Investigation toward improvement of postmarketing safety measures in Japan

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Abstract

Information on safety of drug products is collected continuously from the pre-approval stage to the post-approval. Postmarketing observational (PMO) studies for re-examination, which are routinely conducted for almost all newly approved drug products in Japan, are expected to collect safety data with quality and credibility in the clinical settings, and are becoming increasingly important with the internationalization of clinical drug development programs. However, there has been no report that investigated systematically the quality of the PMO studies. Against this background, with the aim of improving postmarketing safety measures in Japan, the present research was conducted.

First, differences in profiles of drug product safety information collected before and after approval were investigated. The result showed that the adverse reaction rate in PMO studies was lower than that in intervention studies in most cases. Also, it was suggested that expected and common adverse reactions and non-serious adverse reactions were likely to be subject to underreporting in PMO studies.

Second, the actual status of PMO studies in the clinical settings was investigated through questionnaire surveys to medical institutions and medical representatives (MRs). As a result, the underreporting in the PMO studies was thought to be partially attributed

to insufficient support system within medical institutions at the stage of actual data collection, which brings about unclarity in the case report form preparation process in the PMO studies.

Third, through a survey to pharmacists at medical institutions, it was revealed that pharmacists actually give priority to the figures of incidence rate of adverse reactions obtained in PMO studies presented in the package insert. Moreover, it was demonstrated that the rate of adverse reactions in the package inserts were presented in the manner of simply combing the results of pre-marketing clinical trials and post-marketing observational studies. This may lead to the underestimation of the safety information.

To minimize the underreporting of adverse reactions, we believe that the products for which PMO studies are conducted should be selected, and also that survey items should be restricted to important information such as unknown/ severe adverse reactions. At the same time, it is important to strengthen other measures such as medical information database and adverse event report database and to proactively utilize them, which can lessen the burden on medical institutions.

In terms of utilization of the package insert, we should not be caught up only in the figures of adverse reaction rates in the package insert, but should verify the data source of the safety information.

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Abbreviations

ATC classification	anatomical therapeutic chemical classification
A	alimentary tract and metabolism
B	blood and blood forming organs
C	cardiovascular system
D	dermatologicals
G	genitourinary system and sex hormones
H	systemic hormonal preparations, excl. sex hormones and insulins
J	anti-infectives for systemic use
L	antineoplastic and immunomodulating agents
M	musculoskeletal system
N	nervous system
P	anti-parasitic products, insecticides and repellents
R	respiratory system
S	sensory organs
V	various
CRA	clinical research associate
CRC	clinical research coordinator
CTE	clinical trial experience
EDC	electronic data capture
GCP	good clinical practice
GPSP	good post-marketing study practice
IP	investigational product
IRB	institutional review board
MedDRA	medical dictionary for regulatory activities
MR	medical representative
NDA	new drug application
PMI studies	postmarketing intervention studies
PMO studies	postmarketing observational studies
PMS	postmarketing surveillance
REC	research ethics committee
RMP	risk management plan
SOC	system organ class

Chapter 1 Introduction

Information on safety of drug products is collected continuously from the pre-approval stage to the post-approval. Before approval, highly accurate information is obtained through intervention studies (phase 1, 2, and 3 clinical trials) conducted in specific populations. After approval, safety information is primarily collected based on spontaneous reports of adverse reactions and/or observational studies performed in daily medical practice [1].

Generally, intervention studies are conducted in randomized and double-blinded manners, intended to verify hypotheses and to obtain results with a high level of evidence. However, clinical studies prior to approval are usually conducted under a limited range of conditions, which has been referred to as "5 toos" (too few, too simple, too narrow, too median-aged and too brief) [2], making it difficult to obtain all necessary safety information solely with such studies. In contrast, observational studies are beneficial for forming hypotheses because of their potentially large sample size. However, control groups are virtually never included and the level of evidence of the results, therefore, is not very high. Also, it has been pointed out that safety information collected post-approval has a limitation of "underreporting" of adverse reactions. Bäckström et al. showed that at least 80% of adverse reactions occurring postmarketing are not reported [3]. Lopez-Gonzalez et al. attributed underreporting to such causes as "ignorance/preconceptions" (a belief that only serious adverse reactions need to be

reported) and a "sense of security" (a feeling that only safe drug products are allowed onto the market) [4].

In recent years, with the advance of internationalization of clinical drug development programs, more new drug products with limited safety information on Japanese patients have been approved and marked in Japan [5]. Also, the number of drugs, such as anticancer drugs and biologics, for which serious adverse reactions are expected in the postmarket are increasing. In this context, "collection of safety information at the postmarketing stage" especially through observational studies is becoming increasingly important.

Regarding the regulation of postmarketing drug safety in Japan, postmarketing surveillance (PMS) studies are required for newly approved drug products to ensure further collection of safety information in the clinical settings. "PMS study" is a general term that encompasses postmarketing observational (PMO) studies and postmarketing intervention (PMI) studies. Each PMS study is conducted under contracts between the pharmaceutical company and medical institutions in accordance with Good Post-marketing Study Practice (GPSP) Ministerial Ordinance (Ministry of Health, Labour and Welfare (MHLW) Ministerial Ordinance No. 171, issued December 20, 2004). The results are submitted to the MHLW as a part of the application documents for re-examination.

"Re-examination" is a regulatory system to re-examine safety and efficacy of

marketed new drugs in the clinical settings within a certain period of time (normally 8 years) after approval. This examination is conducted primarily based on the results of PMO studies for re-examination and spontaneous reports of adverse reactions. Because of this system, many PMO studies are routinely conducted postmarketing sponsored by pharmaceutical companies.

Information collected in PMO studies for re-examination is structured, unlike that in spontaneous reports, and study plans are submitted in advance to the MHLW. In addition, PMO studies are conducted by medical professionals under contracts signed between the pharmaceutical companies and medical institutions. Therefore, PMO studies for re-examination are expected to collect safety data with higher quality and credibility compared with that collected under other observational studies. However, most of these PMO studies are conducted in a target sample size of 3000 patients without a control group; this sample size is regarded as sufficient to detect, with a 95% probability, relatively rare adverse reactions occurring in about 1 out of 1000 patients (an incidence of 0.1%) [5]. Neither the sample size nor the study purpose takes into account the characteristics of the safety information that was collected prior to the drug product approval. For this reason, safety information obtained from PMO studies are seldom used for postmarketing safety actions such as revision of package inserts [6].

Conversely, in PMI studies for re-examination, the objectives of which may include collecting additional efficacy information not having been collected in the clinical

studies conducted prior to approval, control groups are established and randomization is often performed. But such PMI studies are conducted only occasionally and for a limited number of new drugs. In fact, according to the ClinicalTrials.gov registry, there are few industry-funded PMI studies being conducted in Japan.

In the European Union (EU), postmarketing safety monitoring systems have been strengthened, including the implementation of pharmacovigilance legislation in 2012 [7]. In Japan as well, a guideline on risk management plan (RMP) for drugs was issued in 2012, and, since April 2013, companies applying for marketing approval of a new drug have been required to submit a draft RMP that contains postmarketing pharmacovigilance and risk minimization plans [8]. Japan is currently in the process of developing a new pharmacovigilance system.

Against this background, with the aim of improving postmarketing safety measures in Japan, we conducted the present research focusing on the following three points.

1) To identify differences in profiles of drug product safety information collected through intervention studies and observational studies, as well as before and after approval. Also, to investigate in which situation the underreporting of adverse reactions occurs (Chapter 2).

2) To clarify the actual status of PMO studies for re-examination in the clinical settings through questionnaire surveys addressed to medical institutions (department of pharmacies) and medical representatives (MRs) (Chapter 3 and 4).

3) To investigate how pharmacists see and utilize information on the package insert and whether safety information collected postmarketing is properly provided to the medical personnel via the package insert (Chapter 5 and 6).

Based on the above studies, we discuss how we should improve postmarketing safety measures and practice in Japan.

Chapter 2

Characteristics of safety information obtained from postmarketing observational studies for re-examination in Japan

2.1. Introduction

In recent years, there has been more internationalization of clinical drug development programs. This has resulted in approval in Japan of new drug products for which only limited safety information on Japanese patients had been collected and evaluated [5]. Therefore, "collection of safety information at the postmarketing stage especially through observational studies" is becoming increasingly important.

In Chapter 2, we focused on safety data collected in PMO studies in Japan, which are routinely conducted under the framework of the pharmaceutical regulation known as re-examination. We addressed whether the issue of underreporting, generally considered to be associated with observational studies, occurs in PMO studies based on the comparison of adverse reaction rates before and after approval. In addition, we investigated potential causes of such underreporting.

2.2. Method

2.2.1. Extraction of analysis sets

When a re-examination is completed for a product, its package insert is revised based on

the results of PMS studies. This revision is considered a "milestone revision," making it possible to comprehensively identify the postmarketing safety information that was collected, primarily by the pharmaceutical company.

