Postmarketing Risk Evaluation of First-in-class Drugs in the U.S. based on Analyses of Postmarketing Safety Regulatory Actions

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Abstract

First-in-class (FIC) drugs with a novel mechanism of action provide effective therapies. However, since new FIC drugs do not have enough safety information, they might bring some critical postmarketing safety issues. The purpose of this study was to evaluate postmarketing risk of FIC drugs based on analyses of important postmarketing safety-related regulatory actions (PSRAs) focusing on new drugs approved in the United States (U.S.), where most FIC drugs have been approved first prior to any other country. This thesis consists of two parts. In Part I, which is an exploratory part, we compared the incidence of important drug-specific PSRAs for FIC drugs with those for other new drugs to investigate relationship between FIC drugs and the occurrence of important drug-specific PSRAs. In Part II, which is a confirmatory part, we analyzed comprehensively the factors related to the occurrence of important PSRAs with a focus on FIC drugs to clarify postmarketing risk of newly approved drugs.

New molecular entities and new therapeutic biologics excepting diagnostic agents and vaccines, approved in the U.S. between January 1, 2003 and December 31, 2013, were investigated in this study. In Part I, the odds of occurrence of important drug-specific PSRA was compared between FIC drugs and other new drugs. In addition, key baseline characteristics were analyzed. In Part II, the relationships between baseline characteristics

and the occurrence of PSRAs were investigated using a multivariate binomial logistic regression model. An additional analysis using a multivariable Cox proportional hazards model to clarify the factors affecting the relationship with the time to occurrence of the first important drug-specific PSRA was performed.

The odds ratio of occurrence of important drug-specific PSRAs in FIC drugs was 2.06 (95%CI: 1.20–3.55, p=0.0091) compared with other new drugs, indicating a strong relationship between FIC drugs and the occurrence of important drug-specific PSRAs in Part I. The odds ratio of the occurrence of important drug-specific PSRAs for Anatomical Therapeutic Chemical (ATC) Classification category L drugs (antineoplastic and immunomodulating agents) was 2.24 (95%CI: 1.54–4.91, p=0.0007) compared with other category drugs, indicating a strong relationship between ATC category L drugs and the occurrence of important drug-specific PSRAs. Various kinds of ADRs were related to any PSRAs and no specific trend was observed in FIC drugs.

In Part II, ATC category L and FIC drug classification were shown to be statistically significant factors related to the occurrence of important drug-specific PSRAs, with odds ratios of 2.15 (95% CI: 1.12-4.11; p = 0.0203) and 1.87 (95% CI: 1.06-3.31; p = 0.0309), respectively. ATC category L, review period and FIC drugs were also significant factors for time to occurrence of the first event.

The results of the present study indicated that postmarketing safety risk for FIC drugs is higher than that for other new drugs which have same-class drugs at approval. It is therefore important to carefully consider the risks of FIC drugs and to develop an optimal risk minimization plan, and to conduct pharmacovigilance efforts based on the drug profile at an early stage after approval.

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Abbreviations

Abbreviation	Definition
AA	Accelerated approval
ADRs	Adverse drug reactions
ATC	Anatomical Therapeutic Chemical
BBWs	Black box warnings
CI	Confidence interval
DILI	Drug induced liver injury
FIC	First-in-class
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
NMEs	New molecular entities
NTBs	New therapeutic biologic
OR	Odds ratio
PSRAs	Postmarketing safety-related regulatory actions
PT	Preferred term
RR	Relative risk
REMS	Risk Evaluation and Mitigation Strategies
SOC	System organ class
MedDRA	Medical Dictionary for Regulatory Activities
U.S.	United States

1 Introduction

Recent advances in human genome analysis and the development of novel molecular biological techniques have led to a major shift in drug discovery toward target-based approaches. This change has resulted in an increased number of new first-in-class (FIC) drugs with novel mechanisms of action [1] and has provided new therapeutic options [2]. However, FIC drugs have been reported to be associated with higher incidence of serious adverse drug reactions (ADRs) than less novel drugs [3]. Because there is not enough safety information available for drugs with a similar mode of action [3, 4], FIC drugs can cause unpredictable safety issues and lead to frequent postmarketing safety-related regulatory actions (PSRAs) [5, 6]. We hypothesized that FIC drugs with a novel mechanism of action might be associated with a higher incidence of PSRAs than other new drugs which have same-class drugs.

Important PSRAs such as safety-related market withdrawals, and the addition of black box warnings (BBWs) or warnings are effective parameters for evaluating postmarketing safety risks [5, 6], because they are taken with decision of regulatory authorities based on serious safety issues. [7, 8]. Studies analyzing the factors related to the occurrence of PSRAs for new molecular entities (NMEs) in the U.S. have reported that new therapeutic biologics (NTBs) are associated with a higher incidence of PSRAs based on

immunomodulatory infection-related ADRs [5]. Orphan drugs by accelerated approval, oncological drugs and drugs for gastrointestinal and metabolism indications may have a higher risk for PSRAs [6], and new oncological drugs were associated with a higher incidence of PSRAs [9]. These studies suggested that the occurrence of PSRAs were related to therapeutic area or drug types. Furthermore, other studies reported that the deadline for the completion of drug review by FDA was related to PSRAs [10], the issuance of a BBW at approval and priority review designation were significant factors of the occurrence of PSRAs [11], and biologics, drugs for psychiatric diseases drugs and accelerated approval (AA) were statistically significantly associated with higher rates of PSRAs [12]. These studies suggested that the occurrence of PSRAs were related to FDA's act or policy. However, these studies did not focus on FIC drugs, and the analyses did not include FIC clarification as an explanatory variable. No data are available on the relationship between FIC drugs and the occurrence of PSRAs for drugs approved in the U.S., where more than half of all FIC drugs are developed and approved first in the world. Therefore, we intended to analyze factors related to the occurrence of PSRAs for novel therapeutics in the U.S., including FIC drug as a factor.

The aim of this study was to evaluate postmarketing risk of FIC drugs based on analyses of PSRAs. This thesis consists of two parts. In Part I, which is an exploratory part, we

compared the occurrence of important drug-specific PSRAs for FIC drugs with those for other new drugs to explore relationship between FIC drugs and important drug-specific PSRAs. In Part II, which is a confirmatory part, we analyzed comprehensively the factors related to the occurrence of PSRAs with a focus on FIC drugs to clarify postmarketing risk of newly approved drugs.

2 Part I Important Postmarketing Safety-related Regulatory Actions Related to Drug-Induced Adverse Drug Reactions of First-in-Class Drugs: A Retrospective Double-Cohort Study

2.1 Background and Aims

FIC drugs do not have enough safety information, and they might bring some critical postmarketing safety issues. We hypothesized that FIC drugs with a novel mechanism of action might be associated with a higher occurrence of PSRAs than other new drugs which have same-class drugs at approval.

The issuance of BBWs in the U.S. has revealed that the decision making of the U.S. Food and Drug Administration (FDA) regarding the addition of new BBWs is not always consistent because the available safety information before approval can vary depending on the timing of review, the drug profile, and the target diseases [13]. PSRAs occur in multiple drugs due to ADRs from the same-class drugs or ADRs from a pooled analysis [12]. In addition, rare ADRs are generally not identifiable in preapproval clinical trials such as drug allergies (hypersensitivity, serious skin reactions) and DILI. These rare ADRs are generally dose independent, and it is difficult to evaluate the relationship between such ADRs and the mode of action [8]. From the above reasons, the events leading to PSRAs, the causes of PSRAs, and the associated ADRs vary across drugs. Considering the various PSRAs, we identified important drug-specific PSRAs safety-

related market withdrawals, and new BBWs and warnings due to drug-induced ADRs, excluding class effects, drug allergies and DILI for evaluating PSRAs due to individual drug ADRs.

The aim of Part I study in this thesis was to explore the relationship between FIC drugs and important drug-specific PSRAs by comparing the occurrence of that for FIC drugs with that for other new drugs.

