that turned out to be adverse drug reactions increased notably after approval and decreased over the lifetime of the pharmaceutical products [23]. A publication regarding signals identified by the Pharmacovigilance Risk Assessment Committee (PRAC), which plays an important role in signal management in the EU, also showed that most of the signals discussed on the PRAC agenda were for new drugs that have been on the market for less than 10 years [24]. Based on our results and this knowledge, we can say that data mining supports the early detection of safety issues for new drugs.

Surprisingly, signals from the FAERS were still identified for old drugs that had been on the market for more than 20 years, although the safety profiles of these drugs seemed to have already been established. Most of the signals for old drugs were statistically significant in our disproportionality analysis. The signal of the oldest drug was the risk for anaphylactic reaction of heparin. The root cause of this signal was the quality of the manufacturing process [25]. After this signal was posted, heparin products were recalled. Spontaneous case reports also contribute to safety issues related to quality.

Other examples of the signals for old drugs were the signals of hepatosplenic T-cell lymphoma for mercaptopurine (time on the market is 57 years) [26-27] and angioedema for conjugated estrogens (time on the market is 67 years) [28]. For old drugs, there is a possibility that unknown and unexpected safety issues occur many years after the approval due to the acceleration of reporting associated with additional indications, changes in dosage form and usage patterns, long-term use, and other factors. Data mining is also effective when the continuous monitoring of old drugs is conducted in addition to the early detection of safety issues for new drugs.

Remarkably, the proportion of the signals for "serious" events was significantly higher in the group of non-signals by ROR than in the group of detected signals by ROR. A similar result was obtained when the range of the definition of "serious" events was widened to include malignant tumors, progressive multifocal leukoencephalopathy (PML), drug rash with eosinophilia and systemic symptoms (DRESS), and acute febrile neutrophilic dermatosis (Appendix 2). Serious events are given attention regularly, so they are identified easily as safety signals by qualitative evaluation regardless of statistical significance. The EMA has created a document describing medical events that are inherently serious and particularly remarkable, which is called the "Designated Medical Event (DME) list" [29]. The EMA utilizes the DME list not only as a support tool to determine the seriousness of a case report but also as a safety net in signal detection [29]. For the structure of signal detection in routine pharmacovigilance practice, it is important to catch "serious" events that are missed by quantitative evaluation (such as data mining), due to the limitation of the statistical power, by other means such as the DME list. In the group of detected signals by ROR, 43.6% of the signals were for "nonserious" events, which were not described in the list. Most of the "nonserious" events were procedural

complications, but some rare AEs, such as fluorosis and sarcoidosis, were included. Usually, less attention is paid to nonserious events, and we tend to fail to notice them. Data mining makes it easier for us to recognize the signals of those events to which we pay less attention in daily practice.

When classifying the signals according to time to onset of AEs, we noticed that the time to onset of most of the AEs was <30 days. When the time to onset of the AE is short, the reporter can easily recognize it as an adverse drug reaction and report it accurately. Therefore, it is easier to detect a signal from spontaneous case reports for the event whose time to onset is shorter. On the other hand, it is difficult to detect signals for events whose time to onset is longer from spontaneous case reports due to underreporting. However, among the signals whose time to onset was more than 30 days (N=85), 54 signals were statistically significant in our results of disproportionality analysis. This outcome suggests that data mining is useful to detect the signals for such events from spontaneous reports. For some signals for the events whose time to onset was longer, additional investigations (observational study, epidemiological survey, post marketing clinical trial) were conducted. It is important for such events to be assessed further by additional investigations using other sources because evaluating them only by spontaneous case reports is often difficult.

Some limitations exist in this study. First, we chose ROR as the algorithm for our disproportionality analysis. However, the FDA has employed the empirical Bayes multi-item gamma Poisson shrinker (MGPS) as a quantitative method in a routine screening for potential signals from the FAERS [30]. Bayesian methods such as MGPS are believed to be more robust than frequentist methods such as ROR or PRR when the number of reports is small [30-31]. Among the signals evaluated in this study, the

percentage of the signals that had very few cases (less than 3 cases) was 9.4%. Therefore, we believe that they do not have a large influence on the results. Second, we include only primary suspected drugs in our disproportionality analysis. If the range of suspected drugs was widened, it may have decreased the proportion of non-signals by ROR. However, we were aware of increasing noise and overestimating signals, so we limited our disproportionality analysis to primary suspected drugs. Third, in the classification of the signals according to the time to onset of the AEs, we calculated the time to onset of the AEs based on the date information from the FAERS. However, because of the many missing values for the date information, reports used for the calculation were limited, and we could not calculate the time to onset for the AEs for 19 signals. Finally, the FDA identifies the signals from the FAERS in consideration of the information from other sources [4]. We did not take information from sources other than the FAERS into account for our investigation.

Based on the results of the present study, data mining is particularly effective in the following situations: 1) early detection of safety issues for newly marketed drugs, 2) continuous monitoring for safety issues for old drugs, and 3) signal detection of nonserious AEs to which little attention is usually given.

2.5 Part 1: Conclusion

Many pairs of drugs and AEs are reported daily through spontaneous case reports. Because the types of potential risks are various, it is important to select and combine suitable methods to identify risks by considering the characteristics of drugs and AEs. Data mining is a useful pharmacovigilance method, and regular screening of safety signals from spontaneous case reports using a data mining technique is strongly

recommended to enhance the structure for routine pharmacovigilance practice.

3 Part 2: Factors influencing regulatory decision-making in signal management: Analysis based on the signals identified from the FAERS

3.1 Part 2: Objectives

This study aimed to identify factors that influence the decision to take safety regulatory actions in routine signal management based on spontaneous reports. For this purpose, we analyzed the safety signals identified from the Food and Drug Administration (FDA) Adverse Reporting System (FAERS) and related information.

3.2 Part 2: Methods

3.2.1 Selecting signals for this study

In accordance with Title IX, Section 921 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), the FDA creates a quarterly report called "Potential Signals of Serious Risks/New Safety Information Identified from the FAERS" (the FAERS quarterly report) [6, 14]. The FAERS quarterly report consists of three columns (columns 1-3). Column 1, titled Product name: active ingredient (trade) or product class, indicates the suspected drug for the signal. Column 2, Potential signal of serious risk/new safety information, indicates the AE for the signal. Column 3, Additional information, reports the regulatory actions that were taken for the signal [14]. From the FAERS quarterly reports between 2008 1Q and 2014 4Q, we extracted the signals that resulted in regulatory action and those that were closed with no action. We determined that the signal

resulted in regulatory action if the following information was contained in the column of additional information: labeling update, Risk Evaluation and Mitigation Strategies (REMS), product recall, withdrawal. We determined that the signals that were closed with no action if the following statements or similar contents were contained in the column of additional information:

・The FDA decided that no action is necessary at this time based on available information.

・The FDA has determined that the current labeling is adequate and that no further regulatory action is needed at this time.

In addition, several signals had multiple AEs in different fields of disorders. Among the drug and AE pairs for such signals, some did not clearly indicate whether regulatory action was taken. In such cases, we determined that the pairs resulted in no regulatory action. We determined that the assessment of the signal was ongoing and excluded the signal from the present study if the following statement or similar contents were contained in the column of additional information:

・The FDA is evaluating the need for regulatory action.

3.2.2 Factors that are recommended for consideration in signal management

According to some guidelines related to signal management, factors that are potentially important during signal assessment were defined and classified broadly into 3 categories: strength of evidence, previous awareness, and clinical relevance/context [5]. A Guideline for pharmacovigilance practices and pharmacoepidemiologic assessment created by the FDA contains similar contents for evaluating signals [32]. Specific factors in each category were extracted from the FAERS quarterly reports and the published FAERS data. The rationale for and definitions of classification of the collected factors are

explained below.

3.2.2.1 Strength of evidence

・Presence of disproportionate reporting

The guidelines for good pharmacovigilance practices in the EU and the US recommend employing statistical or mathematical approaches (called data mining) to examine reported AEs [32-33]. We calculated reporting odds ratios (RORs) to confirm the disproportionate reporting of the signals using the published FAERS data set [15-16]. The signals were considered disproportionately reported if 2 or more cases were reported and the lower bound of the 95% confidence interval of the ROR was greater than 1. The disproportionality analysis is explained in detail in our previous article [34].

・Positive dechallenge or rechallenge

The presence of positive dechallenge or rechallenge provides consistent evidence that the reported AE was caused by the suspected drug. Positive dechallenge was considered present if there was at least 1 report of positive dechallenge (the field [DECHALLENGE] in the demo txt was “Y”) among the cases that were extracted during our disproportionality analysis. Similarly, positive rechallenge was considered present if there was at least 1 report of positive rechallenge (the field [RECHALLENGE] in the demo.txt was “Y”).