We searched the package inserts of drug products for which re-examinations were completed between January 2009 and December 2014. Among them, we identified package inserts for 189 drug products that included information categorized as "adverse reaction rate in clinical studies for new drug application (NDA)" and "adverse reaction rate in PMS studies" and used these inserts for our investigation. We also extracted information listed under "adverse reaction rate in PMI studies for re-examination," either from the package insert or the re-examination report of the product. We used the package insert search tool of the Pharmaceuticals and Medical Devices Agency to obtain package inserts, re-examination reports and drug product interview forms for the drug products included in our analysis.

2.2.2. Information extraction and tabulation

2.2.2.1. Comparison of overall adverse reaction rates before versus after approval

From the package inserts of the aforementioned 189 drug products, we extracted the overall adverse reaction rate in clinical studies for NDA (ARR-NDA) and the overall adverse reaction rate in PMO studies for re-examination (ARR-PMO), and prepared a scatter plot. Furthermore, for drug products for which PMI studies for re-examination

were conducted following approval, we extracted the overall adverse reaction rates in PMI studies for re-examination (ARR-PMI) and prepared a scatter plot against those for the ARR-NDA.

The number of ARR-NDA and ARR-PMO were calculated in the following way.

- ARR-NDA (%) = total number of all adverse reactions / total number of subjects in clinical studies for NDA

- ARR-PMO (%) = total number of all adverse reactions / total number of subjects in PMO studies for re-examination

2.2.2.2. Comparison of incidence rates of the most common adverse reactions in clinical studies for NDA versus in postmarketing observational studies for re-examination

For each of the 189 drug products, we specified the most common adverse reaction in clinical studies for NDA based on their package inserts and then calculated the difference between this incidence rate and that obtained in PMO studies for re-examination. We calculated the difference between overall adverse reactions data from ARR-NDA and ARR-PMO and prepared a scatter plot.

Each adverse reaction for the investigation was classified by the system organ class of the Medical Dictionary for Regulatory Activities (MedDRA / J Ver.19.0J), and also categorized as serious or non-serious based on the presence or absence in the section of

"serious adverse reactions" of the package insert.

2.3. Results

We identified 189 drug products for which the information of adverse reaction rates both in clinical studies for NDA and in PMS studies were available. Among these, both the ARR-NDA and ARR-PMO were available for 176 products and both the ARR-NDA and ARR-PMI were available for 45 products. For 162 of the drug products, it was possible to compare incidence rate of the most common adverse reaction obtained in clinical studies for NDA to that obtained in PMO studies for re-examination. Characteristics of these products are shown in Table 1.

2.3.1. Comparison of overall adverse reaction rates before versus after approval

First, we compared the ARR-NDA and ARR-PMO. We defined a drug product whose package inserts contained both the ARR-NDA and ARR-PMO for an individual indication as 1 set and obtained 206 sets of such information from 176 products (Table 1). We prepared a scatter plot with the ARR-NDA along the vertical axis and the ARR-PMO along the horizontal axis (Fig.1). This plot showed that the overall adverse reaction rates in clinical studies for NDA were higher than those in PMO studies for re-examination in 88.3% of the information sets (182 of 206 sets).

We next compared the ARR-NDA and ARR-PMI. We extracted the adverse reaction

rates in PMI studies for re-examination from the package insert or the re-examination reports of 189 drug products, obtaining 48 sets of ARR-NDA and ARR-PMI data for 45 products (Table 1). We prepared a scatter plot with the ARR-NDA along the vertical axis and the ARR-PMI along the horizontal axis (Fig.2). This plot showed that the overall adverse reaction rates in clinical studies for NDA were higher than those in PMI studies in 56.3% of the information sets (27 of 48 sets).

2.3.2. Difference of incidence rates of the most common adverse reaction in clinical studies for NDA versus in postmarketing observational studies for re-examination

We prepared a scatter plot for the 192 sets of data obtained for 162 drug products as follows: differences between the incidence rates of the most common adverse reaction in clinical studies for NDA and those in PMO studies for re-examination on the horizontal axis, differences between the overall adverse reactions in ARR-NDA and those in ARR-PMO on the vertical axis (Fig.3). This plot showed that the two variables were correlated (Spearman's $r = 0.800$, $p < 0.0001$). Each adverse reaction was classified by the MedDRA system organ class (MedDRA SOC) (Table 2). Serious adverse reactions were observed more often in "metabolism and nutrition disorders", "vascular disorders" and "cardiac disorders".

Table 1 Characteristics of the products investigated (176 drug products for Fig. 1, 45 drug products for Fig. 2 and 162 drug products for Fig. 3)

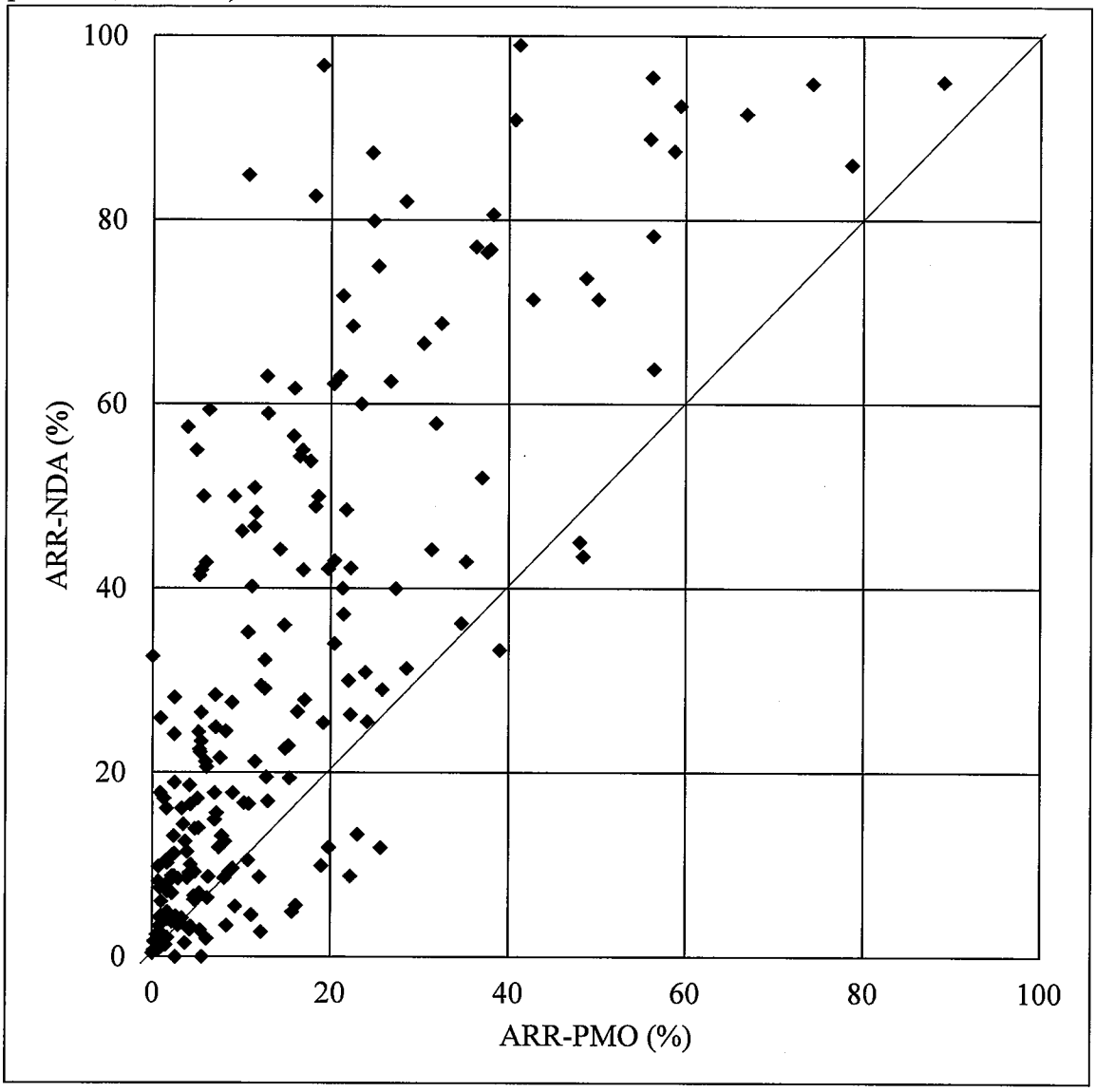
	A 176 drug products	B 45 drug products	C 162 drug products
Therapeutic group (ATC classification)			
A. alimentary tract and metabolism	18	8	17
B. blood and blood-forming organs	9	3	8
C. cardiovascular system	20	3	20
D. dermatologicals	6	3	5
G. genitourinary system and sex hormones	13	1	13
H. systemic hormonal preparations, excluding sex hormones and insulins	7	1	6
J. anti-infectives for systemic use	25	5	23
L. anti-neoplastic and immunomodulating agents	10	3	10
M. musculoskeletal system	6	3	6
N. nervous system	24	8	23
P. anti-parasitic products, insecticides, and repellents	2	0	1
R. respiratory system	15	4	10
S. sensory organs	6	1	6
V. various	15	2	14
Completion date of re-examination period			
January 2009 to December 2009	45	6	42
January 2010 to December 2010	44	13	42
January 2011 to December 2011	30	9	27
January 2012 to December 2012	21	5	20
January 2013 to December 2013	19	8	16
January 2014 to December 2014	17	4	15