2.2 Method

2.2.1 Design and Setting

This retrospective double-cohort study involved all NMEs and NTBs approved by the FDA between January 1, 2003, and December 31, 2013, excluding agents for nontreatment purposes, such as diagnostic agents, sunscreens, drug adjuvants, nontherapeutic vaccines, antidotes, and radiation agents. FIC drugs were defined as drugs that had a novel mechanism of action at the time of FDA approval, according to the overview by Eder et al. [14], and all drugs were classified as either FIC drugs (FIC cohort) or other new drugs (control cohort).

2.2.2 Primary Endpoint and Other Endpoints

The primary endpoint was the odds of occurrence of important drug-specific PSRA,

and the primary analysis was a comparison between the FIC cohort and the control cohort using the odds ratio. Other endpoints were the odds of occurrence of important PSRAs due to class effects, PSRAs due to drug allergies, and all PSRAs due to ADRs including class effects and drug allergies, as well as the type of ADRs (system organ class [SOC], preferred term [PT], and PT group) related to important drug-specific PSRAs, all of which were compared between the cohorts.

2.2.3 Definition of Important PSRAs

In this study, important PSRAs were defined as safety-related market withdrawals, and new BBWs and warnings. Most previous studies defined important PSRAs as only market withdrawals and BBWs [7, 8, 11, 12]. However, new ADRs and other safety information obtained after-market launch are generally added to the warnings section of the labeling. Thus, in the present study, we defined important PSRAs as safety-related market withdrawal or the addition of BBWs or other new warnings to the labeling.

Important PSRAs were manually identified from the history of labeling changes in the Drugs@FDA database to determine the number of labeling changes (BBWs and warnings) based on safety information that had not been included on the labels at the time of approval [15, 16]. The background and reasons for labeling changes were investigated

using letters and reviews issued by the FDA at the time of the change, the MedWatch Archives (1996–2008) [17], MedWatch [18], and the Drug Safety Labeling Changes database [19] to identify ADRs related to PSRAs. For prestandardized labels (prior to 2008), both warnings and precautions were investigated using the MedWatch Archives (1996–2008) to determine the reasons for changes.

2.2.4 ADRs Related to Important PSRAs and Drug-specific PSRAs

ADRs related to PSRAs were coded by SOC and PT according to the Medical Dictionary for Regulatory Activities (MedDRA) Terminology (version 20.1) and summarized. To exclude PSRAs due to nonspecific ADRs such as drug allergies and DILI, all PTs were investigated, and relevant ADRs were excluded. For exploratory comparisons between the cohorts, the coded PTs were classified into the following PT groups: drug allergy and DILI, cardiovascular/renal, psychiatric/nervous system, infection/immune system (except allergic events), blood/endocrine/metabolism, and other.

We identified important drug-specific PSRAs, which were due to individual drug-induced ADRs reported through postmarketing surveillance, clinical studies, and spontaneous reporting, and nonspecific important PSRAs, which were due to class effect ADRs caused by other drugs and drug allergy/DILI; this approach allowed us to

categorize drugs based on whether important drug-specific PSRAs occurred or whether only nonspecific PSRAs occurred. Drugs for which both important drug-specific PSRAs and nonspecific PSRAs occurred were included in drugs for which important drug-specific PSRAs occurred. Minor changes and corrections of the label information were excluded from PSRAs. Labeling changes that were not based on safety information such as ADRs (e.g., the addition of warnings about instructions for devices used for medication) were also excluded.

If both BBWs and warnings were added for one PSRA or if two or more warnings were simultaneously added for one PSRA, the changes were counted as one action. A PSRA that included BBWs or warnings caused by both drug-specific and nonspecific ADRs was regarded as drug specific.

2.2.5 Key Baseline Characteristics

The key baseline characteristics we focused on were biologics, ATC category L (antineoplastic and immunomodulatory agents), and orphan designation at approval.

The drugs were classified into two types, NMEs and NTBs, because a study by Giezen et al. suggested an association between NTBs and the occurrence of PSRAs [5].

According to the ATC classification [20], the drugs were classified as category L drugs (antineoplastic and immunomodulatory agents) and other new drugs because the

occurrence of PSRAs was reported to be associated with antitumor drugs [7].

Given that a study by Heemstra et al. [6] demonstrated that the features of orphan drugs differ from those of other drugs in the context of PSRAs, we also categorized drugs depending on whether they were designated as an orphan drug. The Orphan Drug Product designation database [21] was used to determine whether each new drug was designated as an orphan drug for the first approved indication.

These key baseline characteristics were compared between the cohorts, and important drug-specific PSRAs were also compared between NMEs and other new drugs, between antitumor drugs and other new drugs, and between orphan drugs and other new drugs in the same manner described for the primary analysis. This approach allowed us to evaluate the effects of these characteristics on the primary endpoint in an exploratory manner.

2.3 Statistical Analysis

Descriptive statistics were used to determine characteristic differences between the cohorts. The odds ratio of the occurrence of important drug-specific PSRAs, which was the primary endpoint, and the 95% confidence interval (CI) were calculated by univariate logistic regression analysis, with the occurrence of important drug-specific PSRAs as a dependent variable and designation as an FIC drug (the FIC cohort) or another type of new drug (the control cohort) as an explanatory variable to evaluate between-cohort

differences. We also evaluated other endpoints: incidence of important PSRAs due to class effects, incidence of important PSRAs due to drug allergies and DILI, and incidence of all important PSRAs due to ADRs including class effects and drug allergies, in the same manner described for the primary analysis. In the secondary analysis, between-cohort differences in the proportions of drugs (with a breakdown) for which any important PSRAs and important drug-specific PSRAs occurred were evaluated by Chi square tests.

An exploratory analysis of key baseline characteristics (NMEs/other type drugs, antitumor drugs/other category drugs, and orphan drugs/nonorphan drugs) was performed in the same manner described for the primary analysis.

All analyses were performed using JMP software version 13.2 (SAS Institute Inc. California).

2.4 Results

2.4.1 Key Baseline Characteristics

A total of 264 drugs were included in this study; 84 were included in the FIC cohort, and 180 were included in the control cohort. The key baseline characteristics are presented in Table 2-1. Among the drugs included in this study, 43 drugs were categorized as NTBs (25 [29.8%] in the FIC cohort and 18 [10.0%] in the control cohort), 65 drugs

were categorized as ATC category L (22 [26.2%] in the FIC cohort and 43 [23.9%] in the control cohort), and 83 drugs were classified as designated orphan drugs (34 [40.5%] in the FIC cohort and 49 [27.2%] in the control cohort), indicating that there were higher proportions of NTBs and orphan drugs in the FIC cohort than in the control cohort.

Table 2-1 Key Baseline Characteristics

	All	%	FIC	%	Control	%
Drug type						
New molecular entities (NMEs)	221	83.7	59	70.2	162	90.0
New therapeutic biologics (NTBs)	43	16.3	25	29.8	18	10.0
ATC Classification						
Category L: antineoplastic and immunomodulating agents	65	24.6	22	26.2	43	23.9
Other class	199	75.4	62	73.8	137	76.1
Orphan designation						
Orphan	83	31.4	34	40.5	49	27.2
Nonorphan	181	68.6	50	59.5	131	72.8

2.4.2 Important Drug-specific PSRAs

PSRAs occurred for 137 drugs (43 in the FIC cohort and 94 in the control cohort). Based on the background leading to PSRAs and the relevant ADRs for 137 drugs in which PSRAs occurred, only nonspecific PSRAs due to class effects or drug allergies occurred for 53 drugs (7 in the FIC cohort and 46 in the control cohort); these 53 drugs were excluded. For the remaining 84 drugs (36 in the FIC cohort and 48 in the control cohort), important drug-specific PSRAs occurred at least once (Figure 2-1).

The 84 drugs for which important drug-specific PSRAs occurred (43 in the FIC cohort

and 84 in the control cohort) included 2 drugs that were withdrawn from the market (1 in the FIC cohort and 1 in the control cohort), 16 drugs with issued or added BBWs (12 in the FIC cohort and 9 in the control cohort), and 83 drugs with added warnings (35 in the FIC cohort and 48 in the control cohort) (Table 2-2).