・Temporal relationship

In evaluating the causal relationship between suspected drugs and AEs, the

temporal relationship (the timing of administration of the suspected drugs and the occurrence of AEs) is an important factor. A temporal relationship was considered present if there was at least 1 report containing an explicable indication that the AE occurred after the administration of the suspected drug ([EVENT_DATE] in the demo.txt is later than [START_DATE] in the THER.txt).

・Mechanistic plausibility

The presence of mechanistic plausibility offers supporting information to explain causality in terms of drug action mechanisms. In this study, three authors (CF, YH and MN) independently judged the mechanistic plausibility of each drug and AE pair of signals based on their biological and pharmacological knowledge. To prevent a big difference in the interpretation of mechanistic plausibility, the following criteria were set in advance; mechanistic plausibility was considered present if the causality was able to be hypothesized or explained in terms of the drug's mechanism of action; mechanistic plausibility was not considered present only if the risks related to the AEs had been listed in the drug's label or if the AEs had been considered as class effects. The inter-rater reliability among the authors was good (kappa = 0.77). If their answers were not unanimous, presence of the mechanistic plausibility for the signal was decided by consensus.

・Number of cases in the most recent one-year period since the signal report

An exponential increase in reports over a short period may indicate an increasing risk. We counted the number of signals that were reported in the most recent one-year period before the publication of the signal report.

3.2.2.2 Previous awareness

Previous awareness is defined as whether the signal relates to an adverse reaction has already been included on the label for the active substance of interest or other medicinal products containing the same substance, or whether the association was assessed in the initial application for marketing authorization or any other regulatory procedure based on information held or known by any organization [5]. To determine the presence of previous awareness of the signals, we referred the previous label of the suspected drug updated before the quarter when the signal was posted to check whether information relevant to the signal was already included. For example, in the case of a signal associated with drug X for hepatic failure, if the previous label of drug X described AEs related to the liver (e.g., liver functional impairment or hepatotoxicity etc.), we determined that previous awareness of this signal existed. We collected the labels of suspected drugs from the Drug@FDA database (https://www.accessdata.fda.gov/scripts/cder/daf/). If no label before the signal identification was available, we confirmed checked the relevant information using the edition of the Physician's Desk Reference published before the signal was identified. If the relevant information could not be confirmed in anywhere, we excluded the signals from the analysis.

3.2.2.3 Clinical relevance and context

・Seriousness of the AEs

Serious and unusual events are likely to be reported [35]. There are serious AEs that must always receive attention in pharmacovigilance activities [20]. We assessed the seriousness of the AEs for the signals based on the Council for International Organizations

of Medical Sciences (CIOMS) Working Group V report [20]. If the AE was listed on the report, it was considered “serious”. In addition, even if they were not listed in the report, we judged the following AEs as “serious”: malignant tumors, progressive multifocal leukoencephalopathy (PML), drug rash with eosinophilia and systemic symptoms (DRESS), and acute febrile neutrophilic dermatosis.

・Fatal outcome

Outcomes after the occurrence of AEs should be considered during signal assessment. Fatal outcomes were considered present if there was at least one fatal case among the signals.

・Age of drug

Spontaneous reports increase immediately after a drug is marketed (Weber effect) [36], so it is assumed that signals for new drugs are likely to be identified more easily than those for old drugs. We calculated the period of time for the drug on the market (the time from the marketing approval of the suspected drug to the identification of the signal). We classified the signals into the following 2 categories: time of marketing authorization <5 years or ≧5 years.

・Risks for special populations

Consideration of whether the risk occurs in a special population (e.g., pediatrics, pregnant women, patients who have a certain risk factor) is recommended during signal assessment. We determined whether the signals were specific to a special population based on the descriptions of the FAERS quarterly reports.

3.2.3 Data analysis

For factors expressed as continuous values (number of cases with positive dechallenge/rechallenge, number of cases indicating a temporal relationship, number of cases reported in the most recent one-year period since the identification of the signals, number of cases with fatal outcomes, and the age of the drug), we compared the values between the group with and without regulatory action using the Mann-Whitney U test.

To assess the influence of various factors on the decision to take regulatory action, we defined the presence or absence of each of the factors by binary variable. At first, we performed a univariate logistic regression analysis. Factors associated with regulatory actions that had a p-value<0.2 were included in the multivariate logistic regression analysis. We determined that factors with $p<0.05$ were statistically significantly associated with the regulatory actions. The results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The analyses were performed using StatsDirect version 2.7.9 (StatsDirect, Ltd., Altrincham, Cheshire, UK).

3.3 Part 2: Results

Between 2008 1Q and 2014 4Q, 258 signals were listed in the FAERS quarterly reports. Among these signals, signals for which evaluations were ongoing (N=17) and signals for quasi-drugs (N=1), combination drugs (N=1), drug-drug interactions (N=9) and comprehensive AEs not definable by MedDRA terms (N=14) were excluded. A total of 216 signals were examined in this study. Among them, 165 led to regulatory actions and 51 were assessed and closed with no action (Fig. 1). The regulatory actions taken for the 165 signals were labeling changes (N=159), REMS (N=2), REMS and labeling

changes (N=2), product recall (N=1), and withdrawal (N=1) (Table 1). For the 51 signals that were closed with no action, the reasons were “no action is necessary at this time based on available information.” (N=31), “the current labeling is adequate and no further regulatory action is needed” (N=16) and unknown (N=4) (Table 2).

Table 2 Safety actions in response to the 165 signals from the FAERS

Safety action	N (%)
Labeling changes	159 (96.4)
REMS	2 (1.2)
Labeling changes and REMS	2 (1.2)
Product recall	1 (0.6)
Withdrawal	1 (0.6)

Table 3 Reasons for no-action judgments in response to 51 signals

	N (%)
No action is necessary at this time based on available information.	31 (60.8)
The current labeling is adequate and no further regulatory action is needed at this time.	16 (31.4)
The reason was unclear based on additional information in the FAERS quarterly reports.	4 (7.8)