A) Drug products for which both the adverse reaction rate in clinical studies for NDA and in postmarketing observational (PMO) studies were available (Fig. 1)

B) Drug products for which both the adverse reaction rate in clinical studies for NDA and in postmarketing intervention (PMI) studies were available (Fig. 2)

C) Drug products for which the incidence rate of the most common adverse reaction in clinical studies for NDA and in PMO studies for re-examination were available (Fig. 3)

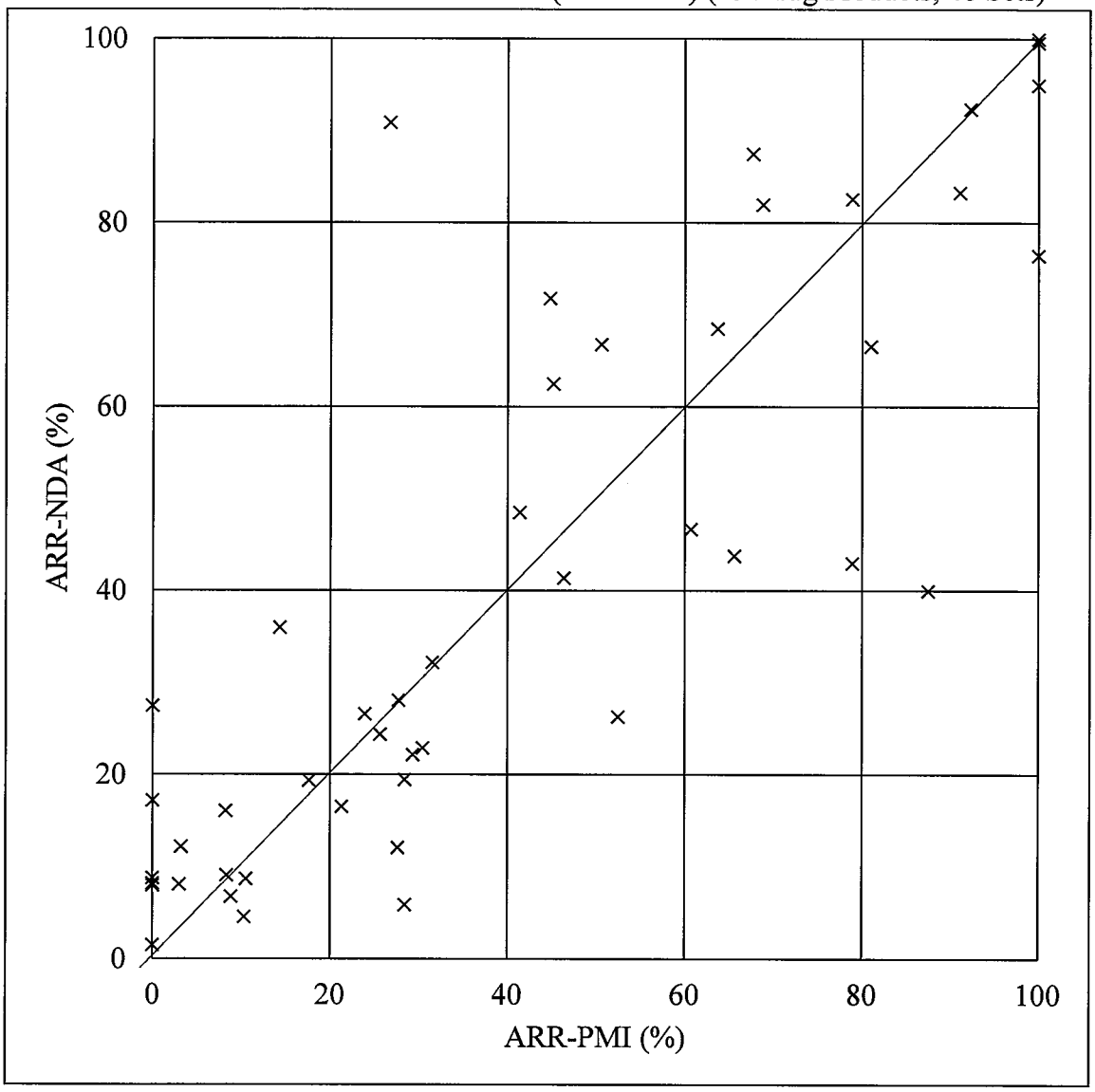
Fig. 1 Scatter plot of the adverse reaction rate in clinical studies for NDA (ARR-NDA) and the adverse reaction rate in PMO studies for re-examination (ARR-PMO) (176 drug products, 206 sets)



Vertical axis: ARR-NDA, adverse reaction rate in clinical studies for NDA

Horizontal axis: ARR-PMO, adverse reaction rate in postmarketing observational studies for re-examination

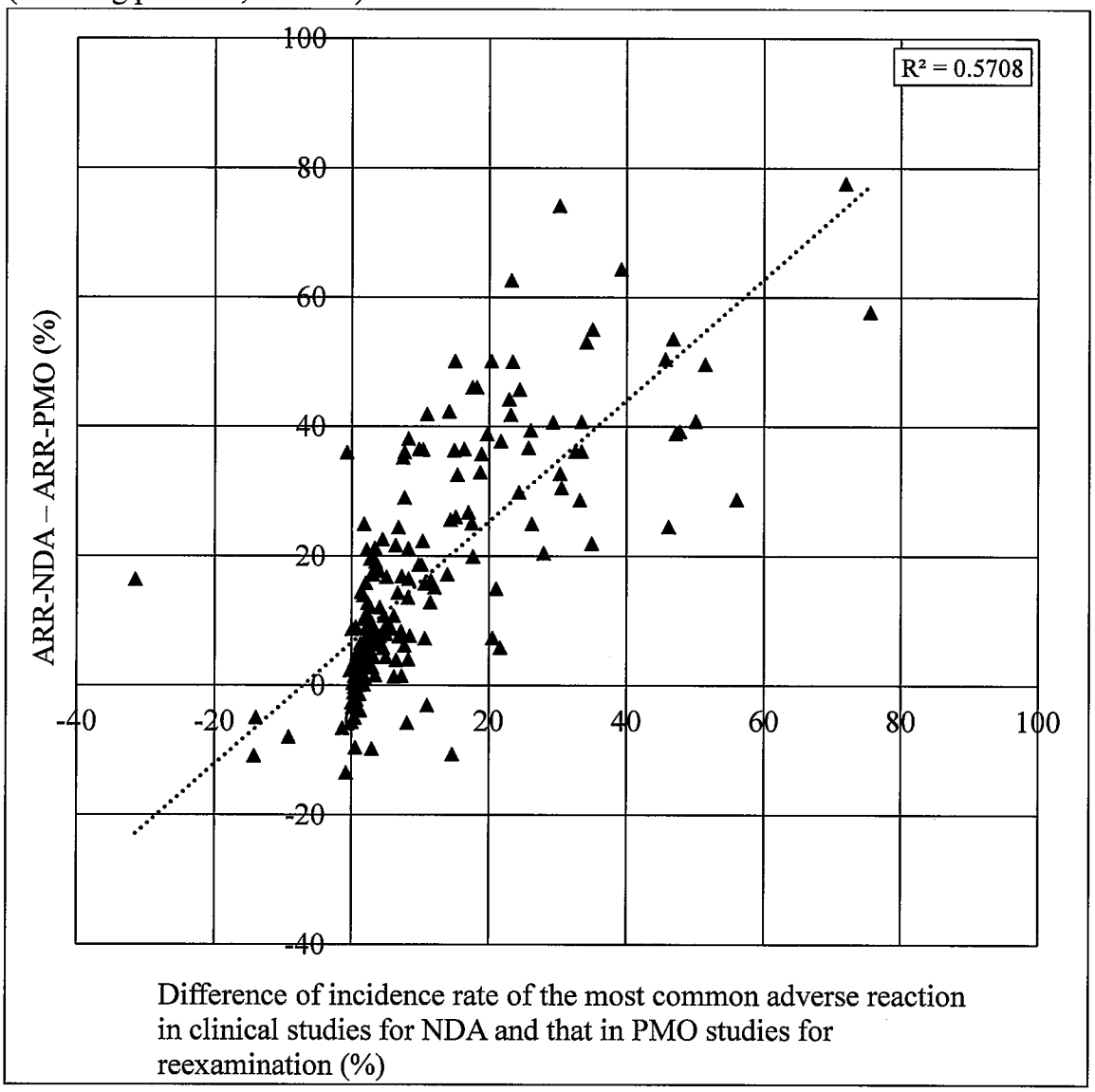
Fig. 2 Scatter plot of the adverse reaction rate in clinical studies for NDA (ARR-NDA) and the adverse reaction rate in PMI studies (ARR-PMI) (45 Drug Products, 48 Sets)