In the FIC cohort, any PSRA occurred for 43 of 84 drugs (50.6%), and important drug-specific PSRAs occurred for 36 of 43 drugs (83.7%). In the control cohort, any PSRA occurred for 94 of 180 drugs (52.6%), and important drug-specific PSRAs occurred for 48 of 94 drugs (52.2%).

Table 2-2 Number of Important PSRAs

PSRAs/Label changes		All						Drug-specific					
		ALL	%	FIC	%	Control	%	ALL	%	FIC	%	Control	%
PSRAs [a)]	No	128	48.3	41	48.8	86	47.8	180	68.2	48	57.1	132	73.3
	Yes [b)]	137	51.5	43	50.6	94	52.2	84	31.8	36	42.9	48	26.7
Withdrawals	No	262	99.2	83	98.8	179	99.4	262	99.2	83	98.8	179	99.4
	Yes	2	0.8	1	1.2	1	0.6	2	0.8	1	1.2	1	0.6
BBWs	No	229	86.7	69	82.1	160	88.9	251	95.1	72	84.5	171	95
	Yes	35	13.3	15	17.9	20	11.1	13	4.9	12	14.3	9	5
Warnings	No	128	48.5	42	50.0	86	47.8	181	68.6	49	58.3	132	73.3
	Yes	136	51.5	42	50.0	94	52.2	83	31.4	35	41.7	48	26.7

a) PSRAs: postmarketing safety-related regulatory actions

b) Duplicates were eliminated

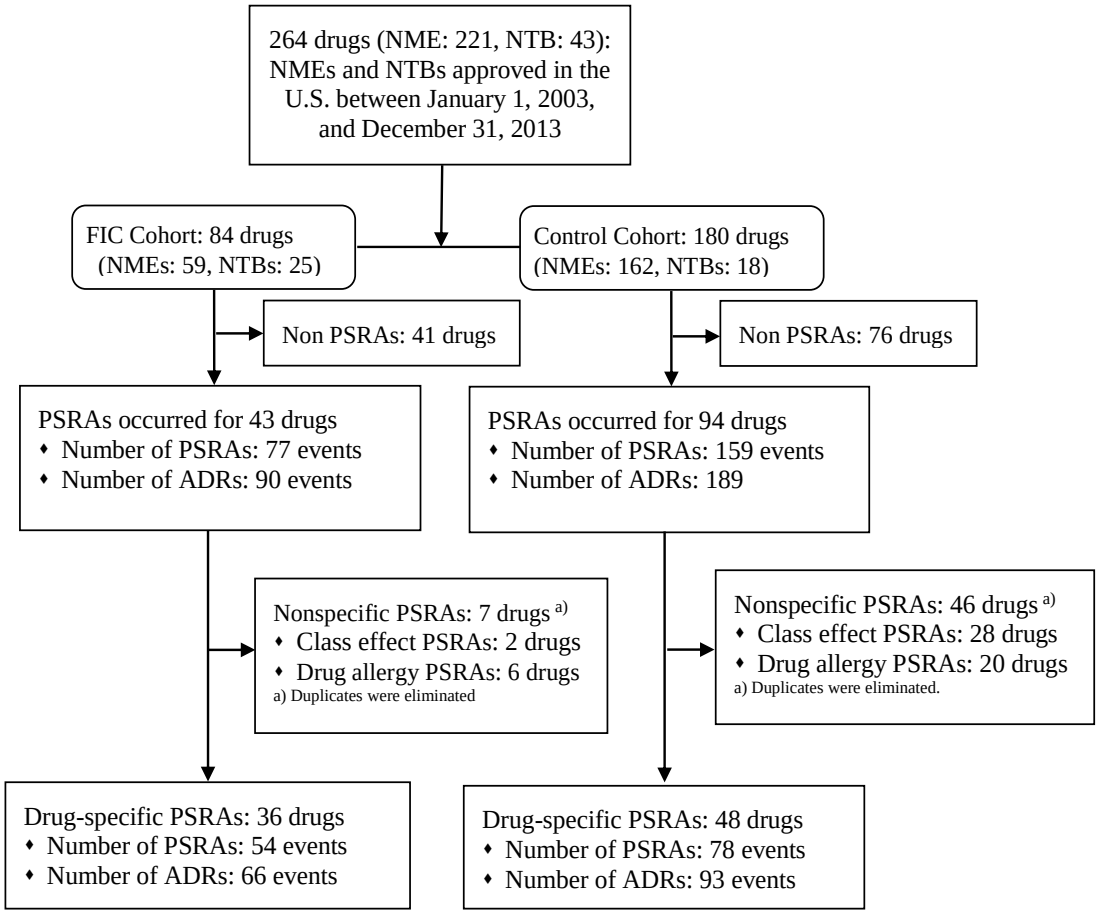


Figure 2-1 Definition of Important Drug-specific PSRAs

2.4.3 Primary Endpoint and Other Endpoints

The odds ratio of the occurrence of important drug-specific PSRAs, which was the primary endpoint, in the FIC cohort was 2.06 (95%CI: 1.20–3.55, p=0.0091) compared with the control cohort, indicating that important drug-specific PSRAs were approximately two-fold more likely to occur in the FIC cohort than in the control cohort.

The odds ratio of the occurrence of all important PSRAs, including nonspecific

important PSRAs, in the FIC cohort was 0.96 (95%CI: 0.57–1.61, p=0.8758) compared with the control cohort, with no difference in odds between the cohorts. The odds ratio of the occurrence of important PSRAs due to class effect ADRs in the FIC cohort was 0.33 (95%CI: 0.13–0.82, p=0.0171), with significantly lower odds in the FIC cohort than in the control cohort. The odds ratio of the occurrence of important PSRAs due to drug allergy ADRs in the FIC cohort was 0.81 (95%CI: 0.64–1.40, p=0.5691), with no difference in odds between the cohorts (Table 2-3).

Table 2-3 Relationship between the Occurrence of Important Drug-specific PSRAs and Cohort by an Unvitiated Logistic Regression Model

PSRAs [a)]	Cohort	Odds	95%CI	p
Drug-specific PSRAs	Control	1.00		
	FIC	2.06	1.20-3.55	0.0091
Nonspecific PSRAs				
Class effect PSRAs	Control	1.00		
	FIC	0.33	0.13-0.82	0.0171
Drug allergy PSRAs	Control	1.00		
	FIC	0.81	0.64-1.40	0.5691
All PSRAs	Control	1.00		
	FIC	0.96	0.57-1.61	0.8758

a) PSRAs: postmarketing safety-related regulatory actions

Table 2-4 shows the results of the exploratory analysis of the effects of key baseline characteristics (drug type, ATC classification, and orphan designation) on the occurrence of any important PSRAs and important drug-specific PSRAs using univariate logistic regression analysis. Although the proportions of NTBs and drugs designated as orphan drugs at the time of approval were higher in the FIC cohort than in the control cohort,

there was no difference in the odds ratio of any important PSRAs or important drug-specific PSRAs for NTBs or orphan drugs, suggesting that NTB or orphan status was not a factor in PSRA occurrence. In contrast, ATC category L drugs had higher odds of occurrence for both important PSRAs and drug-specific PSRAs, with the odds of important drug-specific PSRAs for ATC category L drugs being more than two-fold higher than that for other category drugs (odds ratio: 2.24, 95%CI: 1.54–4.91, p=0.0007).

Table 2-4 Relationship between the Occurrence of Important Drug-specific PSRAs and Key Baseline Characteristics by an Unvitiated Logistic Regression Model

Characteristics		All PSRAs [a)]			Drug-specific PSRAs [a)]		
	Cohort	Odds	95%CI	p	Odds	95%CI	p
Drug type	NMEs	1.00			1.00		
	NTBs	0.96	0.50-1.86	0.9165	1.33	0.67-2.63	0.4178
ATC classification	Other	1.00			1.00		
	ATC L [b)]	1.83	1.03-3.25	0.0390	2.24	1.54-4.91	0.0007
Orphan designation	Other	1.00			1.00		
	Orphan	1.06	0.63-1.80	0.8055	1.56	0.68-2.68	0.1128

a) PSRAs: postmarketing safety-related regulatory actions

b) ATC L: antineoplastic and immunomodulating agents

2.4.4 ADRs Related to Important PSRAs

A total of 279 ADRs related to any important PSRAs occurred for 137 drugs. The ADRs were coded according to MedDRA and summarized by SOC and PT in each cohort

ADRs related to drug allergy and DILI were identified to extract important drug-specific PSRAs; 54 ADRs (18 in the FIC cohort and 36 in the control cohort) were related to drug allergy and DILI, and 26 drugs were associated with the occurrence of only

PSRAs due to ADRs related to drug allergy and DILI (6 in the FIC cohort and 20 in the control cohort) (Table 2-3, Figure 2-1). The ADRs (PT) related to drug allergy and DILI that were associated with these 26 drugs were drug reaction with eosinophilia and systemic symptoms, hypersensitivity, rash, skin reaction, Stevens-Johnson syndrome, DILI, hepatotoxicity, liver disorder, and liver injury.