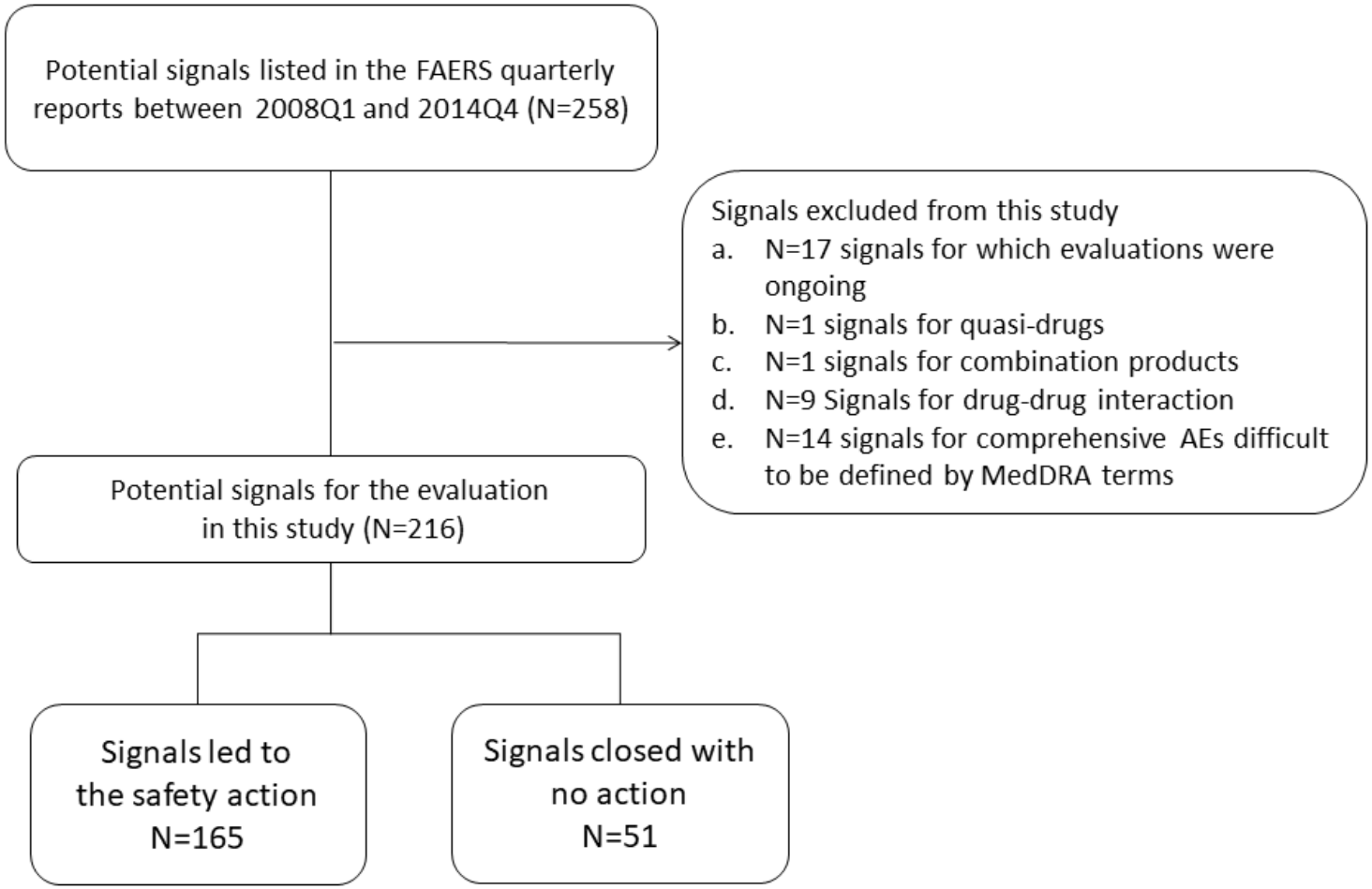

Fig. 5 Flowchart of selecting the signals for the evaluation in this study

For the factors expressed as continuous values, we compared the values between the groups for which regulatory action was and was not taken using the Mann-Whitney U test (Fig. 2). No difference was observed between the two groups in the quantity of the available information from spontaneous reports (numbers of cases with positive dechallenge/rechallenge, number of cases with a temporal relationship, number of cases reported in the most recent year from the identification of signals and number of cases with fatal outcomes). Signals for new drugs (0-2 years old) received regulatory action in most cases; however, the median of time of marketing authorization between the two groups did not differ greatly [9 vs 7 years, $p=0.28$].

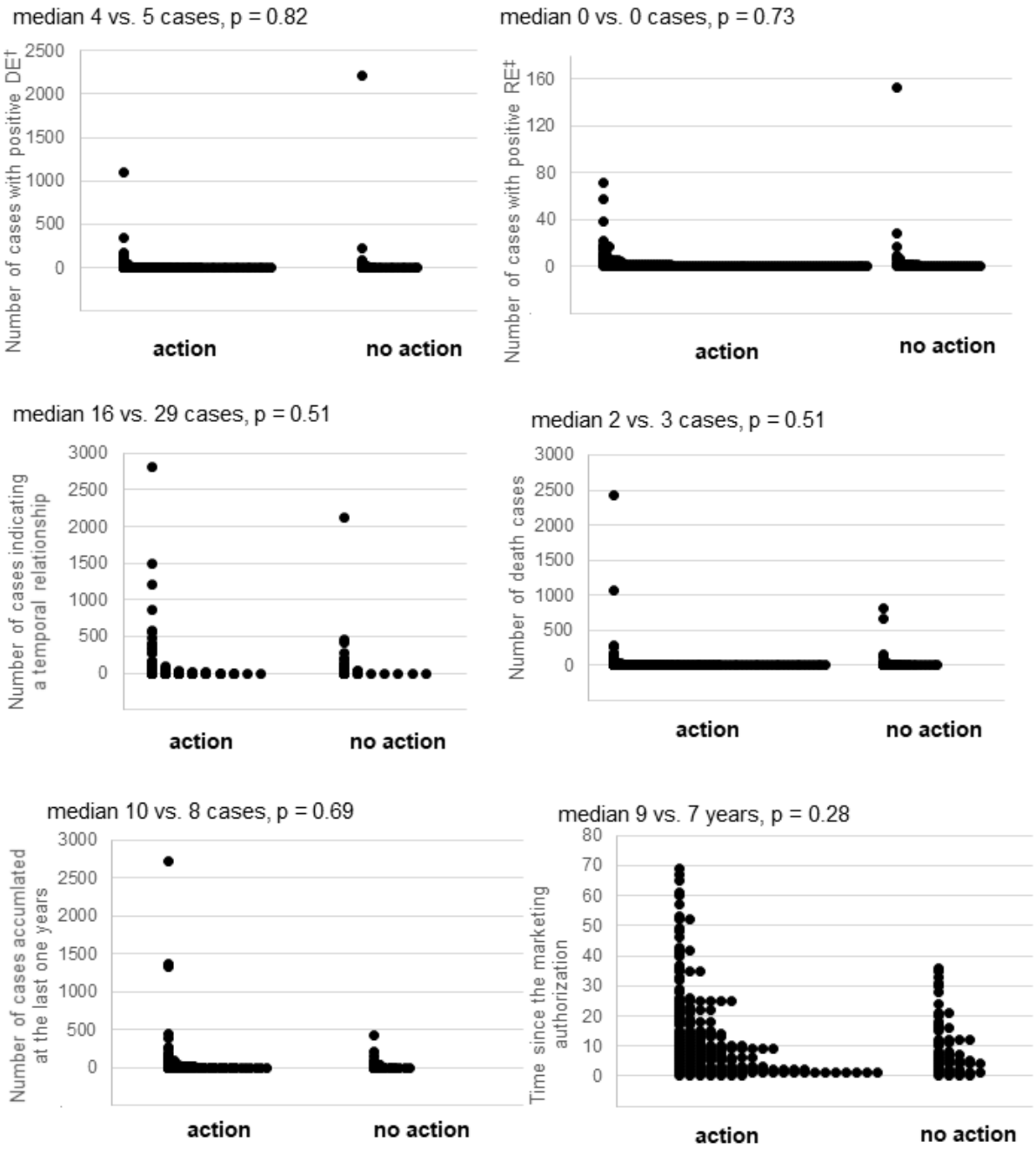

Fig. 6 Comparison of the signals' characteristics between the groups with and without the regulatory actions by Mann-Whitney U test

† DE: dechallenge, ‡ RE: rechallenge

As a result of the univariate logistic regression analysis, temporal relationship (unadjusted OR 2.23, [95% CI 0.82, 6.09]), previous awareness (2.33, [1.19, 4.54]), and risks for special populations (3.92, [0.46, 30.9]) showed p-values <0.2. These factors were included in the multivariate logistic regression model. Finally, previous awareness was statistically significantly associated with regulatory action (unadjusted OR 2.08, [95% CI 1.07, 4.04]). For the 88 signals with previous awareness, relevant information was already described in the pre- or post-marketing AEs section (N=85), the warning and precautions section (N=45), or the contradictions (N=12) of the previous labels of the suspected drugs (Fig. 7).

Table 4 Results of univariate logistic regression analysis

	Factors		ALL（n = 216）	Signals that resulted in action (n (%))	Signals that resulted in no action (n (%))	Crude odds ratio (95% CI)	p-value
Strength of the evidence	Disproportionate reporting	ROR of the signal satisfied the thresholds†	146	113 (77.4)	33 (22.6)	1.19 (0.61-2.30)	0.61
	Positive dechallenge	Case with positive dechallenge ≧1	163	127 (77.9)	36 (22.1)	1.39 (0.69-2.81)	0.36
	Positive rechallenge	Case with positive dechallenge ≧1	96	74 (77.1)	22 (22.9)	1.07 (0.57-2.02)	0.83
	Temporal relationship	Case with temporal relationship ≧1	198	154(77.7)	44(22.3)	2.23(0.82-6.09)	0.12*
	Mechanistic plausibility	Mechanistic plausibility for the signal could be hypothesized or explained	92	74 (80.4)	18 (19.6)	1.49 (0.78-2.86)	0.23

	Number of cases accumulated in the last year	≧10	109	85 (78.0)	24 (22.0)	1.20 (0.64-2.24)	0.58
Previous awareness		Information relevant to the signal was included in the previous label of the suspected drug §	105	88 (83.8)	17 (16.2)	2.33 (1.19-4.54)	0.01*
Clinical relevance and context	Seriousness of the event	AE for the signal was listed on the CIOMS Working Group V report‡	142	107 (75.4)	35 (24.6)	0.84 (0.43-1.65)	0.61
	Number of death cases	≧1 cases	150	113 (75.3)	37 (24.7)	0.82 (0.41-1.65)	0.58
	Age of drug	＜5 years	70	52 (74.3)	18 (0.26)	0.84 (0.44-1.63)	0.61
	Risks for special populations		13	12 (80.0)	1 (20.0)	3.92 (0.46-30.9)	0.19*

†If the signal had 2 or more cases and the lower bound of the 95% confidence interval of the reporting odds ratios (ROR) was greater than one, we determined that the ROR of the signal satisfied the thresholds.

‡Malignant tumors, progressive multifocal leukoencephalopathy (PML), drug rash with eosinophilia and systemic symptoms (DRESS), and acute febrile neutrophilic dermatosis were judged as serious, even if those events were not listed on the Council for International Organizations of Medical Sciences (CIOMS) Working Group V report.

§ 6 signals were excluded from the analysis, because the relevant information could not be confirmed in anywhere.