Vertical axis: ARR-NDA, adverse reaction rate in clinical studies for NDA

Horizontal axis: ARR-PMI, adverse reaction rate in postmarketing intervention studies

Fig. 3 Relationship between: the *difference of incidence rate of the most common adverse reaction* in clinical studies for NDA and that in PMO studies; and the *difference of the overall adverse reaction rate* in clinical studies for NDA and that in PMO studies (162 drug products, 192 sets)



Vertical axis: difference of the *overall adverse reaction rate* in clinical studies for NDA and that in PMO studies for re-examination (ARR-NDA–ARR-PMO)

Horizontal axis: difference of *incidence rate of the most common adverse reaction* in clinical studies for NDA and that in PMO studies for re-examination

Table 2 Characteristics of the most common adverse reaction in clinical studies for NDA (162 drug products, 192 sets for Fig. 3)

System Organ Class	Serious adverse reaction 20 sets in total	Non-Serious adverse reaction 172 sets in total
Blood and lymphatic system disorders	1	1
Cardiac disorders	3	0
Eye disorders	0	8
Gastrointestinal disorders	0	42
General disorders and administration site conditions	1	26
Hepatobiliary disorders	2	1
Immune system disorders	1	0
Investigations	0	24
Metabolism and nutrition disorders	6	3
Musculoskeletal and connective tissue disorders	0	2
Nervous system disorders	1	30
Psychiatric disorders	0	1
Renal and urinary disorders	0	1
Reproductive system and breast disorders	0	5
Respiratory, thoracic and mediastinal disorders	0	2
Skin and subcutaneous tissue disorders	0	17
Vascular disorders	5	9

2.4. Discussion

Of the 189 drug products analyzed in our study, we focused on those package inserts that had the information categorized as "adverse reaction rate in PMO studies for re-examination," and compared these to information described as "adverse reaction rate in clinical studies for NDA." We found that, in 88.3% of the 206 sets of information obtained for 176 drug products (182 of 206 sets), the adverse reaction rate in clinical studies for NDA was higher than that in PMO studies for re-examination (Fig.1). On the contrary, as shown in Fig.2, the adverse reaction rate in PMI studies for re-examination, which were conducted postmarketing, exhibited a profile similar to that found in clinical studies for NDA. Furthermore, as shown in Fig.3, the proportion by which the incidence rate of the most common adverse reaction in clinical studies for NDA decreased postmarketing correlated to the proportion by which the incidence rate of the overall adverse reactions decreased postmarketing.

Results of this study indicated that, even in observational studies controlled by the pharmaceutical regulations in Japan—that is, PMOs—the adverse reaction rate was lower than that in intervention studies in most cases. In contrast, intervention studies conducted either prior to or after approval exhibited similar profiles in terms of adverse reaction rate. In addition, our findings suggest that one reason for a lower adverse reaction rate in PMO studies was that the number of reports of adverse reactions that had occurred frequently prior to approval decreased postmarketing; in other words, expected and common

adverse reactions and non-serious adverse reactions were likely to be subject to underreporting in PMO studies for re-examination.

In Japan, PMI studies and clinical studies for NDA are conducted under Good Clinical Practice (GCP) Ministerial Ordinance (MHLW Ministerial Ordinance No. 28, issued March 27, 1997). However, GCP does not apply to PMO studies for re-examination even though these provide most of the data in the re-examination application. Therefore, unlike PMO studies, PMI studies are expected to have a level of quality that is equivalent to that of clinical studies for NDA and appear to have a similar safety profile. But even for PMO studies, it is usually stipulated in study protocols that all adverse events (regardless of causality) that occur during a specified period following the administration of the drug product in question be reported, and there consequently should be no differences in the safety information collected between before and after approval. Nevertheless, one of the reasons that observational studies have a different safety profile than intervention studies conducted before or after approval appears to be the lack of a GCP requirement dictating activities, such as monitoring, that ensure reliability. Furthermore, PMO studies for re-examination are often so-called "3000-case studies." In a questionnaire survey of physicians about PMO studies, 32% of the respondents indicated that they believed "there is no scientific validity" and 43% that "scientific validity is not required" of such studies [9]. These results suggest that low motivation of investigators at participating medical institutions also contributes to the underreporting.

Hazell L et al. showed that the median underreporting rate across 37 studies (not including Japanese) was 94% and the reason for not reporting included a lack of time, difficulty in accessing reporting form, etc. [10]. In Japan, each PMS study is conducted in accordance with GPSP. Nevertheless, the results of our investigation suggest that it is difficult to prevent underreporting even in the observational studies that, unlike spontaneous reports, are conducted under contracts signed between pharmaceutical companies and medical institutions as specified by regulations.

The limitations of our investigation include the small sample size of PMI studies compared with that of PMO studies. Another limitation is that, in our investigation of underreporting, changes in all individual adverse reactions were not investigated; we only investigated the changes before versus after approval in the number of adverse reactions most frequently reported prior to approval.

In Japan, to date, the most common studies to collect safety information after drug approval have been PMO studies. Now, similar to the situation in the EU and United States, a guideline on RMP has existed in Japan since 2012. This guideline requires that companies applying for market approval submit a RMP that contains postmarketing pharmacovigilance and risk minimization plans, accounting for the potential risks of the drug product. In addition, a system allowing direct adverse reaction reporting by patients was introduced in March 2012 in Japan; patient adverse reaction reporting systems were introduced in 1993 in the United States and subsequently in Europe, emphasizing the

importance of information reported directly by patients [11]. Furthermore, similar to the Sentinel Initiative in the United States, a large-scale (tens of millions of persons) health care information database sentinel project was initiated in Japan in 2011. Thus, systems for safety information surveillance following approval have reached a major turning point.

There is a need for increased types of PMS activities, including those using large-scale health care information databases. One option might be to exclude expected and non-serious adverse reactions that have already been identified by clinical studies for NDA, and which are more likely to be underreported, from specific pharmacovigilance activities. For important potential adverse reactions, PMI studies should be proactively planned and conducted with a control group to identify the degree of risks. Conducting PMS studies only in specific medical institutions with quality systems in place would be another potential solution. Through such efforts, postmarketing safety data might be collected in a better and more efficient way to enhance patient safety.

Chapter 3

Questionnaire Survey of Postmarketing Surveillance in Departments of Pharmacy

3.1. Introduction

PMO studies for re-examination, which have constituted a main part of the PMS in Japan are observational studies whose aim is to collect information of safety and efficacy of a newly approved drug product in the clinical settings. Those studies are conducted according to GPSP under a contract between a pharmaceutical company and a medical institution. Compared with clinical trials for marketing approval, PMO studies are said to be somewhat onerous for medical practitioners to perform owing to the lack of adequate physical and financial support.

So far, no report has explored how the departments of pharmacy engage in the activities of PMO studies in medical institutions. Therefore, we carried out a questionnaire survey for medical institutions in Tokyo to obtain information about their implementation systems of PMO studies.

3.2. Method

We mailed our questionnaire sheet "Questionnaire on Implementation of Postmarketing Observational Studies for Re-examination in Medical Institutions" (Appendix 1, in Japanese) to the drug divisions, pharmacy departments (sections), and pharmacies

(hereafter, pharmacy departments) of 599 medical institutions registered with the Tokyo Metropolitan Society of Health System Pharmacists as of August 26, 2013. The survey period was from October 25 to November 22, 2013. We obtained responses by mail using enclosed envelopes or by e-mail.

3.3. Results

3.3.1. Characteristics of the medical institutions

We sent questionnaires to 599 medical institutions, and obtained response from 166 institutions (27.7%). The characteristics of these institutions are indicated in Table 3.

3.3.2. Departments responsible for PMO studies for re-examination

When multiple selections were allowed to answer concerning the departments within the medical institutions mainly responsible for PMO studies for re-examination, medical and pharmacy departments were each selected in 76 facilities. When asked whether PMO studies were even partially conducted in the pharmacy department, 77 facilities (47.0%) answered yes and 87 (53.0%) answered no.

In the 77 facilities where pharmacy departments were involved in PMO studies, 27 facilities (35.1%) had more than 400 beds. On the other hand, in the 87 facilities where pharmacy departments were not involved, 29 facilities (33.3%) had fewer than 100 beds (Table 4).