Various PT and SOC designations of ADRs were related to any important PSRAs and important drug-specific PSRAs, and no specific trend was observed. We then grouped PTs for an exploratory evaluation of between-cohort differences (Table 2-5). No difference of 10% or more in the incidence of ADRs was observed between PT groups, resulting in a failure to detect any difference in the type and incidence of ADRs related to any important PSRAs and important drug-specific PSRAs between the cohorts (Table 2-5).

An exploratory comparison of the incidences of ADRs related to important drug-specific PSRAs in each PT group based on the respective key baseline characteristics (Table 2-5) showed that the incidence of ADRs in the immune system/infection PT group was more than 10% higher for NTBs than for NMEs. The incidences of ADRs in the cardiovascular/renal/respirator PT group was more than 10% higher for ATC category L drugs than for other category drugs. No orphan drug had a PT group with a difference of

at least 10% in the incidence of ADRs; thus, there were no marked difference between orphan drugs and nonorphan drugs in any PT group. The results of PT grouping of ADRs related to important drug-specific PSRAs suggested that NTBs and ATC category L drugs had distinct characteristics. We then examined SOCs and PTs of ADRs related to important drug-specific PSRAs for NTBs and ATC category L drugs.

Infections and infestations (SOC) occurred for 16.3% of NTBs (6 events for 43 drugs), and 3 of these events were progressive multifocal leukoencephalopathy (PT), an ADR that is characteristically observed with antibody drugs, with an incidence of 7.0% (3 events for 43 drugs). The remaining 4 events were all infections due to the effects of antibody drugs on the immune system and ADRs specific to antibody drugs.

For ATC category L drugs, 9 vascular disorders (SOC) and 7 cardiac disorders (SOC) occurred, and cardiovascular ADRs were more likely to occur with these drugs due to the use of kinase inhibitors.

Table 2-5 Proportion of ADRs (Preferred Term Group) Related to Important PSRAs

PSRAs and Important Drug-specific PSRAs (FIC cohort and control cohort)

Preferred term group	PSRAs [a)]						Drug-specific PSRAs [a)]					
	ALL	%	FIC	%	Control	%	ALL	%	FIC	%	Control	%
Drug Allergy	54	19.3	18	21.4	36	20.0	-		-		-	
Cardiovascular, Renal, Respiratory	63	22.5	23	27.4	40	22.2	59	37.1	23	27.4	36	20.0
Immune system, Infection	17	6.1	8	9.5	9	5.0	13	8.2	7	8.3	6	3.3
Psychiatric, Nervous system	45	16.1	9	10.7	36	20.0	18	11.3	7	8.3	11	6.1
Blood, Endocrine, Metabolism	23	8.2	9	10.7	14	7.8	11	6.9	6	7.1	5	2.8
Other	76	27.1	24	28.6	52	28.9	58	36.5	23	27.4	35	19.4
Total	278		91		187		159		66		93	

a) Postmarketing safety-related regulatory actions: PSRAs

Important Drug-specific PSRAs (NTBs and NMEs, ATC L and Other, Orphan and Other)

Group	ALL (n=264)	%	NTBs (n=43)	%	NMEs (N=211)	%	ATC L [b)] (n=65)	%	Other (n =199)	%	Orphan (n=83)	%	Other (n=181)	%
Cardiovascular, Renal, Respiratory	59	22.3	8	18.6	59	22.3	22.0	33.8	31	15.6	20	24.1	39	21.5
Immune system, Infection	13	4.9	8	18.6	13	4.9	8.0	12.3	5	2.5	6	7.2	7	3.9
Psychiatric, Nervous	18	6.8	2	4.7	18	6.8	5.0	7.7	13	6.5	4	4.8	14	7.7
Blood, Endocrine, Metabolism	11	4.2	1	2.3	11	4.2	8.0	12.3	3	1.5	6	7.2	5	2.8
Other	58	22.0	13	30.2	58	22.0	28.0	43.1	36	18.1	26	31.3	32	17.7
Total	159		32		159		71.0		31		62		97	

a) Postmarketing safety-related regulatory actions: PSRAs

b) ATC L: antineoplastic and immunomodulating agents

2.5 Discussion

Of the 264 drugs included in this study, PSRAs occurred for 137 drugs, and important drug-specific PSRAs occurred for 84 drugs. The incidence of important drug-specific PSRAs in the FIC cohort was approximately twice as high as that in the control cohort, demonstrating that important drug-specific PSRAs were more likely to occur with FIC drugs. The results support the hypothesis that FIC drugs with a novel mechanism of action might be associated with a higher incidence of PSRAs than other new drugs.

Our study took different approaches toward the factor analyses of PSRAs; in preceding studies, all the PSRAs were included as the outcome variable [10, 11, 12]. The present study focused on PSRAs for FIC drugs with novel mechanisms of action and individual drug-induced ADRs related to PSRAs, and separated PSRAs due to class effect ADRs for the same-class drugs. We also considered it meaningful to rule out PSRAs due to nonspecific ADRs such as drug allergy and DILI. Since these effects are dose independent, it is difficult to evaluate the relationship between such ADRs and the mode of action. Therefore, we defined important drug-specific PSRAs due to ADRs related to class effects, drug allergy, and DILI as nonspecific PSRAs and ruled these PSRAs out when investigating the primary endpoint. Based on our approach in this study, it was indicated that the incidence of important drug-specific PSRAs for FIC drugs was significantly

higher than that for other new drugs, suggesting a strong relationship between FIC drugs and the occurrence of important drug-specific PSRAs. This finding has not been reported in previous studies.

Given that the incidence of PSRAs due to ADRs related to drug allergy and DILI was higher in both the FIC cohort and the control cohort, drug allergy and DILI were considered to be important postmarketing safety issues. However, these ADRs are generally rare and are not identifiable in preapproval clinical trials. To reduce the postmarketing safety issues based on drug allergy and DILI, it seems to be more important to establish a nonclinical model that can predict the risks of these events in advance.

The exploratory analysis of the effects of the key baseline characteristics on the occurrence of any important PSRAs and drug-specific PSRAs showed that drug type (NMEs or NTBs) and orphan designation (orphan drugs or nonorphan drugs) did not affect the incidence of any important PSRAs or important drug-specific PSRAs in this study. In contrast, ATC classification (ATC category L drugs or other category drugs, which had nearly equal proportions in the two cohorts) was suggested to be related to important drug-specific PSRAs independently of FIC drugs because the incidence of any important PSRAs and drug-specific PSRAs were significantly higher in ATC category L drugs. Our finding concurs with the results of Lu D. et al. [9], who reported that PSRAs

occurred with a high incidence in antitumor drugs. We believe that ATC category L drugs is related to the occurrence of important drug-specific PSRAs independently of FIC drugs.