＊p-value <0.2

Table 5 Result of multivariate logistic regression analysis

Factors	Crude odds ratio (95% CI)	p-value
Temporal relationship	2.41(0.75-7.66)	0.13
Previous awareness	2.08(1.07-4.04)	0.03**
Risk for special populations	3.97(0.45-35.05)	0.21

** p-value <0.05

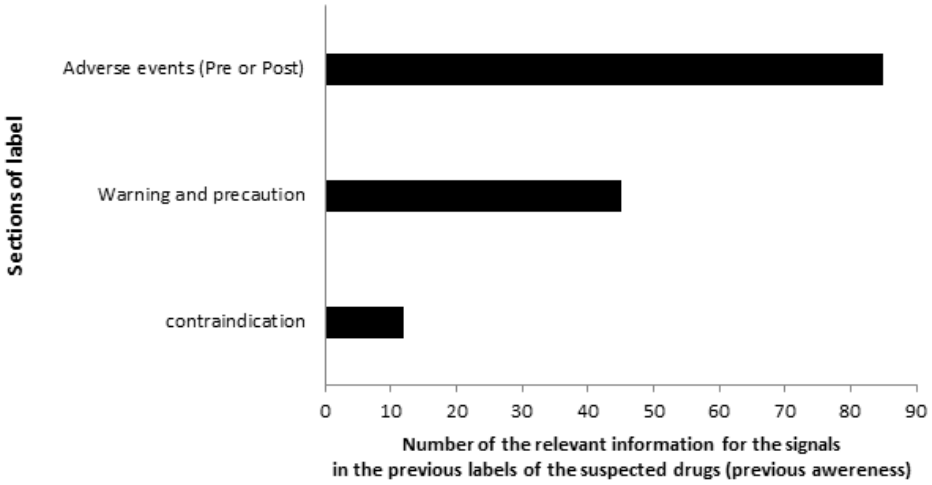

Fig. 7 Number of the relevant information by section of the label described in the previous labels of the suspected drugs

3.4 Part 2: Discussion

In the present study, we explored the factors that influenced the decision to take regulatory action in signal management. We found that previous awareness of the risk was associated with the decision to take regulatory action. Among the 165 signals for which regulatory actions were taken, relevant information was already included in the previous label of the suspected drug in 88 cases. The information was primarily reflected in the adverse reactions section (pre- and/or post marketing experience) and the warnings and precautions. This finding suggests that past safety results determined during the pre- and post-marketing stages would be useful references in current signal management.

Currently, establishment of a pharmacovigilance plan based on important identified risks, important potential risks, and important missing information at the time of new drug application is recommended [3]. The FDA manages significant safety issues that are identified during the evaluation of new-drug application (NDA) or biologic license application (BLA) in an integrated fashion; it may require REMS or post marketing requirement (PMR) to address the safety issues that are identified during the pre-marketing period as tracked safety issues (TSI) [37]. It was assumed that signals related to TSIs arising from spontaneous reports accumulated in the FAERS led to further regulatory actions.

While the FDA took regulatory actions for 88 signals with previous awareness, no such action was taken for 16 signals because the current labeling was adequate and no further regulatory action was needed at the time. To avoid confusion resulting from excess information, selecting information should be done in labeling updates.

Although previous awareness was identified as the factor that most strongly affected the decision to take regulatory action in this study, it is noted that the unknown

risks without previous awareness (N=71) also resulted in regulatory action. Routine signal management based on spontaneous reporting plays a role not only in the follow-up of risks for which there is previous awareness but in the identification of unknown risks.

Other factors included in the multivariate logistic regression model in this study were temporal relationships and risks for special populations. Those factors may be potentially associated with the decision to take regulatory action during signal management. Information about the presence of a temporal relationship is available from spontaneous reports, and it is essential to evaluate the relationship between suspected drugs and AEs. We often depend on temporal relationships when assessing the quality of individual case safety reports and causality. In addition to temporal relationships, dechallenge/rechallenge information from individual case safety reports is also useful for establishing causality. However, our results did not show statistical significance for the association between dechallenge/rechallenge and the decision to take regulatory action. In addition, our results showed that the quantities of available information from spontaneous reports were not differ between the group for which regulatory actions were taken and the group for which no regulatory actions were taken. A study based on spontaneous reports of adverse drug reactions from the Catalan Pharmacovigilance Center reported that more than one third of the reports from manufacturers did not include information that was considered a limiting factor to evaluate any causal relationship [38]. While available information from spontaneous repots is essential to evaluate causality, it is not always sufficient. So it is would be difficult to make a decision to take regulatory actions for signals only by available information from spontaneous reports.

During the premarketing stage, safety information for special populations, such as pediatrics, pregnant women, and patients with a particular risk factor, is usually lacking.

It is difficult to include those populations in clinical trials due to the limited number of patients and ethical concerns. As an alternative, spontaneous reports are often used to examine drug safety in those populations [39-42]. Some studies have evaluated the effects of drug exposure on pregnant women and their infants using spontaneous reports [39-40]. Other studies have investigated the performance of signal detection focusing on pediatrics based on spontaneous reports [41-42]. Pharmacovigilance for special populations still owes a great deal to spontaneous reports.

Our results differed from those of a previous study on some points [13]. The presence of evidence in multiple types of data sources was among the signal characteristics related to PI changes in the previous study. However, we could not perform a similar analysis because signal assessment evidence from sources other than the FAERS was not available from the FAERS quarterly reports. Among the signals we evaluated in our study, 24 led to FDA Drug Safety Communication actions. Based on the description in the Drug Safety Communication data summary, we organized the evidence used to evaluate these 24 signals. The assessment of these 24 signals considered evidence from the literature, observational studies, epidemiological studies, clinical trials, and the results of mini-sentinel pilot studies (Appendix 3). These signals led to the regulatory actions considering not only spontaneous reports but also evidence from other sources. As mentioned previously, well-described cases are very limited. Therefore, we need to consider information other than spontaneous reports in signal management.

Mechanistic plausibility was associated with PI changes in the previous study; however, our results did not show an association between mechanistic plausibility and the decision to take regulatory actions. In our study, three authors with different backgrounds individually judged mechanistic plausibility. Initially, our judgements were not in accord

absolutely. Mechanistic plausibility is left to the judgment of the evaluators at the time. Hill AB gave the following explanation of “plausibility” in his criteria for determining causation [47]: “What is biologically plausible depends upon the biological knowledge of the day.” It is difficult to consistently judge mechanistic plausibility, although it is a helpful factor in signal assessment.

Signals for serious events tended to lead to the PI changes mentioned in the previous study. Most of the signals evaluated in our study were for serious events; however, the seriousness of the AEs had no relevance to the decision to take regulatory action in our study. The signals for serious events for which no action was taken included aripiprazole for torsade’s de pointes, clozapine for death, and levonorgestrel for syncope, etc. The assessments for these signals were closed because no action was deemed necessary at the time based on the available information [14]. Regulatory action may not be taken when supportive evidence is lacking, despite the seriousness of the events.

The previous study stated that age of drugs ≤5 years is a signal characteristic associated with PI changes. According to our distribution map, most of the signals led to regulatory actions for new drugs (0-2 years). However, our logistic regression results did not show an association between drug age (<5 years) and the decision to take regulatory action. There was a signal with no action for etravirine (aged 0.2 years) for hemarthrosis. No action was taken for this signal because “The FDA has received one report since etravirine (Intelence) was approved and is continuing to monitor for additional reports [14].” In some cases, decision-making for new drugs is difficult because sufficient information is not collected.

The presence of disproportionate reporting, the number of cases in the most recent year from the identification of signals, and fatal outcomes were not associated with

the decision to take regulatory action in this study. Disproportionate reporting is a statistical tool to help detect safety signals from numerous reports; however, clinical judgment should always be involved in signal assessment [4-5, 32]. According to the comparison of the distribution maps, some signals in the group for which regulatory actions were taken had more than 100 cases accumulated in the most recent one-year period; however, the medians of the number of cases did not differ between the two groups. The same can be said for fatal outcomes. This result implies that the current pharmacovigilance system can identify safety issues earlier than the expansion of risks. It is necessary to confirm the number of cases over time to prevent the increase of risks, even if this factor is not directly associated with the decision to take regulatory actions.

This study has some limitations. First, all of the explanatory variables in this study were obtained from published information. We could not consider information that was not available publicly. Second, among factors that are available from spontaneous reports, those which we did not selected in the present study may have influenced the decision to take regulatory action, such as complications, concomitantly used drugs. In addition, information related to regulatory actions in countries other than the US or safety evaluation based on periodic safety update reports may also have influenced the decision to take regulatory action. Third, we assessed the association between each factor and the decision to take regulatory action using a logistic regression model. However, in practice, judgments regarding regulatory action are based on combinations of multiple factors. We did not consider the combined influence of multiple factors on the decision to take regulatory action.

3.5 Part 2: Conclusion

Spontaneous reports are a valuable source for detecting safety signals in routine pharmacovigilance practice. However, they are often inadequate to assess whether a signal is truly a risk. Therefore, signal management should include versatile viewpoints. To strengthen the evidence level of signals from spontaneous reports, we should review the accumulated safety results from the pre- and post-marketing stages and also verify the signals using other data sources.