3.3.3. Activities in which the pharmacy department involved

The 77 facilities that responded that their pharmacy department was involved (even partially) in PMO studies for re-examination were asked if they undertook the following activities for conducting such studies as a pharmacy department:

(i) Consultation for physicians and drug company representatives

(ii) Contract procedures

(iii) Selection of study patients

(iv) Case registration

(v) Preparation of case report forms, excluding medical assessments

(vi) Responses to review

Among these, (i) and (ii) were clerical activities and (iii)–(vi) were activities directly linked to data collection.

We found that of the 77 facilities, 69 (89.6%) were involved in activity (i) and 50 (64.9%) in activity (ii), which showed a high rate of implementing administrative operations prior to PMO studies. On the contrary, we observed that 19 (24.7%) facilities were involved in activity (iii), 16 (20.8%) in activity (iv), and 18 (23.4%) in activity (v), which showed a low rate of conducting data collection in the PMO studies (Fig. 4).

We examined differences among the types of PMO studies for which pharmacy departments were involved. Respondents were asked to select among the following: "All studies in principle"; "Studies that target all patients the products were administered"

(hereafter, all-case surveillance); "Studies with long study periods"; "Studies with a large number of cases within the institution"; and "Studies with special clinical examination," and most answered "All studies in principle"; thus, we could not determine differences in the case report form.

Similarly, we queried the 77 facilities responding that their pharmacy department was even partially involved in PMO studies whether the pharmacy department had experience in conducting all-case surveillance; 51 facilities (66.2%) answered that they had such experience; 26 facilities (33.8%) responded that they lacked such experience. For the 51 facilities with experience in conducting all-case surveillance, the stratified involvement rate for each activity in implementing PMO studies appears in Fig. 4. In the 51 facilities involved in all-case surveillance, 16 (31.4%), 13 (25.5%), 12 (23.5%) and 16 facilities (31.4%) were involved in activity (iii), (iv), (v) and (vi), respectively, which showed a little higher rate of conducting data collection compared to the 77 facilities without the involvement in all-case surveillance.

We also asked the 51 facilities involved in all-case surveillance about the overloaded activity compared to usual PMS in multiple selections. The rates of the activity (i), (ii), (iii), (iv), (v), (vi) and others were 56.9%, 39.2%, 11.8%, 23.5%, 9.8%, 3.9% and 5.9%, respectively.

3.3.4. Incentives for the pharmacy department

We also queried the 77 facilities with pharmacy departments that indicated involvement in PMO studies for re-examination whether there were incentives, such as research funding allocation, for conducting those studies. Eleven facilities (14.3%) answered "Yes", 64 facilities (83.1%) answered "No" and 2 facilities (2.6%) did not answer (Table 5). Further, facilities that indicated receiving incentives were queried as to the type: 8 facilities answered, "Allocation of research funds" or "X% of research funds is allocated", 2 facilities responded "Allocated as office expenses in the pharmacy department", and 1 facility replied "Ethics review fee."

3.3.5. Future involvement in PMO study for re-examination activities

We asked the 87 facilities that responded that their pharmacy department was not currently involved in PMO studies for re-examination whether they had plans to participate in the future. Only 4 facilities (4.6%) responded that they had such plans to participate, and 79 facilities (90.8%) answered that they lacked such plans. Four facilities did not respond.

Table 3 Size of medical institutions and number of pharmacists (n = 164)

Size of medical institution	Number of medical institutions (%)	Mean number of full-timers *)	Mean number of part-timers †)
No beds	27 (16.5)	1.8	0.74
Fewer than 100 beds	39 (23.8)	3.1	0.86
100–199 beds	34 (20.7)	5.1	0.85
200–299 beds	17 (10.4)	8.3	1.8
300–399 beds	12 (7.3)	11.6	1.3
400 or more beds	34 (20.7)	27.4	2.5
No response	1 (0.6)	-	-

*) Full-time pharmacists with agreed hours of over 32 hours/week

†) Part-time pharmacists with agreed hours of less than 32 hours/week

Table 4 Relationship between the size of medical institution and involvement of the pharmacy department to PMO studies

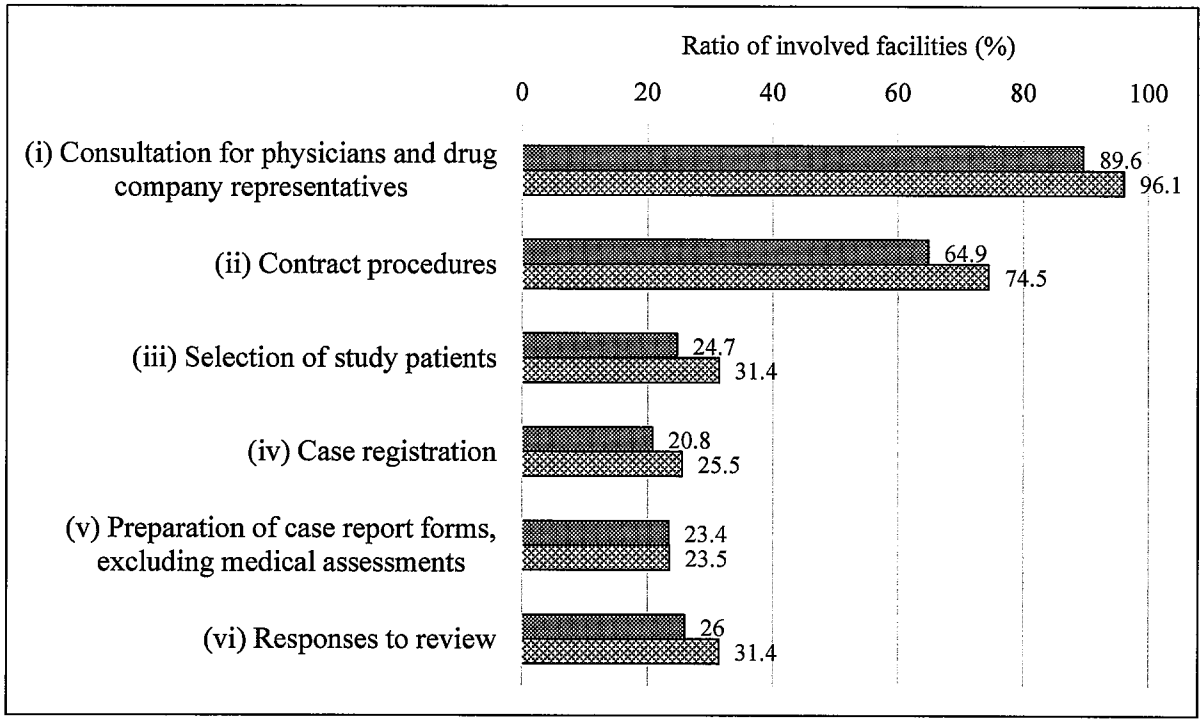
Size of medical institution	A (n = 77)	B (n = 87)	C (n =51)
No beds	4 (5.2)	23 (26.4)	2 (3.9)
Fewer than 100 beds	10 (13.0)	29 (33.3)	3 (5.9)
100–199 beds	16 (20.8)	18 (20.7)	9 (17.6)
200–299 beds	9 (11.7)	8 (9.2)	7 (13.7)
300–399 beds	10 (13.0)	2 (2.3)	9 (17.6)
400 or more beds	27 (35.1)	7 (8.0)	20 (39.2)
No response	1 (1.3)	-	1 (2.0)

A) Number of facilities with the involvement of the pharmacy department (%)

B) Number of facilities without the involvement of the pharmacy department (%)

C) Number of facilities with the involvement of the pharmacy department in the all case-surveillance (%)

Fig. 4 Involvement of the pharmacy department in each activity of PMO studies (multiple selections)



Facilities in which PMO studies for re-examination were even partially conducted in the pharmacy department; 77 facilities

Facilities in which all-case surveillance was even partially conducted in the pharmacy department; 51 facilities

Table 5 Relationship between the size of medical institution and incentives for the pharmacy department

Size of medical institution	With incentive (n = 11)	No incentive (n = 64)	No response (n = 2)
No beds	-	4	-
Fewer than 100 beds	-	9	1
100–199 beds	-	16	-
200–299 beds	3	6	-
300–399 beds	3	7	-
400 or more beds	5	21	1
No response	-	1	-

PMO studies for re-examination were even partially conducted in the pharmacy department of 77 facilities.

Table 6 Relationship between the activities of PMO studies for re-examination and incentives for the pharmacy department (multiple selections)

Activities of PMO studies for re-examination	With incentive (n = 11)	No incentive (n = 64)	No response (n = 2)
(i) Consultation for physicians and drug company representatives	10	57	2
(ii) Contract procedures	7	41	2
(iii) Selection of study patients	2	16	1
(iv) Case registration	3	13	0
(v) Preparation of case report forms, excluding medical assessments	2	16	0
(vi) Responses to review	3	17	0

PMO studies for re-examination were even partially conducted in the pharmacy department of 77 facilities.