In the present study, we comprehensively investigated ADRs related to PSRAs and coded the ADRs by SOCs and PTs according to MedDRA to identify ADRs related to drug allergy and DILI, as well as ADRs characteristic of FIC drugs. However, many different kinds of ADRs related to PSRAs were identified as postmarketing safety issues, and no specific trend could be identified, even when the SOCs, PTs, and PT groups were compared between the FIC cohort and the control cohort. In contrast, an exploratory comparison of PT groups according to the respective key baseline characteristics suggested that NTBs produced more ADRs related to the immune system and infection than NMEs and that ATC category L drugs produced more cardiovascular ADRs than other category drugs. These findings are similar to those of Giezen TJ. et al. who reported that biologics produced more ADRs related to PSRAs associated with the immune system and infection [5]. Furthermore, these PTs were infections caused by the effects of antibody drugs on the immune system, such as infection, progressive multifocal leukoencephalopathy, and reactivation of hepatitis B virus, which are characteristically observed with antibody drugs. This result is comparable to that of Lu D. et al., who reported a relationship between antitumor drugs and the occurrence of PSRAs [9]. By

SOC, ATC category L drugs were associated with more cardiovascular ADRs than other category drugs, including 9 vascular disorders (SOC) and 7 cardiac disorders (SOC), all of which resulted from the use of kinase inhibitors. Tyrosine kinase inhibitors are designed to enhance selectivity toward target kinases, but they also act on both tyrosine kinases expressed in the cardiovascular system and platelets and therefore cause problems from which cardiovascular ADRs develop [23]. These reports suggested that the characteristics of ADRs were related to therapeutic area or drug type. Our results support these previous findings. On the other hand, the analysis of ADRs related to important drug-specific PSRAs was not useful for characterizing FIC drugs.

Taken together, the present study suggested a strong relationship between FIC drugs and the occurrence of important drug-specific PSRAs. In addition, ATC category L drugs appeared to be related to the occurrence of important drug-specific PSRAs independently of FIC drugs.

Because of the limited factors included in this study, confounding factors included in the primary analysis could not be adequately considered. Most labeling changes were identified manually, which precluded program-based data verification. The information on warnings and precautions provided in prestandardized labels varied widely among drugs, which did not allow us to identify the reasons for revision of the standardized labels

for some drugs. Because we excluded ADRs related to drug allergy and DILI, which are important postmarketing safety issues, ADRs might have been evaluated from a perspective other than pharmacovigilance. Although ADRs were coded according to MedDRA, determining a PT was difficult for some ADRs; for example, increasing mortality was coded to death.

3 Part II Analysis of Factors Related to the Occurrence of Important Drug-specific Postmarketing Safety-related Regulatory Actions: A Cohort Study Focused on First-in-class Drugs

3.1 Background and Aims

In Part I study of this thesis, which is an exploratory part, we compared the incidence of important drug-specific PSRAs for FIC drugs with those for other new drugs which have same-class drugs at approval to explore relationship between FIC drugs and the occurrence of important drug-specific PSRAs. The odds ratio of occurrence of important drug-specific PSRAs in FIC drugs was 2.06 (95%CI: 1.20–3.55, p=0.0091) compared with other new drugs, indicating that a strong relationship existed between FIC drugs and the occurrence of important drug-specific PSRAs. Based on these results, we investigated comprehensively the factors related to the occurrence of PSRAs with a focus on FIC drugs to clarify postmarketing risk of newly approved drugs in this Part II.

The aim of Part II study in this thesis was to analyze the factors related to the occurrence of important drug-specific PSRAs for NMEs and NTBs approved in the U.S. The definition of important drug-specific PSRAs in this study was any PSRAs due to drug-induced ADRs excluding class effects, drug allergy and DILI in the same manner of Part I. Factor analysis was performed focusing on important drug-specific PSRAs due to ADRs as the outcome variable.

3.2 Methods

3.2.1 Design and Setting

This was a cohort study covering all NMEs and NTBs approved in the U.S. between January 1, 2003, and December 31, 2013, excluding agents for non-treatment purposes such as diagnostic agents, sunscreens, drug adjuvants, non-therapeutic vaccines, and radiation agents. NMEs and NTBs approved during this period were extracted manually from the FDA's website Drugs@FDA: FDA Approved Drug Products [15].

As the outcome variable, important drug-specific PSRAs were identified for each drug based on publicly available postmarketing safety information [16]. The definition of important drug-specific PSRAs in this study was any PSRA due to drug-induced ADRs, excluding class effects, drug allergy and DILI. The most important PSRA is market withdrawal. When the benefits of a new drug can no longer be balanced against the risks in view of newly obtained safety information, the pharmaceutical company or the FDA will make the decision to withdraw the drug from the market. We identified only safety-related market withdrawals, excluding withdrawals due to economic or patent-related reasons. A BBW, which highlights important safety risks with a black border on the first page of drug labeling, is added by the FDA when a life-threatening postmarketing safety risk is detected. In addition, new ADRs and other safety information obtained after-

market launch are added to the warnings section of the labeling. Thus, in the present study, we defined important PSRAs as safety-related market withdrawal or the addition of BBWs or other new warnings to the labeling.

We manually identified newly added BBWs and warnings based on the history of labeling changes linked to the Drugs@FDA database [16, 17] to determine the number of safety-related changes (BBWs and warnings) for which there was no description on the label at the time of approval and the reasons for the changes. For prestandardized labels (prior to 2008), we identified changes to the warnings and precautions sections and reviewed the MedWatch Archives (1996-2007) [18]. The reasons for changes were identified using letters and reviews issued by the FDA at the time of the change, the MedWatch Archives (1996-2007), and the Drug Safety Labeling Changes database [19]. Of the identified labeling changes, PSRAs based on drug-related ADRs were included in the analysis, and changes due to class effects, drug allergy such as hypersensitivity and drug-induced liver injury were excluded. Slight changes and modifications in descriptions were not included. Labeling changes not based on ADR-related safety information (e.g., the addition of warnings concerning the usage of medical devices for drug administration) were also excluded. We also prepared monthly data for important drug-specific PSRAs and evaluated the relationship between the time to occurrence of the first drug-specific

PSRA and the factors involved.

Two separate databases were developed by two authors and compared to automatically verify the data. If “unmatched” data were identified, we manually confirmed the data source. Cases of differences based on an author’s selections were resolved by consensus among all authors.

3.2.2 Key Baseline Characteristics

Baseline characteristics were the characteristics of each drug at the time of approval. The evaluated baseline characteristics were FIC classification, ATC classification, drug type, review type, approval type, orphan designation, other designations (fast track or breakthrough), BBWs at approval, review period and before and after the FDA Amendments Act (FDAAA). FIC was defined as a drug with a novel mechanism of action at approval based on the definition reported by Eder et al. [10]. We classified the drugs into two categories: FIC drug and other.

We classified the drugs according to their ATC classification (level 1) [20], since preceding studies suggested that the occurrence of PSRAs was associated with therapeutic class [12]. The drugs were classified into two types, NMEs and NTBs, since a report by Giezen et al. suggested that NTBs were related to the occurrence of PSRAs [5, 23].

A study by Schick et al. demonstrated that priority review designation is associated with the occurrence of PSRAs [11]. We identified drugs that received a priority review from the FDA website to categorize drugs as either priority review or standard review, since promising new drugs often receive priority review, in which the FDA complete its initial regulatory review within 6 months instead of the standard 10 months [24]. For priority review designation, pharmaceutical companies supply evidence (e.g., increased effectiveness in the treatment, prevention or diagnosis of a condition or the elimination or substantial reduction of a treatment-limiting drug reaction) to the FDA. A study by Downing et al. indicated that AA is associated with the occurrence of PSRAs [12]. NMEs or NTBs that address a serious unmet medical need may undergo AA and will be approved based on clinical trials using surrogate markers of disease as end points in a confirmatory study. Surrogate endpoints typically require less time to acquire [24]. We therefore use the FDA website to classify the drugs as those with or without an AA designation.

A study by Heemstra et al. suggested that orphan drugs have different characteristics than other drugs in terms of PSRAs [6]. Therefore, whether the drugs were designated orphan drugs was assessed as a factor. The presence or absence of an orphan designation was identified by whether the drug received designation for its first approved indications

using the Orphan Drug Product designation database [25]. The drugs were divided into those designated fast track and others to evaluate the relationship between this designation and the occurrence of PSRAs. The breakthrough therapy designation, which was not implemented until 2014, was not included in this study.

Schick et al. reported that the incidence of PSRAs is higher among drugs with a BBW at approval [11]. We therefore searched information on labeling changes in the Drugs@FDA database to check for BBWs at approval.