4 Overall Discussion

In the present study, we tackled two questions encountering in signal management including signal detection using the technique of data mining. From the research Part 1, data mining was shown to be particularly effective in the following situations: 1) early detection of safety issues for newly marketed drugs, 2) continuous monitoring for safety issues for old drugs, and 3) signal detection of nonseries AEs to which little attention is usually given. Many pairs of drugs and AEs are reported daily through spontaneous case reports. Selecting a suitable method according to the characteristics of drugs and AEs leads to the efficient evaluation of spontaneous reports. From the research Part 2, it was suggested that available information from spontaneous reports was not enough to decide whether a signal is truly a risk. It showed that past safety results obtained from the pre- and post- marketing stages contributed to the strength of evidence for the signal.

In recent years, activities that complement routine drug safety signal analysis based on spontaneous reports using administrative claims data or electronic health data

have been actively carried out mainly in the EU and the US. These activities should also be conducted in Japan to make pharmacovigilance activities more advanced. To do this, firstly, we need to know what risk is difficult to be evaluated by spontaneous reports. The result of the research Part 1 showed that signals for late-onset AEs were difficult to be detected from spontaneous case reports. It is important that such AEs should be assessed further by additional investigations using other data sources. Most signals for late-onset AEs in the present study were related to liver disorders. For the detailed investigation of liver disorders, electronic health data may be a more suitable source of information because clinical examination data for liver is available from it.

We believe that other medical databases, such as administrative claims data or electronic health data, are useful in verifying signals detected from spontaneous reports in some cases, but they cannot be applicable to all risks. Pilot studies for risk assessments using these databases in the EU or the US showed that some risks were able to be assessed reasonably but others were not. It is mostly important for us to analyze what tool is suitable to assess the risk. This is true not only for traditional tools (e.g., spontaneous reports) but also for new tools (e.g., electronic health data).

In the introduction of this thesis, we stated that the FDA and the EMA incorporate signal management based on spontaneous reports and monitoring reported AEs employing statistical analyses into their regulation. We do not propose to enforce signal management or signal detection using data mining based on spontaneous reports in Japan, but, based on the present study, to review the practice of collecting and evaluating individual case safety reports; in particular, we should examine whether spontaneous reports are collected sufficiently, whether the current methods detect all the important risks, and what risks are difficult to be evaluated by spontaneous reports. We expect that

the knowledge obtained from the present study will contribute to the improvement of post-marketing surveillance activities in Japan.

5 References

1. Sharrar RG, Dieck GD. Monitoring product safety in the postmarketing environment. Ther Adv Drug Saf. 2013; 4(5): 211 –219
2. Brewer T, Colditz GA. Postmarketing Surveillance and Adverse Drug Reactions. JAMA. 1999; 281(9): 825-829
3. ICH HARMONISED TRIPARTITE GUIDELINE PHARMACOVIGILANCE PLANNING E2E Recommended for Adoption at Step 4 of the ICH Process on 18 November 2004.
4. CIOMS Working Group. Practical aspects of signal detection in pharmacovigilance. Geneva; 2010.
5. EMA. Guideline on good pharmacovigilance practices, Module IX: signal management. 2012.
6. Manual of Policies & Procedures (CDER) 6700.9 FDA Posting of Potential Signals of Serious Risks Identified by the Adverse Event Reporting System. https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM248882.pdf. cited 2017 November 29.
7. Lindquist M. Use of triage strategies in the WHO signal-detection process. Drug Saf. 2007; 30 (7):635-37.
8. Meyboom RHB, Lindquist M, Egberts ACG, Edwards IR. Signal selection and

follow-up in pharmacovigilance. Drug Saf. 2002; 25(6):459-65.

9. Japanese Adverse Drug Event Report database. https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0003.html cited 2019 April 26.
10. Rolfes L, Kolfschoten J, Hunsel F, Puijenbroek E. The validity and reliability of a signal impact assessment tool. Pharmacoepidemiol Drug Saf. 2016; 25(7): 815-819
11. Waller P, Heeley E, Moseley J. Impact analysis of signals detected from spontaneous adverse drug reaction reporting data. Drug Saf. 2005; 28(10): 843-50
12. Van Puijenbroek SR, Van Grootheest K, Diemont WL, Leufkens HGM, Egberts ACG. Determinants of signal selection in a spontaneous reporting system for adverse drug reactions. Br J Clin Pharmacol. 2001; 52(5): 579-586
13. Insani WN, Pacurariu AC, Teeuwisse AKM, Martirosyan LG. Characteristics of drugs safety signals that predict safety related product information update Pharmacoepidemiol. Drug Saf. 2018; 27(7):789–796
14. Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS). https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm.
    cited 2017 November 29.
15. FDA Adverse Event Reporting System (FAERS): Latest Quarterly Data Files. https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm.
    cited 2017 November 29.
16. The Adverse Event Reporting System (AERS): Older Quarterly Data Files. https://wayback.archive-

it.org/7993/20170404211700/https:/www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm083765.htm.
cited 2017 November 29.

17. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf. 2004; 13: 519–23.
18. Meyboom RH, Egberts AC, Edwards IR, Hekster YA, de Koning FH, Gribnau FW. Principles of signal detection in pharmacovigilance. Drug Saf. 1997; 16: 355–65.
19. Poluzzi E, Raschi E, Piccinni C, Ponti FD. Data Mining Techniques in Pharmacovigilance: Analysis of the Publicly Accessible FDA Adverse Event Reporting System (AERS). IntechOpen, doi: 10.5772/50095. Available from: https://www.intechopen.com/books/data-mining-applications-in-engineering-and-medicine/data-mining-techniques-in-pharmacovigilance-analysis-of-the-publicly-accessible-fda-adverse-event-re
20. CIOMS Working Group. Current challenges in pharmacovigilance: Pragmatic approaches. Geneva; 2001.
21. Lester J, Neyarakally GA, Lipowsi E, Graham CF, Hall M, DalPan G. Evaluation of FDA safety-related drug label changes in 2010. Pharmacoepidemiol. Drug Saf. 2013; 22:302-5.
22. Moore TJ, Singh S, Furberg CD. The FDA and New Safety Warnings. Arch Intern Med.2012; 172(1):78-80.
23. Candore G, Juhlin K, Manlik K, et al. Comparison of statistical signal detection methods within and across spontaneous reporting databases. Drug Saf. 2015; 38:577-87 doi: 10.1007/s4026401502895
24. Pacurariu AC, Coloma PM, Haren Av et al. A description of signals during the first

18 months of the EMA pharmacovigilance risk assessment committee. Drug Saf. 2014; 37:1059-1066 doi:10.1007/s4026401402401

25. FDA's Information on Heparin http://wayback.archive-it.org/7993/20171115054435/https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm112597.htm.

    cited 2018 August 7.

26. Drug Safety communication http://wayback.archive-it.org/7993/20171115033743/https://www.fda.gov/Drugs/DrugSafety/ucm250913.htm.

    cited 2018 August 7.

27. Mercaptopurine (Purinethol) Labeling approved May 27, 2011 (PDF - 60KB) https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009053s032lbl.pdf.

    cited 2018 August 7.

28. Conjugated estrogens (Premarin) labelling approved October 28, 2011 (PDF - 310KB) https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/004782s162s164s167lbl.pdf.

    cited 2018 August 7.

29. EMA. Designated medical events. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac0580727d1b.

    cited 2017 November 29.

30. FDA. White Paper. https://www.fda.gov/ScienceResearch/DataMiningatFDA/ucm446239.htm.

cited 2017 November 29.