3.4. Discussion

In this survey, we investigated the degree and situation of pharmacy departments' involvement in PMO studies for re-examination in medical institutions. We found that involvement of pharmacy departments in activities directly linked to data collection was no more than around 30%.

We hypothesized that one reason for the low involvement rate was lack of incentives for the pharmacy department to conduct PMO studies. As a result, out of 77 facilities with the pharmacy departments participating in PMO studies, only 11 facilities were found to have provided incentives to their pharmacy departments. We understand that it is because most of the activities, such as (i) ("Consultation for physicians and drug company representatives") and (ii) ("Contract procedures"), are clerical in nature. Further, we found that only 3 facilities provided incentives—even when the facilities had departments participating in activities directly linked to data collection such as (iii) ("Selection of study patients"), (iv) ("Case registration"), (v) ("Preparation of case report forms, excluding medical assessments") and (vi) ("Responses to review"). Thus, it indicated little relationship between the activity and incentive to the pharmacy department (Table 6).

When all-case surveillance is subjected to approval for certain pharmaceutical products, medical institutions that use these products must cooperate in PMO studies regardless whether incentives to pharmacy departments will be provided or not. In such

cases, although all-case surveillance is mandatory for approval, preparation of case report forms and response to the review have to be addressed by a certain department within the medical institution. It may be considered that these activities are a burden to the medical institution concerned, and if incentives could be provided to the departments involved in the study—regardless of whether they are pharmacy departments—assistance from the departments would be easier to obtain. In this way, high-quality PMO studies could be conducted.

As a guideline, according to pharmaceutical company notices and standards related to the Fair Competition Code, Enforcement Regulation, Operational Standard III-4 Study and Research Evaluation (Revised December 22, 2005, Fair Trade Commission), the total amount of remuneration related to study costs for PMO studies should not exceed 10,000 JPY per case. Even if the study designs are especially difficult and require long working hours, costs should not exceed the guideline figure of 30,000 JPY per case. Labor-intensive studies, such as with all-case surveillance, may require special handling. However, in any event, the small income obtained by medical institutions makes it difficult to provide appropriate incentives to the departments concerned. As a result, PMO studies are implemented by the medical offices. As for the early postmarketing phase vigilance, an examination of intervention effects and costs under the involvement of the pharmacy department has been reported [12]. In PMO studies, there is a need to discuss ways of distributing incentives that are tied to activity volume within a large

framework, including both medical institutions and pharmaceutical companies.

One limit of this questionnaire survey is that among the 599 medical institutions in Tokyo, we obtained responses from only approximately 30%, which is not very high. Also, we could only grasp the situation of pharmacy departments' involvement in PMO studies in the 77 institutions out of 164 where PMO studies were even partially conducted in that department.

If such studies are solely dependent on medical offices, as at present, there will be a progressively greater burden on physicians; that could adversely affect the quality of PMO studies, which play an extremely useful role as a postmarketing source of information.

Chapter 4

Questionnaire Survey of Medical Representatives on the Practice of PMO Studies in Medical Institutions

4.1. Introduction

PMO studies for re-examination have constituted a main part of the PMS in Japan. However, for medical practitioners, it appears onerous to conduct such studies owing to the lack of sufficient support compared with clinical trials. GCP applies to clinical trials, and such clinical trials for marketing approval are conducted under the rigorous control of clinical research coordinators (CRCs) and clinical research associates (CRAs). Conversely, there is not such an enforcement system for PMO studies.

So far, no reports have investigated the quality of PMO studies in medical institutions. In the present study, we focused on pharmaceutical companies, who plan and conduct PMO studies, and conducted a questionnaire survey to medical representatives (MRs) on the practice of PMO studies practice in medical institutions.

4.2. Method

Using the MR roster of the Kitasato Institute Hospital Department of Pharmacy, we sent an invitation e-mail regarding the "Questionnaire on Postmarketing Observational Studies for Re-examination as Observed by Medical Representatives" (Appendix 2, in

Japanese) simultaneously to 149 named MRs. The recipient of the e-mail was encouraged to distribute it to other MRs. The method of response was to access the Web questionnaire form on the URL indicated in the e-mail and to anonymously answer online (from January 21 to February 28, 2014). The targeted PMO studies questioned was those for the past 5 years from April 2009 to December 2013 (hereafter, previous 5 years); it included all PMO studies for which the MR was responsible, including those for the previous companies. We used IBM SPSS Statistics Version 21 (IBM Japan Ltd., Tokyo) for data analysis. We employed Fisher's exact test (significance level, 5%).

4.3. Results

4.3.1. Respondent background

We obtained responses from 203 individuals (Table 7). After excluding 15 individuals who responded that they had not been involved in PMO studies, we conducted the analysis on responses from the remaining 188 respondents.

4.3.2. Speed and quality of PMO studies for re-examination

Regarding the speed of the PMO studies, 49.5% of the respondents indicated that they were "somewhat dissatisfied" with the studies; when this figure is combined with the 8.5% who stated that they were "dissatisfied," it is clear that most of the respondents felt discontented with the PMO studies (Fig. 5). The reasons cited most often in this regard were as follows: "Even if evaluable cases exist, they are not registered"; "Even if cases

are registered, case report forms are recorded slowly and retrieval takes time"; and "It takes time for the requested modification to take effect" (Table 8).

In contrast, regarding the quality of the PMO studies, 59.6% were "somewhat satisfied" with the studies; combined with the 25.5% who stated that they were "satisfied," approximately 80% were contented (Fig. 5). The reasons given for being "somewhat dissatisfied" or "dissatisfied" were mostly as follows: "Incomplete information on concomitant drugs and therapies that should have been used"; "Incomplete basic patient information (such as medical history, complications)"; and "Modification requested to the case report form were not complied with" (Table 8). Regarding the speed and quality of PMO studies, we did not observe significant differences in the respondents with different degree of experience of PMO studies over the previous 5 years (Fisher's exact test: $P = 0.38$ for speed, $P = 0.93$ for quality).

4.3.3. Preparation of the case report form

With regard to the MRs' experience of being declined by the physicians to make additions or modifications to the case report form to correct information, 26.6% of the respondents stated that they had such experience. As to the reason, the most common response was the physicians' "Lack of time" (Table 9).

We also queried MRs if they had experience of being requested by physicians to fill in a part of the case report form instead of them: 78.7% and 21.3% replied no and yes,

respectively. Further, to the question if they had actual experience of assisting with filling in a part of the case report form, 68.6% said no and 31.4% said yes.

4.3.4. Reporting status of information in the case report forms

When we asked the respondents about their satisfaction with the case report forms submitted by the physicians from the viewpoint of sufficiency of the described information, the responses were as follows: 58.0%, "more than three-quarters" of the case report forms were satisfactory; 35.6%, "about half"; and 6.4%, "less than one-quarter." When we asked the participants' evaluation as to the degree of completeness of information filled in the case report form, all items in the case report form were fairly high degree of completeness. However, we observed a little difference. While the totals for "well reported" and "fairly well reported" exceeded 90% for "patient background," "drug medication record," and "adverse events relevant to key survey monitoring," the totals for "well reported" and "fairly well reported" were about 80% for "concomitant drugs and therapies," "typical clinical laboratory values," "clinical laboratory values associated with adverse events," and "typical adverse events" (Fig. 6).

4.3.5. Underreporting of adverse reactions

When questioned about the extent they believed underreporting (unreported situations despite the occurrence of adverse events) to occur, 42.6% of the respondents stated that they had little experience of underreporting; 30.9% had some experience of

underreporting. Regarding underreporting experience, we did not observe significantly difference among the respondents with different degree of experience of PMO studies over the previous 5 years (Fisher's exact test: $P = 0.76$).

We asked additionally about the underreporting of adverse events to the 67 respondents who answered "strongly experienced" or "moderately experienced", as for what kind of adverse events they felt the existence of underreporting. The majority of responses were accounted for by "when a mild adverse event occurred," "when an adverse event of unknown cause occurred," and "when a known adverse event occurred" (Table 10).

4.3.6. Considerations for future PMO studies for re-examination

The great majority of the responses pointed out "a simple case report form focused on priority items should be prepared," followed by "personnel from the development department in pharmaceutical company should also be involved in PMO studies for re-examination" in order to improve the quality of PMO studies in future (Table 11).