Preceding studies indicated that the review period is associated with the occurrence of PSRAs. We therefore manually extracted key dates in the regulatory review process from FDA approval letters linked to the Drugs@FDA database. Following calculation of the review period from the date of submission to the date of either FDA approval or a complete response letter, the drugs were classified as having a review period of within 1 year (365 days) or longer than 1 year. The review period was defined as the total of all review cycle periods necessary for approval.

The year of approval was determined from the Drugs@FDA database. The FDAAA of 2007 extended the agency's regulatory authority over drug products that have been shown to place patients at risk. The FDAAA contains important new authorities allowing the FDA to require postmarketing studies and clinical trials, safety labeling changes, and Risk

Evaluation and Mitigation Strategies (REMS). In addition, the FDA launched the Sentinel Initiative, a long-term FDA effort to create a national electronic system for monitoring product safety 26]. As the safety monitoring system may be affected by PSRAs, we determined the year of approval from the Drugs@FDA database and evaluated the influence of the FDAAA by classifying drugs as approved either prior to 2008 or in 2008 or later.

3.3 Statistical Analysis

Descriptive statistics were used to evaluate the baseline characteristics of the NMEs and NTBs. The relationships between baseline characteristics and the occurrence of important drug-specific PSRAs were investigated using a multivariate binomial logistic regression model as the final model. We used forward and backward stepwise regression to select the explanatory variables for the final model. Only those baseline characteristics that contributed to the model at $p = 0.20$ were retained in the model. The relationships of the baseline characteristics selected as explanatory variables in the final model with the occurrence of important drug-specific PSRAs, the outcome variable, are expressed as the odds ratio (OR) and 95% confidence interval (CI).

We performed an additional analysis using a multivariable Cox proportional hazards model to clarify the factors that showed a relationship with the time to occurrence of the

first important drug-specific PSRAs as an explanatory variable. We used the explanatory variables that had been selected by stepwise regression as stated above in this analysis. Only those baseline characteristics that contributed to the model at p = 0.20 were retained in the model. Relative risk (RR) and 95% CI are obtained using this model. We also used Kaplan-Meier estimates to plot the occurrence of the first important drug-specific PSRA as a function of time and 2-sided log-rank tests to assess the differences in events over time according to the prespecified classification of each factor.

All analyses were conducted using SAS JMP software version 11.2 (SAS Institute, Inc.).

3.4 Results

3.4.1 Important Drug-specific PSRAs

Of the 264 drugs included in the study, 138 were found to have a total of 260 safety-related PSRAs. Two of the PSRAs were market withdrawal, 38 were BBWs, and 220 were the addition of new warnings (Table 3-1).

Of the 260 PSRAs found, a total of 165 important drug-specific PSRAs were identified for 83 drugs. Two of the important drug-specific PSRAs were market withdrawal, 25 were BBWs, and 138 were the addition of new warnings (Table 3-1).

Table 3-1 Number of Important Drug-specific PSRAs

	PSRAs [a]		Drug-specific PSRAs [a]	
Type	Number of Actions	Number of Drugs	Number of Actions	Number of Drugs
Market Withdrawal	2	2	2	2
Black Box Warning	38	36	25	25
Warning	220	136	138	77
Total	260	138 [b]	165	83 [b]

a) Postmarketing safety-related regulatory actions: PSRAs

b) Duplicates were eliminated.

3.4.2 Baseline Characteristics

The baseline characteristics of the 264 drugs included in the study are shown in Table 3-2 and Figure 3-1. We identified 84 FIC drugs out of the 264 drugs; moreover, 221 of the included drugs were NMEs, 43 were NTBs, 143 were standard reviews, 121 were priority reviews, 234 were standard approval, 30 were AA, and 83 had an orphan designation. Regarding other designations, 95 drugs were designated fast track. There were 83 drugs with BBWs at the approval stage, 162 drugs were approved within 1 year from the time of application, and 152 drugs were approved prior to 2008.

The ATC classifications of the drugs are shown in Figure 3-1. ATC category L (antineoplastic and immunomodulating agents) was the most common, accounting for approximately 25% (65/264) of all included drugs. Common categories other than

category L were category J (anti-infectives for systemic use, 42 drugs), A (alimentary tract and metabolism, 40 drugs), and N (nervous system, 37 drugs). We introduced binomial variables corresponding to category L and other ATC classification into a multivariate model, since a study by Giezen et al. [5, 23] suggested a relationship between antitumor agents and the occurrence of PSRAs for biologics, and ATC category L accounted for 25% of the drugs evaluated in our study.

Table 3-2 Baseline Characteristics 1

Characteristic	Classification	Number
First-in-class	Yes	84
	No	180
Drug Type	NME	221
	NTB	43
Review Type	Priority	121
	Standard	143
Approval Type	Accelerated	30
	Standard	234
Orphan Designation	Orphan	83
	Other	181
Other Designation	Fast truck	95
	Other	169
Black Box Warning	Yes	83
	No	181
Review Period	≤ 1 year	162
	> 1 year	102
Year of Approval	Prior to 2008	152
	2008 or later	112

NME: new molecular entity, NTB: new therapeutic biologic

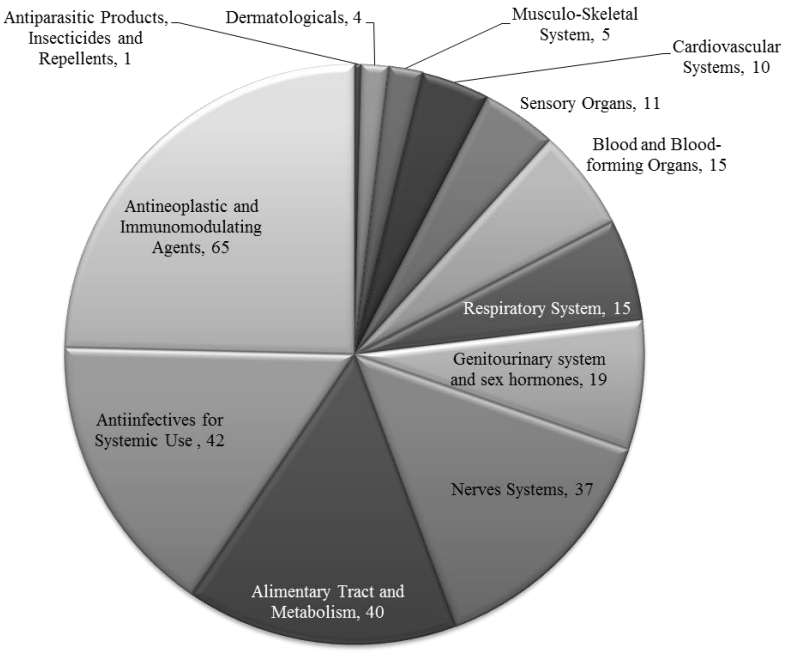


Figure 3-1 Baseline Characteristics 2: ATC Classification

3.4.3 Proportion of Important Drug-specific PSRAs

The proportion of important drug-specific PSRAs (%; the number of drugs to which safety regulatory actions were applied divided by the number of drugs evaluated) was calculated for each factor, and the results are shown in Table 3-3. Factors for which there was a difference of 10% or more between classifications were FIC classification, ATC classification, review type, approval type, other designations, and review period. Among them, differences of more than 20% were found between category L and other in ATC classification (49.2% vs. 26.7%) and between AA and standard approval in approval type (24.9% vs. 53.3%).