31. Almenoff JS, LaCroix KK, Yuen NA, Fram D, DuMouche W. Comparative performance of two quantitative safety signalling methods: Implications for use in a pharmacovigilance department. Drug Saf. 2006; 29 (10): 875-887.
32. Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071696.pdf. cited December 2018
33. Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions. https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-ix-addendum-i-methodological-aspects-signal_en.pdf.

    cited 2018 December 2.
34. Fukazawa C, Hinomura Y, Kaneko M, Narukawa M. Significance of data mining in routine signal detection: Analysis based on the safety signals identified by the FDA. Pharmacoepidemiol. Drug Saf. 2018; 27(12): 1402-1408
35. Belton KJ, Lewis SC, Payne S, Rawlins MD. Attitudinal survey of adverse drug reaction reporting by medical practitioners in the United Kingdom. Br J Clin Pharmacol. 1995; 39(3): 223-226.
36. McAdams MA, Governale LA, Swartz L, Hammad TA, Dal Pan GJ. Identifying patterns of adverse event reporting for four members of the angiotensin II receptor blockers class of drugs: revisiting the Weber effect. Pharmacoepidemiol. Drug Saf. 2008; 17(9): 882-889

37. Tracking of Significant Safety Issues in Marketed Drugs -- Use of the DARRTS Tracked Safety Issue (PDF - 100KB) https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM164967.pdf.
cited December 2018.
38. Plassis L, Gomez A, Garcia N et al. Lack of essential information in spontaneous reports of adverse drug reactions in Catalonia; a restraint to the potentiality for signal detection. Eur J Clin Pharmacol. 2017; 73(6): 751-758
39. Montastruc F, Salvo F, Arnaud M, Begaud B, Pariente A. Signal of gastrointestinal congenital malformations with antipsychotics after minimising competition bias: A disproportionality analysis using data from Vigibase. Drug Saf. 2016; 39(7):689–696
40. Moro P, Baumblatt J, Lewis P et al. Surveillance of adverse events after seasonal influenza vaccination in pregnant women and their infants in the vaccine adverse event reporting system, July 2010–May 2016. Drug Saf. 2017; 40(2): 145–152
41. Osokogu OU, Fregonese F, Ferrajolo C et al. Pediatric drug safety signal detection: A new drug–event reference set for performance testing of data-mining methods and systems. Drug Saf. 2015; 38(2): 207–217
42. Osokogu OU, Dodd C, Pacurariu A et al. Drug safety monitoring in children: Performance of signal detection algorithms and impact of age stratification. Drug Saf. 2016; 39(9): 873–881
43. Star K, Watson S, Sandberg L, Johansson J, Edwards IR. Longitudinal medical records as a complement to routine drug safety signal analysis. Pharmacoepidemiol Drug Saf. 2015; 24(5): 486–494.
44. Donegan, K, Owen, R, Bird, H et al. Exploring the Potential Routine Use of

Electronic Healthcare Record Data to Strengthen Early Signal Assessment in UK Medicines Regulation: Proof-of-Concept Study. Drug Saf. 2018; 41(9): 899-910

45. Coloma PM, Schuemie MJ, Trifiro G et al. Combining electronic healthcare databases in Europe to allow for large scale drug safety monitoring: the EU ADR Project. Pharmacoepidemiol Drug Saf. 2011; 20(1): 1 to
46. The Sentinel Initiative https://www.fda.gov/downloads/safety/fdassentinelinitiative/ucm233360.pdf cited 2018 December 2.
47. Hill AB. The Environment and Disease: Association or causation? Proc R Soc Med. 1965; 58(5): 295-300

6 Acknowledgement

First and foremost, I would like to express my deep appreciation to Professor Mamoru Narukawa. From him, I received not only insightful comments and suggestions for the present study, I also received his moral influence. He has extensive knowledge and idea of being well-balanced in the various regions of drug development strategy including post-marketing safety measures. I am really impressed by his high level of knowledge and virtue. The four years receiving his instruction is irreplaceable time for me.

I give special thanks to Assistant Professor Masayuki Kaneko for his instruction, support and advice, especially from the statistical point of view. I am also thanks to Mr. Yasushi Hinomura for providing me valuable advice. Without their help, the present study would not have materialized.

I would like to thank all colleagues in our department for a fresh incentive, warm encouragement and support through my Ph.D. course. I am also grateful to Ms. Takako Nakata and Ms. Yukiko Minami for kindly providing me with an administrative support.

I am very grateful to Mr. Takahisa Murakami, the president of JAPIC, for giving me the opportunity of taking pharmaceutical degree. I am also grateful to JAPIC members who supported me in both research and work.

Finally, I am extremely grateful to my family and friends for continuous support and encouragement throughout my PhD course.

Appendix 1

Table I The time interval from signal identification to label change (N=152)

Quarter †	Suspected drug ‡	Adverse events §	Final date of the quarter of the signal identification	Date of the label change	The time interval (Year)
2008 1Q	Arginine Hydrochloride Injection (R-Gene 10)	Pediatric overdose due to labeling / packaging confusion	2008/3/31	2010/1/17	1.8
2008 1Q	Desflurane (Suprane)	Cardiac arrest	2008/3/31	2009/4/14	1.1
2008 1Q	Duloxetine (Cymbalta)	Urinary retention	2008/3/31	2009/11/19	1.7
2008 1Q	Icodextrin (Extraneal)	Hypoglycemia	2008/3/31	2009/4/7	1.0
2008 1Q	Insulin U-500 (Humulin R)	Dosing confusion	2008/3/31	2011/3/21	3.0
2008 1Q	Lapatinib (Tykerb)	Hepatotoxicity	2008/3/31	2008/7/7	0.3
2008 1Q	Lenalidomide (Revlimid)	Stevens Johnson Syndrome	2008/3/31	2009/2/23	0.9
2008 1Q	Nitroglycerin (Nitrostat)	Overdose due to labeling confusion	2008/3/31	2010/7/12	2.3
2008 1Q	Octreotide Acetate (Sandostatin injection)	Ileus	2008/3/31	2012/3/23	4.0
2008 1Q	Perflutren Lipid Microsphere (Definity)	Cardiopulmonary reactions	2008/3/31	2011/10/24	3.6
20081Q	Phenytoin Injection (Dilantin)	Purple Glove Syndrome	2008/3/31	2011/11/13	3.7
2008 1Q	Telbivudine (Tyzeka)	Peripheral neuropathy	2008/3/31	2009/5/8	1.1
2008 1Q	Tumor Necrosis Factor (TNF) Blockers	Cancers in children and young adults	2008/3/31	2009/8/4	1.4
2008 2Q	Furosemide (Lasix), Torsemide (Demadex),	Serious skin reactions	2008/6/30	2010/1/27	1.6

	Spironolactone (Aldactone)				
2008 2Q	Leukotriene receptor antagonists	Suicidal behavior and suicide	2008/6/30	2009/8/19	1.2
2008 2Q	Orlistat (Xenical, Alli)	Rectal bleeding	2008/6/30	2012/1/20	3.6
2008 2Q	Sulfonylurea antidiabetic drugs	Hemolytic anemia in patients with and without G6PD deficiency	2008/6/30	2009/11	1.4
2008 2Q	Temsirolimus (Torisel)	Labeling confusion resulting in incorrect dose	2008/6/30	2011/6/16	3.0
2008 2Q	Trazodone	Prolongation of the electrocardiogram QT interval	2008/6/30	2010/2/2	1.6
2008 3Q	Bupivacaine and other local anesthetics intraarticular injection given by infusion pump	Chondrolysis	2008/9/30	2010/2	1.4
2008 3Q	Mefloquine HCl (Lariam)	Psychiatric events	2008/9/30	2009/8/20	0.9
2008 3Q	Minocycline	Thyroid disorders	2008/9/30	2010/9/14	2.0
2008 3Q	Propylthiouracil and Methimazole	Hepatotoxicity	2008/9/30	2010/4	1.5
2008 3Q	Terbinafine (Lamisil) oral use	Psychiatric events	2008/9/30	2010/12/2	2.2
2008 4Q	Apomorphine (Apokyn)	Psychiatric events	2008/12/31	2010/9/2	1.7
2008 4Q	Clomiphene citrate (Clomid)	Visual disorders	2008/12/31	2012/10/22	3.9
2008 4Q	Drospirenone/ethinyl estradiol (Yasmin)	Pancreatitis	2008/12/31	2012/2/13	3.2
2008 4Q	Fibrin sealant products, human (Evicel, Tisseel, Artiss)	Air embolism	2008/12/31	2010/4	1.3
2008 4Q	Human chorionic gonadotropin products Choriogonadotropin alfa	Anaphylactic reactions	2008/12/31	2010/6/2	1.4

	(Ovidrel) Chorionic gonadotropin (Pregnyl)				
2008 4Q	Imiquimod cream (Aldara)	Dysuria due to severe local reactions during use in the genital area	2008/12/31	2010/10/14	1.8
2008 4Q	Modafinil (Provigil) and Armodafinil (Nuvigil)	Serious skin reactions	2008/12/31	2010/10/21	1.8
2008 4Q	Muscarinic Receptor Antagonists	Angioedema and other allergic reactions	2008/12/31	2010/7/12	1.6
2008 4Q	Orlistat (Xenical, Alli)	Hepatotoxicity	2008/12/31	2010/5/25	1.4
2008 4Q	Raltegravir (Isentress)	Psychiatric events	2008/12/31	2009/11/4	0.9
2008 4Q	Testosterone gel (Androgel, Testim)	Adverse events from accidental exposure	2008/12/31	2009/9/18	0.7
2008 4Q	Varenicline (Chantix)	Angioedema, serious skin reactions, accidental injury	2008/12/31	2009/7/1	0.5
2009 1Q	Alpha interferon products	Pulmonary Hypertension	2009/3/31	2009/9	0.4
2009 1Q	Ceftriaxone (Rocephin)	Hemolytic anemia	2009/3/31	2009/6/7	0.2
2009 1Q	Diclofenac epolamine patch (Flector)	Hypersensitivity reactions	2009/3/31	2011/1/31	1.9
2009 1Q	Didanosine (Videx)	Portal hypertension	2009/3/31	2010/1/25	0.8
2009 1Q	Entacapone (Comtan) and carbidopa/levodopa/ entacapone (Stalevo)	Colitis	2009/3/31	2010/10/11	1.6
2009 1Q	Gadolinium-based contrast agents	Anaphylaxis	2009/3/31	2009/10/2	0.5
2009 1Q	Mecasermin products (Increlex, Iplex)	Hypersensitivity reactions	2009/3/31	2011/2/16	1.9
2009 1Q	Methylnaltrexone	Gastrointestinal	2009/3/31	2010/7/23	1.3