Table 7 Respondent background (n = 203)

Table 7-1 Age of respondents and their experience of PMO studies

	A	B	C	D	Total (%)
20s	8	14	10	6	38 (18.7)
30s	4	42	38	15	99 (48.8)
40s	2	21	12	19	54 (26.6)
50s	1	4	1	6	12 (5.9)
60s	0	0	0	0	0
Total	15 (7.4%)	81 (39.9%)	61 (30.0%)	46 (22.7%)	203

A) Not involved in PMO studies for re-examination
B) 1–4 studies
C) 5–9 studies
D) 10 or more studies

Table 7-2 Respondents' experience of MR duties and PMO studies

	A	B	C	D	Total (%)
Under 1 year	4	0	0	0	4 (2.0)
1–4 years	5	17	5	3	30 (14.8)
5–9 years	3	21	25	11	60 (29.6)
10 or more years	3	43	31	32	109 (53.7)
Total	15 (7.4%)	81 (39.9%)	61 (30.0%)	46 (22.7%)	203

A) Not involved in PMO studies for re-examination
B) 1–4 studies
C) 5–9 studies
D) 10 or more studies

Fig. 5 Satisfaction with speed and quality of PMO studies for re-examination (n = 188)

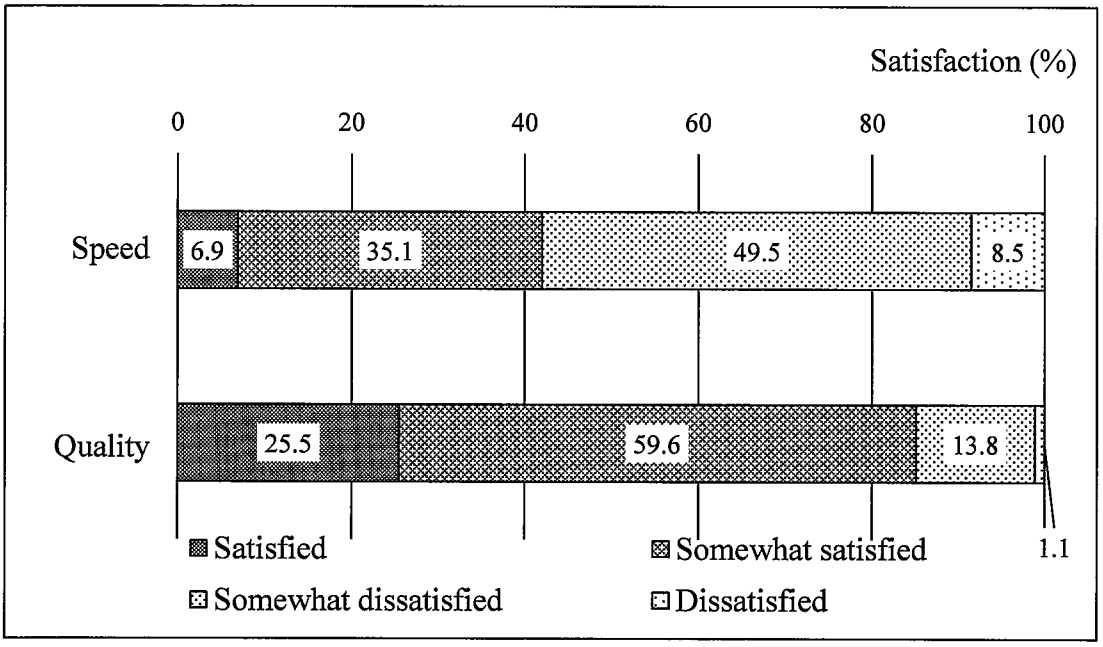


Table 8 Reasons for being "somewhat dissatisfied" or "dissatisfied"

Speed (n = 109, multiple selections)	Number of respondents
Necessary case review by institutional review board and ethics committee	30
Time required for contract	40
Even if evaluable cases exist, they are not registered	74
Even if cases are registered, case report forms are recorded slowly and retrieval takes time	98
It takes time for the requested modification to take effect	50
Not appointed by the physician	32
Others	1
Quality (n = 28, multiple selections)	**Number of respondents**
Incomplete information when a questionnaire was not returned by the data manager	13
Incomplete basic patient information (such as medical history, complications)	14
Incomplete information on concomitant drugs and therapies that should be used	18
Incomplete information on adverse events	8
Modification requested to the case report form were not complied with	17
All cases investigated are not registered	7
Others	1

Table 9 Preparation of the case report form

Table 9-1 Experience of being declined by the physicians to make additions or modifications to the case report form (n = 188)

	Number of respondents (%)
Yes	138 (73.4)
No	50 (26.6)

Table 9-2 Reasons for being declined (n = 50, multiple selections)

	Number of respondents
Lack of time	45
Lack of medical records at hand	15
Deemed unnecessary in terms of medical judgment	12
Not being the attending physician	7
Postponement	17
Others	-

Fig. 6 Reporting status of information in the case report forms (n = 188)

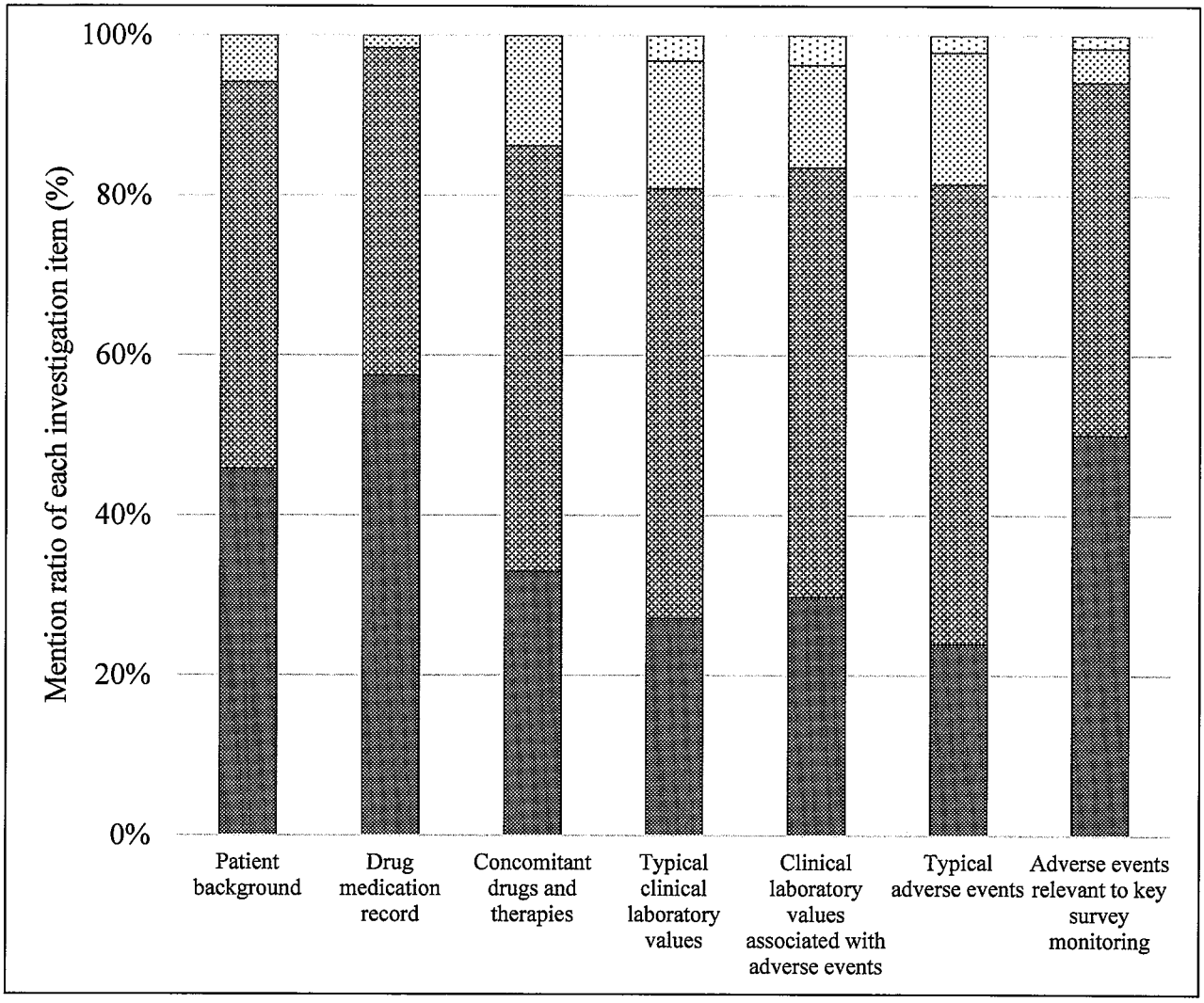


Table 10 Underreporting

Table 10-1 Experience of underreporting (n = 188)

	Number of respondents (%)
Strongly experienced	9 (4.8)
Moderately experienced	58 (30.9)
Little experience	80 (42.6)
No experience	41 (21.8)

Table 10-2 Adverse events associated with underreporting (n = 67, multiple selections)

	Number of respondents
Mild adverse events	55
Severe adverse events	7
Adverse events of unknown cause	27
Known adverse events	22
Unexpected adverse events	4

Table 11 Considerations for future PMO studies for re-examination (n = 203, multiple selections)

	Number of respondents
Revise investigation design to set control group	62
Personnel from the development department in pharmaceutical company should also be involved in PMO studies for re-examination	92
Conduct SDV (including sampling SDV *)	61
A simple case report form focused on priority items should be prepared	99
Others	12

*) SDV, source data verification

4.4. Discussion

In this investigation, based on the questionnaires to MRs, who request medical institutions to conduct PMO studies for re-examination, we attempted to obtain a better understanding of PMO studies conducted at medical institutions. We did not collect information of the respondents' name and affiliation, and also limited the questions to PMO studies during the latest 5 years. Thus, we believe that our results reflect rather honest opinions of the MRs.