Table 3-3 Proportion of Important PSRAs

Factor	Classification	Regulatory Actions (%) (138 drugs)	Drug-specific Regulatory Actions (%) (83 drugs)
First-in-class	Yes (n = 84)	51.2	41.7
	No (n = 180)	52.8	26.7
Product Type	NME (n = 220)	52.5	30.3
	NTB (n = 44)	51.6	37.2
ATC Classification	Category L* (n = 65)	63.1	49.2
	Other (n = 199)	48.7	25.6
Review Type	Priority (n = 121)	56.2	38.8
	Standard (n = 143)	49.0	25.1
Approval Type	Accelerated (n = 30)	63.3	53.3
	Standard (n = 234)	51.9	28.6
Orphan Designation	Orphan (n = 83)	53.0	37.4
	Other (n = 181)	51.9	28.7
Other Designation	Fast truck (n = 95)	61.1	43.2
	Other (n = 169)	47.3	24.9
Black Box Warning	Yes (n = 83)	51.8	26.5
	No (n = 181)	52.5	33.7
Review Period	≤ 1 year (n = 162)	58.5	37.7
	> 1 year (n = 102)	42.1	21.6
Year of Approval	Prior to 2008 (n = 153)	49.3	34.8
	2008 or later (n = 111)	58.5	29.0

*Antineoplastic and Immunomodulating agents

NME: new molecular entity, NTB: new therapeutic biologic

3.4.4 Relationship between the Occurrence of Important PSRAs and Explanatory Variables

Factors used in the final binomial multivariate logistic regression model were selected by a stepwise method considering confounding factors. As a result, ATC classification (category L/other, p = 0.0005), FIC classification (FIC drug/other, p = 0.0170), review period (longer than 1 year/within 1 year, p = 0.1137), and AA (accelerated/standard, p = 0.1971) were selected.

The relationship between the occurrence of important drug-specific PSRAs and the

selected factors was evaluated using the final logistic regression model, and the results are shown in Table 3-4. ATC classification and FIC classification were statistically significant factors, with ORs of 2.15 (95% CI: 1.12-4.11; p = 0.0203) and 1.87 (95% CI: 1.06-3.31; p = 0.0309), respectively, for FIC drugs. These two factors were considered to affect the occurrence of important drug-specific PSRAs.

Table 3-4 Relationship between Occurrence of Important Drug-Specific PSRAs and Explanatory Variables by Logistic Regression Model

Factor	Classification	Odds Ratio	95% CI	p Value
ATC Classification	Other	1		
	Category L*	2.15	1.12 - 4.11	0.0203
First-in-class	No	1		
	Yes	1.87	1.06 - 3.31	0.0309
Review Period	> 1 year	1		
	≤ 1 year	1.56	0.84 - 2.93	0.1548
Accelerated Approval	Normal	1		
	Accelerated	1.73	0.75 - 4.02	0.1971

*Antineoplastic and Immunomodulating agents

3.4.5 Relationship between Time to Occurrence of the First Important Drug-specific PSRAs and Explanatory Variables

The relationship between time to occurrence of the first important drug-specific PSRA and the explanatory variables was evaluated using a Cox proportional hazards model, and the results are shown in Table 3-5. ATC classification, FIC classification, and review period were retained in the model.

ATC classification, FIC classification, and review period were all statistically

significant. The RR was 1.87 (95% CI: 1.15-2.29; p = 0.01070) for category L, 1.56 (95% CI: 1.03-2.48; p = 0.0355) for FIC drug, and 1.67 (95% CI: 1.00-2.85; p = 0.0485) for review period within 1 year. These results demonstrated that these factors were associated with the time to occurrence of the first drug-specific PSRA.

Table 3-5 Relationship between the Time to Occurrence of the First Important Drug-Specific PSRAs and Explanatory Variables by Cox Proportional Hazards Model

Factor	Classification	Relative Risk	95% CI	P Value
ATC Classification	Other	1		
	Category L*	1.87	1.15 - 2.98	0.0107
First-in-class	No	1		
	Yes	1.60	1.03 - 2.48	0.0355
Review Period	> 1 year	1		
	≤ 1 year	1.67	1.00 -2.85	0.0485

*Antineoplastic and Immunomodulating agents

3.4.6 Kaplan-Meier Estimate of Time to Occurrence of First Important Drug-specific PSRAs

The proportion of drugs for which a first important PSRA occurred were estimated by the Kaplan-Meier method based on ATC classification, FIC classification, and review period. Differences in the proportion between classifications were then assessed by the log-rank test.

Kaplan-Meier Plots are shown in Figure 2. The log-rank test showed that the differences in the proportion between classifications were statistically significant for ATC classification (p < 0.0001), review period (p < 0.0023), and FIC classification (p = 0.0141).

The time to occurrence of the first important drug-specific PSRA was shorter for drugs in category L than for those with another ATC classification, for drugs with a review period within 1 year than for those with a review period longer than 1 year, and for FIC drugs than for others.

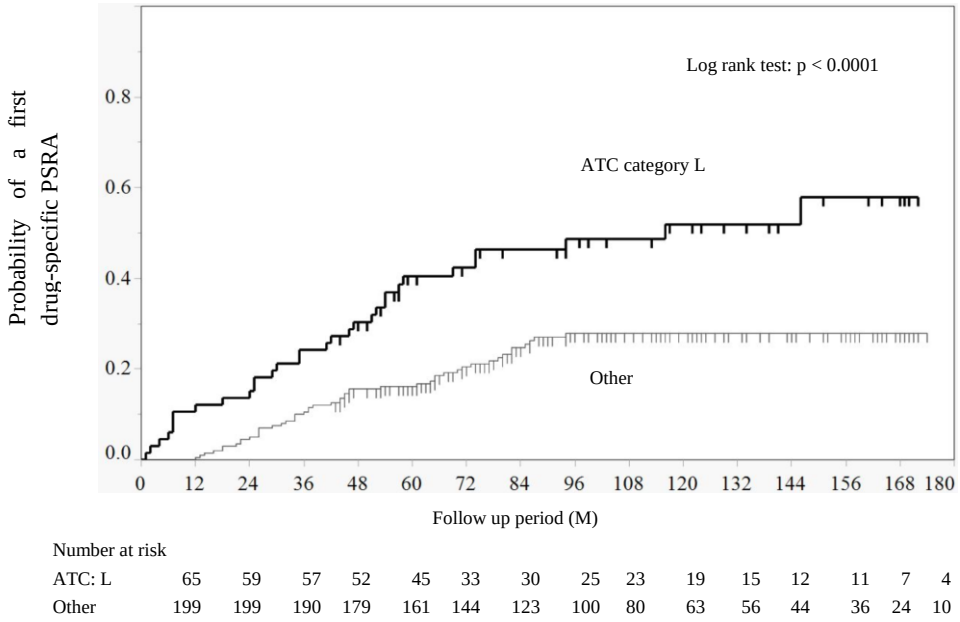
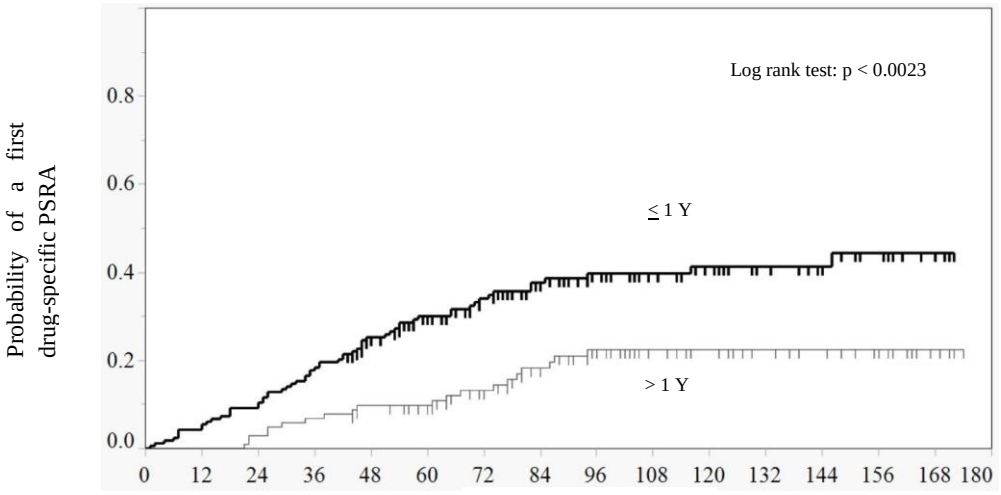