	(Relistor)	perforation			
2009 1Q	Minocycline products (Minocin) (Solodyn)	Autoimmune disorders in pediatric patients, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	2009/3/31	2010/9/14	1.5
2009 1Q	Promethazine injection	Severe tissue injury including gangrene	2009/3/31	2009/9	0.4
2009 1Q	Sunitinib (Sutent)	Liver failure	2009/3/31	2010/7/1	1.3
2009 1Q	Zoledronic acid (Reclast)	Renal impairment	2009/3/31	2009/3/13	0.0
2009 2Q	Aliskiren (Tekturna, Tekturna HCT)	Angioedema requiring intubation	2009/6/30	2009/11/10	0.4
2009 2Q	Antipsychotics	Agranulocytosis	2009/6/30	2009/7	0.0
2009 2Q	Bumetanide (Bumex)	Serious skin reactions (Stevens-Johnson Syndrome, Toxic epidermal necrosis)	2009/6/30	2010/1/21	0.6
2009 2Q	Deferasirox (Exjade)	Deaths	2009/6/30	2010/1/28	0.6
2009 2Q	Gabapentin (Neurontin)	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	2009/6/30	2011/8/10	2.1
2009 2Q	Immunosuppressants (transplant)	BK virus nephropathy	2009/6/30	2009/7	0.0
2009 2Q	Oseltamivir phosphate (Tamiflu)	Hypothermia	2009/6/30	2010/11/5	1.4
2009 2Q	Riluzole (Rilutek)	Interstitial lung disease	2009/6/30	2009/11/16	0.4

2009 3Q	Bendamustine (Treanda)	Infusion site extravasation	2009/9/30	2010/2/26	0.4
2009 3Q	HMG-CoA reductase inhibitors “Statins”	Cognitive effects	2009/9/30	2012/2	2.4
2009 3Q	Lamotrigine (Lamictal)	Central nervous system infection, Aseptic meningitis	2009/9/30	2010/10/24	1.1
2009 3Q	Neuromuscular Blocking Agents	Anaphylactic reactions and potential for cross-reactivity	2009/9/30	2010/11	1.1
2009 3Q	Sirolimus (Rapamune)	Progressive multifocal leukoencephalopathy (PML)	2009/9/30	2010/7/2	0.8
2009 3Q	Tumor Necrosis Factor (TNF) Blockers	Demyelinating neuropathy	2009/9/30	2010/7/29	0.8
2009 3Q	Zonisamide (Zonegran)	Rhabdomyolysis, Pancreatitis	2009/9/30	2012/1/26	2.4
2009 4Q	5-alpha reductase inhibitors Dutasteride, Finasteride (Avodart, Propecia, Proscar)	Male breast cancer	2009/12/31	2010/10/4	0.8
2009 4Q	Corticosteroids (depot formulations)	Serious neurologic events with epidural use.	2009/12/31	2011/6/16	1.5
2009 4Q	Leuprolide acetate (Lupron Depot)	Osteopenia	2009/12/31	2011/6/17	1.5
2009 4Q	Lopinavir and ritonavir (Kaletra)	Hepatotoxicity with post-exposure prophylaxis (PEP) regimens	2009/12/31	2010/4/27	0.3
2010 1Q	Azacitidine (Vidaza)	Acute febrile neutrophilic dermatosis (Sweet’s	2010/3/31	2012/1/24	1.8

		syndrome)			
2010 1Q	Azithromycin (Zithromax)	Liver failure	2010/3/31	2011/1/28	0.8
2010 1Q	Azithromycin extended release 2 g (Zmax)	Pyloric stenosis	2010/3/31	2011/6/7	1.2
2010 1Q	C1 esterase inhibitors (Cinryze, Berinert)	Thromboembolic events in patients with certain thrombogenic risk factors	2010/3/31	2011/12/22	1.8
2010 1Q	Clarithromycin (Biaxin)	Liver failure	2010/3/31	2011/5/27	1.2
2010 1Q	Daptomycin (Cubicin)	Pulmonary eosinophilia, Eosinophilic pneumonia	2010/3/31	2010/8/13	0.4
2010 1Q	Dronedarone hydrochloride (Multaq)	Heart failure	2010/3/31	2011/2/11	0.9
2010 1Q	Estrogens, conjugated (Premarin)	Angioedema	2010/3/31	2011/10/28	1.6
2010 1Q	Prasugrel hydrochloride (Effient)	Thrombotic thrombocytopenic purpura	2010/3/31	2010/12/6	0.7
2010 1Q	Temsirolimus (Torisel)	Infusion site extravasation	2010/3/31	2011/6/16	1.2
2010 2Q	Clindamycin injection (Cleocin)	Overdose due to labeling confusion/ medication errors	2010/6/30	2010/10	0.3
2010 2Q	Doxycycline products	Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme	2010/6/30	2011/3/8	0.7
2010 2Q	Etonogestrel implant (Implanon, Nexplanon)	Convulsions	2010/6/30	2011/5/13	0.9
2010 2Q	Everolimus (Afinitor)	Hepatitis B reactivation	2010/6/30	2010/7/9	0.0

2010 2Q	Febuxostat (Uloric)	Hypersensitivity	2010/6/30	2011/1/28	0.6
2010 2Q	Ferumoxytol injection (Feraheme)	Serious cardiac disorders	2010/6/30	2010/11/24	0.4
2010 2Q	GnRH Agonists (Androgen Deprivation Therapy)	Hyperinsulinemia, Arterial thrombosis	2010/6/30	2011/1	0.5
2010 2Q	Lanthanum carbonate (Fosrenol)	Intestinal obstruction	2010/6/30	2011/4/27	0.8
2010 2Q	Proton Pump Inhibitors (PPIs)	Hypomagnesemia	2010/6/30	2011/6	0.9
2010 2Q	Saquinavir mesylate (Invirase)	Prolonged QT and PR Syndromes	2010/6/30	2010/10/6	0.3
2010 2Q	Simvastatin (Zocor)	Muscle injury with 80mg dose	2010/6/30	2011/6/8	1.0
2010 2Q	Tapentadol hydrochloride (Nucynta)	Convulsions, Hallucinations, Serotonin syndrome	2010/6/30	2010/11/1	0.3
2010 2Q	Trastuzumab (Herceptin)	Neonatal pulmonary hypoplasia	2010/6/30	2010/10/29	0.3
2010 3Q	Benzonatate (Tessalon)	Death from accidental ingestion in children	2010/9/30	2011/1/20	0.3
2010 3Q	Gemcitabine hydrochloride (Gemzar)	Veno-occlusive liver disease	2010/9/30	2011/2/4	0.4
2010 3Q	Lanreotide acetate (Somatuline depot)	Pancreatitis, Hemorrhagic and Necrotizing Pancreatitis	2010/9/30	2011/3/4	0.4
2010 3Q	Lanthanum carbonate (Fosrenol)	Swallowing complications, GI obstruction (attributed to tablet hardness)	2010/9/30	2011/4/27	0.6

2010 3Q	Levetiracetam (Keppra)	Stevens-Johnson's Syndrome, Toxic Epidermal Necrolysis	2010/9/30	2011/12/16	1.2
2010 3Q	Lithium citrate	Brugada Syndrome	2010/9/30	2011/10/20	1.1
2010 3Q	Sodium oxybate (Xyrem)	Death	2010/9/30	2012/12/17	2.3
2010 4Q	Asenapine maleate (Saphris)	Hypersensitivity	2010/12/31	2011/8/9	0.6
2010 4Q	Dronedarone HCl (Multaq)	Liver failure	2010/12/31	2011/2/11	0.1
2010 4Q	Fenofibrate products	Paradoxical decrease in HDL cholesterol	2010/12/31	2012/9/5	1.7
2010 4Q	Golimumab (Simponi)	Hypersensitivity reactions and anaphylaxis	2010/12/31	2011/8/17	0.6
2010 4Q	Oxycodone HCl controlled-release tablets (Oxycontin) [new formulation]	Choking and gastrointestinal obstruction	2010/12/31	2010/11/15	-0.1
2010 4Q	Regadenoson (Lexiscan)	QT prolongation	2010/12/31	2011/9/23	0.7
2010 4Q	Sevelamer HCl (Renagel)	Choking (esophageal obstruction)	2010/12/31	2011/6/16	0.5
2011 1Q	Adalimumab (Humira)	Hepatic dysfunction, Hepatic failure	2011/3/31	2012/5/24	1.2
2011 1Q	Azathioprine (Imuran)	Acute febrile neutrophilic dermatosis (Sweet's syndrome)	2011/3/31	2011/5/24	0.2
2011 1Q	Cetuximab (Erbitux)	Corneal infection, Ulcerative keratitis	2011/3/31	2012/1/24	0.8

2011 1Q	Dronedarone HCl (Multaq)	Renal impairment, Renal failure	2011/3/31	2011/8/22	0.4
2011 1Q	Iron sucrose injection (Venofer)	Anaphylactic reactions	2011/3/31	2011/6/22	0.2
2011 1Q	Malathion (Ovide)	Burns and burning sensations	2011/3/31	2011/12/9	0.7
2011 1Q	Mercaptopurine (Purinethol)	Hepatosplenic T-cell lymphoma	2011/3/31	2011/5/27	0.2
2011 1Q	Prasugrel HCl (Effient)	Hypersensitivity reactions	2011/3/31	2010/12/6	-0.3
2011 1Q	Quinolone products	Pseudotumor cerebri	2011/3/31	2011/10/11	0.5
2011 1Q	Rituximab (Rituxan)	Hypogammaglobulinemia	2011/3/31	2012/2/17	0.9
2011 1Q	Ropinirole HCl (Requip)	Medication errors resulting from similarities in product name and labeling to Risperidone	2011/3/31	2012/3	0.9
2011 2Q	Asenapine maleate (Saphris)	Oral blistering, Oral ulceration, Oral erosion	2011/6/30	2013/3/21	1.8
2011 2Q	Bevacizumab (Avastin)	Osteonecrosis of jaw	2011/6/30	2011/9/30	0.3
2011 2Q	Dronedarone HCl (Multaq)	Pulmonary toxicity	2011/6/30	2011/6/21	0.0
2011 2Q	Everolimus (Afinitor, Zortress)	Acute and chronic pancreatitis, Gallbladder disorder	2011/6/30	2014/2/20	2.7
2011 2Q	Muscarinic receptor antagonist products	Somnolence	2011/6/30	2012/1/17	0.6
2011 2Q	Sodium ferric gluconate complex (Ferrlecit)	Anaphylactic reactions	2011/6/30	2011/8/25	0.2
2011 2Q	Voriconazole (Vfend)	Fluorosis and	2011/6/30	2011/11/1	0.4

		Periostitis with long-term use		6	
2011 3Q	Adalimumab (Humira), Golimumab (Simponi)	Optic neuritis	2011/9/30	2011/12/26	0.2
2011 3Q	Clevidipine butyrate IV emulsion (Cleviprex)	Hypoxemia	2011/9/30	2011/12/8	0.2
2011 3Q	Dabigatran etexilate mesylate (Pradaxa)	Bleeding events including hemorrhage with fatal outcome	2011/9/30	2012/1/17	0.3
2011 3Q	Tumor Necrosis Factor (TNF) blocking agent products	Sarcoidosis	2011/9/30	2011/10/26	0.1
2011 3Q	Valproate products: Valproic acid, Divalproex sodium, Valproate sodium	Liver failure, Liver injury, (involving hereditary mitochondrial disorders such as Alpers-Huttenlocher Syndrome (AHS), and other conditions)	2011/9/30	2013/7	1.8
2011 4Q	Bortezomib (Velcade)	Death from intrathecal administration (medication error)	2011/12/31	2012/1/23	0.1
2011 4Q	Brentuximab vedotin (Adcetris)	Progressive multifocal leukoencephalopathy (PML)	2011/12/31	2012/1/13	0.0
2011 4Q	Fluoroquinolone products	Peripheral sensorimotor neuropathy	2011/12/31	2013/8	1.6
2011 4Q	Gabapentin HCl (Neurontin)	Increase in blood creatine	2011/12/31	2013/5/1	1.4

		phosphokinase levels and rhabdomyolysis			
2011 4Q	Gadolinium-based contrast agents (GBCA) products	Acute kidney injury	2011/12/31	2013/10	1.8
2011 4Q	Iloprost inhalation solution (Ventavis)	Hemoptysis	2011/12/31	2012/4/26	0.3
2011 4Q	Magnesium sulfate for injection	Fetal skeletal demineralization, hypermagnesemia, and other bone abnormalities with continuous long-term use in pregnant women.	2011/12/31	2013/5/29	1.4
2011 4Q	Milnacipran HCl (Savella)	Homicidal ideation	2011/12/31	2012/12/6	1.0
2011 4Q	Pegloticase (Krystexxa)	Anaphylaxis and infusion reactions	2011/12/31	2012/4/16	0.3
2011 4Q	Rubidium Rb 82 generator	Unintended radiation exposure to strontium isotopes following myocardial imaging scans.	2011/12/31	2012/2/8	0.1
2011 4Q	Sorafenib tosylate (Nexavar)	Osteonecrosis of the jaw	2011/12/31	2013/10/30	1.9
2011 4Q	Telaprevir (Incivek)	Serious skin reactions including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson Syndrome (SJS)	2011/12/31	2012/12/14	1.0
2012 1Q	Lacosamide (Vimpat)	Toxic epidermal	2012/3/31	2013/9/25	1.5

		necrolysis			
2012 1Q	Methylergonovine maleate tablets and injection (Methergine)	Myocardial ischemia and infarction associated with Methergine-induced vasospasm. Medication errors involving neonates and adults.	2012/3/31	2012/6/25	0.2
2012 1Q	Montelukast (Singulair)	Stevens-Johnson Syndrome	2012/3/31	2012/9/27	0.5
2012 2Q	Codeine sulfate	Respiratory depression or arrest resulting in death in children taking codeine who are CYP2D6 ultra-rapid metabolizers.	2012/6/30	2013/3	0.9
2012 2Q	Olmesartan medoxomil (Benicar)	Malabsorption resulting in severe diarrhea and weight loss.	2012/6/30	2013/7/3	1.0
2012 3Q	Dalfampridine (Ampyra)	Anaphylaxis	2012/9/30	2013/1/22	0.3
2012 3Q	Lacosamide (Vimpat)	Neutropenia	2012/9/30	2013/4/17	0.6
2012 3Q	Ofatumumab (Arzerra)	Viral infections	2012/9/30	2013/9/24	1.0
2012 4Q	Acetaminophen-containing products	Severe skin reactions	2012/12/31	2013/10	0.8
2012 4Q	Anagrelide HCl (Agrylin)	Torsades de pointes	2012/12/31	2013/7/17	0.6
2013 1Q	Serotonin-3 (5-HT3) receptor antagonist products	Serotonin syndrome	2013/3/31	2014/9	1.4
2013 2Q	Regadenoson (Lexiscan)	Myocardial	2013/6/30	2014/1/3	0.5

		infarction and death			
2014 3Q	Regadenoson (Lexiscan)	Seizures, worsening or recurrence of seizures after use of aminophylline, cerebrovascular accident, and atrial fibrillation/atrial flutter	2014/9/30	2014/9	-0.1

† Quarter: quarter that the signal was identified, ‡ Suspected drug: suspected drug for the signal, § Adverse events: AE for the signal

Among 233 signals evaluated in this study, the date of label change was available for 152 signals. If there were multiple labelling changes occurred due to the existence of multiple suspected drugs for the same signal, the earliest date of the labelling change was adopted in this calculation. For signals for which only the information of year and month of the labelling change was available, the first date of the month was defined as the date of the labelling change in this calculation.

Appendix 2

Table II Classification of the signals based on seriousness of AEs when the definition of "serious" events was widened.

	detected signals by ROR † (%)	non-signals by ROR ‡ (%)
Serious §	95(60.9)	57(74.0)
Nonserious §	61(39.1)	20(26.0)

[p=0.057, Fisher's exact test]

† detected signals by ROR: signals with statistical significance (cases≥2, lower bound for 95% confidence interval >1) by ROR.

‡ non-signals by ROR: signals without statistical significance by ROR.

§ Serious: AEs described in the list of the CIOMS Working Group V and malignant tumors, progressive multifocal leukoencephalopathy (PML), drug rash with eosinophilia and systemic symptoms (DRESS) and acute febrile neutrophilic dermatosis, Nonserious: AEs that are not considered "serious",

Appendix 3

Table III Sources of evidence for the 24 signals leading to drug safety communication

	N	%
AE reports	10	41.7
AE reports + medical literature	9	37.5
AE reports + registries or another database information	4	16.7
AE reports+ evidence from observational studies	1	4.2
AE reports+ evidence from epidemiological studies	1	4.2
AE reports + evidence from mini-sentinel	2	8.3
AE reports + evidence from clinical trials	6	25.0