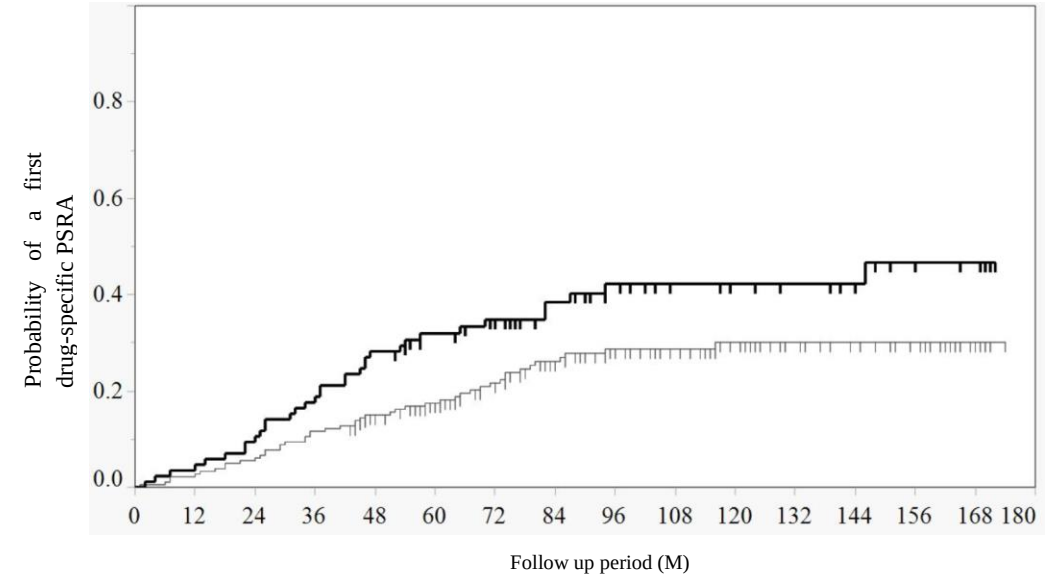
Figure 3-2 Kaplan-Meier Plot of First Important PSRAs by ATC Classification



Number at risk

≤ 1 Y	162	156	148	134	117	93	82	63	53	43	36	27	20	15	7
> 1 Y	102	102	99	96	92	84	72	61	50	40	35	30	26	16	9

Figure 3-3 Kaplan-Meier Plot of Important Drug-specific PSRAs for Review Period of within 1 Year Versus Longer than 1 Year



Number at risk

FIC	84	82	77	70	62	52	45	38	30	24	22	19	15	9	8
Other	180	176	170	161	144	127	109	90	74	59	48	39	32	22	7

Figure 3-4 Kaplan-Meier Plot of Important Drug-specific PSRAs for Antineoplastic and Immunomodulating Agents Versus Other Drugs by FIC Classification

3.5 Discussion

ATC category L (antineoplastic and immunomodulating agents) and FIC drugs were identified as significant factors related to the occurrence of important drug-specific PSRAs in the U.S. In addition, the time to occurrence of the first drug-specific PSRA was shorter for drugs in ATC category L, review period under 1 year and FIC drugs than for others. These results support our hypothesis that FIC drugs are related to PSRAs.

In the present study, ATC category L was identified as a significant factor. With the continuing evolution of oncology drug development, a critical emerging issue is how to determine the dose for maximal efficacy, minimal toxicity, and optimal clinical application. A review of recent publications on oncology drug development suggests the importance of optimizing dose [27, 28, 29]. Serious safety issues were suggested to be more common with biological agents than with small molecules. Regarding oncology agents, especially biologics such as drug antibodies, the analysis of important PSRAs for biologics by Giezen et al. showed that the frequency of PSRAs varied by therapeutic class and route of administration, with a higher frequency for immunomodulatory biologics and a significantly higher hazard ratio for biologics in the FIC drug classification [23]. Our findings support these previous results. In order to prevent or minimize the occurrence of important PSRAs for oncology drugs, it is necessary to optimize the dose

setting in the early clinical phase [28, 29, 30]. Simultaneous analysis methods, such as exposure-safety analysis, are helpful for optimizing the dose of oncology agents. The tolerability risk associated with variations in exposure can be assessed [9]. These new approaches for optimizing dose should be considered in the early clinical phase. In addition, we believe that it is important to carefully monitor safety data during the clinical development of oncology drugs in consideration of the PSRAs taken for approved oncology drugs.

In our study, orphan designation was not related to the occurrence of important PSRAs. Schick et al. and Pacurariu et al. demonstrated that clinical trial sample size prior to approval was not associated with postmarketing BBWs, market withdrawal, or the restriction of indications for NMEs [11, 30]. These findings indicate that increasing the sample size in clinical trials prior to approval may not reduce the occurrence of PSRAs. On the other hand, the number of patients treated with orphan drugs is generally much lower than that treated with non-orphan drugs. Since the opportunities to find PSRAs for orphan drugs are rare, it remains uncertain whether the risk of PSRAs is lower for orphan drugs. Recently, orphan drug development has increased, and it is necessary to keep a close watch on the relationship between PSRAs and orphan drugs.

In summary, FIC drug and ATC category L were identified as factors related to PSRAs.

These factors and review period were also associated with the time to occurrence of the first important drug-specific PSRAs. In the future, we plan to perform a more detailed drug-by-drug analysis of the drugs extracted in the present study.

The present study has some limitations. Since all the data sources were public, some detailed data such as exact dates could not be identified, and it was therefore necessary to perform time-to-event analysis using data based on months rather than days. Prestandardization labels showed marked variability among drugs in the descriptions of warnings and precautions. As a result, for a few drugs, the reasons for changes were unclear (not identifiable). The definition of important drug-specific PSRAs in this study may not reflect real-world pharmacovigilance because of the exclusion of PSRAs due to class effects and drug allergy including DILI.

4 Overall Discussion and Conclusion

The results of this study proved the hypothesis that FIC drugs with a novel mechanism of action might be associated with a higher incidence of PSRAs than other new drugs which have same-class drugs. In addition, the time to occurrence of the first important drug-specific PSRA was shown to be shorter for FIC drugs than for other drugs.

This study took different approaches toward the analyses of PSRAs from the preceding studies, in which all the PSRAs were included as the outcome variable in the factor analyses [9, 11, 22]. PSRAs are generally taken based on information obtained from spontaneous reporting of ADRs, continuing clinical trials, or postmarketing drug surveillance. PSRAs not directly related to drug-specific ADRs may also be taken based on important safety issues detected with other drugs of the same class with the same indications. As the purpose of the present study was to identify factors affecting the occurrence of important drug-specific PSRAs, we excluded PSRAs due to class effects. We also considered it meaningful to rule out PSRAs due to nonspecific ADRs such as drug allergy and DILI. Since these effects are dose independent, it is difficult to evaluate the relationship between such ADRs and the mode of action.

Based on our approach in this study, it was indicated that the incidence of important drug-specific PSRAs for FIC drugs was significantly higher than that for other new drugs,

suggesting a strong relationship between FIC drugs and the occurrence of important drug-specific PSRAs. This finding has not been reported in previous studies.

In Part II study in this thesis, we selected appropriate factors in the final model using a stepwise method. Preceding studies have reported that factors such as accelerated approval system, which provides approval prior to completion of the confirmatory studies, and review period are associated with whether post-marketing safety regulatory actions are performed or not. Highly novel drugs receive designations such as priority review and accelerated approval, and we were concerned about confounding when these designations are introduced as factors. There was a risk that correct factor analysis cannot be performed if the significant factors identified in univariate analysis were directly introduced into a logistic regression model. Thus, we extracted appropriate factors introduced into the final model using a stepwise method.

Recommended actions to be taken to prevent or minimize the occurrence of PSRAs for FIC drugs are, 1) to prepare a preclinical study program that can properly detect on-target toxicity and off-target toxicity, and 2) to identify biomarkers for safety assessment at the preclinical stage and to use them continuously after clinical transition. It is important to conduct consistent safety assessment from preclinical studies to reduce postmarketing risks and to establish safety monitoring system earlier for FIC drugs. In addition, we

should develop a risk minimizing plan considering target diseases and apply pharmacoepidemiological approach effectively by employing new technologies such as medical databases.

In conclusion, the results of this present study indicated that postmarketing safety risk for FIC drugs is higher than that for other new drugs which have same-class drugs. It is therefore important to carefully consider the risks of FIC drugs, to develop an optimal risk minimization plan, and to conduct pharmacovigilance efforts based on the drug profile at an early stage after approval.

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Appendix