In general, MRs were dissatisfied with the speed of PMO studies conducted at medical institutions, though they were reasonably satisfied with the quality. With regard to speed, many complaints were voiced regarding activities under the PMO study implementation rather than contract procedures and institutional review board (IRB) or research ethics committee (REC) processes. The complaints included slow reporting and collection of case report forms (even though the cases were registered) and poor registration of cases (even though the cases were qualified). According to Chapter 3, our findings indicate that the pharmacy departments of medical institutions are often involved in PMO studies duties and the process is reasonably smooth. However, in the implementation phase, such activities as case registration and preparing case report forms are mainly handled by physicians. Many physicians consider PMS to be important, but the workload of PMS is a burden [13]. So, physicians usually cannot conduct such duties in a timely manner due to

busyness, which results in delays in case report form submission. The dissatisfaction with speed is probably connected with this.

About 35% of respondents answered that about half of the case report form had reported the desired information well, which means that the rest half was insufficiently reported. It was suggested that creating, adding to, or modifying case report forms was delayed because the study implementation phase was time consuming. Dissatisfaction with speed and quality is probably connected to this result. Further, with the question about the experience of being requested by physicians to fill in a part of the case report form instead, 21.3% of respondents answered yes. In this study, we did not investigate the specific points at which MRs were requested to do so; thus, we could not determine the impact on quality of PMO studies. However, our results indicate that the case report form creation process was somewhat unclear.

One way to deal with the MRs' dissatisfaction related to PMO studies—including speed and quality, and associated issues of underreporting—is to implement priorities for the studies. The responses in this study notably indicated experience of underreporting for mild adverse events, adverse events of unknown cause, and known adverse events. It is not necessary that all medical institutions in Japan would conduct PMO studies; rather, implementation can be limited to well-staffed medical institutions. It is also important to consider adopting measures that can be used for "active surveillance". Such issues as

omissions and underreporting can be eliminated, and we expect that we can detect known or mild adverse events difficult to find in the current PMO studies.

Another option is to establish priority items in PMO studies based on information from the clinical trials, excluding known or mild adverse events from the investigation. We found, in our survey, that the majority of respondents desired a simple case report form that focused on priority items. Known but serious adverse events as well as unknown or severe adverse events are expected be detected by implementing best-practice investigations and conducting high-quality research. As shown in the results, high percentage of such priority items were well reported, and thus, this finding is considered as an effective measure.

Another course of action is suggested by one report [14], which proposed standardization of case report forms for PMO studies; the wide variety of client-dependent recorded items should be unified. With such an approach, it is expected that the entry method is clarified and entry time is reduced, leading to more information gathering. Recently, the use of electronic case report forms—electronic data capture (EDC)—has increased and replaced paper forms. Compared with paper case report forms, a reduction by half in the review rate and a significantly shorter time from obtaining the case report form until review have been reported for EDC [15]. By utilizing such IT technologies, the burden on both physicians and MRs can be reduced. An improvement in

the implementation environment for PMO studies, including the creation process for case report forms, can lead to betterment in the overall quality.

The limit of this research is that it was not a survey addressed to the medical institution. Also, the survey was conducted anonymously and the information of the respondents' affiliation (company name) was not collected in order that they would report their honest feeling. Further, this study took the form of a questionnaire survey; thus, it was unable to ascertain the reliability of the investigation results using direct techniques, such as direct reading of clinical records. We therefore believe that it isn't necessarily appropriate to generalize the results of the present study to the current conditions in Japan.

Currently, PMO studies are positioned between passive and active surveillance; they are considered to be intended to detect both unknown or serious and known or mild adverse events. In the future, planning should aim toward creating a case report form that focuses on priority items—as supported by the questionnaire responses we received. Other actions, such as limiting the study site to well-equipped medical institutions and utilizing IT technology and medical institution support systems (e.g., EDC), would facilitate incorporation of the advantages of both passive and active surveillance. Such a move could be expected to lead to improvements in the overall speed and quality of PMO studies.

Chapter 5

Questionnaire Survey of Hospital Pharmacists on the Use of Safety Information

5.1. Introduction

Many pharmacists utilize the package insert as a fundamental source of drug information [16]. If new information about the product is obtained after its being on the market, the information in the package insert is revised as appropriate.

When a new drug gets through the re-examination, usually 8 years after the marketing approval, the package insert is revised to reflect the safety information collected post-marketing. We understand that the revision of a package insert after the re-examination is an important milestone for the product. In the revised package insert, "information on adverse reactions obtained before approval" and "information on adverse reactions after approval" are described in parallel.

Under such circumstances, so far, there has been no research that investigated which safety information (frequency of adverse reaction), before or after approval, does a pharmacist prioritize in daily practice. Accordingly, we undertook a questionnaire survey addressed to pharmacists at medical institutions with the aim to clarify how they collect and interpret information about adverse reactions from the package inserts. We also tried to identify differences, if any, among pharmacists with or without the work experiences of clinical trials.

5.2. Method

We mailed our questionnaire sheet "Questionnaire of Hospital Pharmacists on the Use of Safety Information" (Appendix 3, in Japanese) to the drug divisions, pharmacy departments (sections), and pharmacies (hereafter, pharmacy departments) of 599 medical institutions registered with the Tokyo Metropolitan Society of Health System Pharmacists as of August 26, 2013.

To control the bias by affiliation, we limited the number of responses to a maximum of three pharmacists per medical institution; the survey period was approximately 1 month, from October 25 to November 22, 2013. We used IBM SPSS Statistics Version 21 (IBM Japan Ltd., Tokyo) for data analysis. We employed Fisher's exact test (significance level, 5%) to compare data from respondents with and without work experiences of clinical trial (hereafter, clinical trial experience; CTE).

5.3. Results

5.3.1. Respondent Background

We dispatched the questionnaire sheet to 599 medical institutions; from those, we obtained responses from 413 pharmacists. After excluding 4 incomplete responses, we analyzed the responses of 409 pharmacists (Table 12).

As for the CTE, 29.1% (119/409) of respondents had such experience; 70.9%

(290/409) did not. Contents of the respondents' previous CTE were as follows (multiple selections): 80, management of investigational products (within the medical institution); 48, clinical trials office and IRB office duties; and 26, CRC duties. Little experience was reported for duties as CRAs, clinical trial sponsor, or regulatory authority. We observed a relationship between CTE and respondent age category, but not between CTE and size of affiliated medical institution.

5.3.2. Use of information materials to investigate adverse reaction information

Regardless of the degree of CTE, over 80% of respondents frequently used the information in the package insert to investigate adverse reaction information. The differences in the use of package inserts, interview forms, or product brochures were not observed between respondents with or without CTE, excepting the utilization of academic papers. (Fig. 7).

5.3.3. Interpretation of the adverse reaction information in the package insert

Regarding the interpretation of the adverse reaction information in the package insert, regardless of CTE, the most common response was "somewhat inadequate." We observed significantly different responses depending on the degree of CTE (Table 13, Fisher's exact test: $P = 0.024$). Regarding information volume, 237 respondents who indicated "somewhat inadequate" or "inadequate" cited the following reasons (multiple selections): 161, "information sources for the reports are unclear"; 161, "frequency of adverse

reactions is difficult to understand"; 132, "only the frequency of adverse reactions is stated without the information of sample size"; and 109, "reporting methods for adverse reactions are not uniform among pharmaceutical companies."

5.3.4. Judgement on safety information in a mock package insert

We evaluated the judgement of pharmacists on adverse reaction information in a mock package insert. Regardless of the degree of CTE, most respondents judged the information from post-marketing studies as the most reliable frequency of adverse reaction of drug X; there was a different distribution of respondents with and without CTE (Table 14, Fisher's exact test: $P = 0.010$).

5.3.5. Awareness of data sources

Awareness of data sources differed between respondents with and without CTE (Fisher's exact test: $P = 0.010$). In respondents with CTE, the percentages of "quite conscious", "somewhat conscious", "not really conscious" and "not at all conscious" were 18.5% (22/119), 60.5% (72/119), 18.5% (22/119) and 2.5% (3/119), respectively. On the other hand, in respondents without CTE, they were 10.4% (30/289), 48.8% (141/289), 48.8% (141/289) and 35.6% (103/289), respectively. Furthermore, regardless of the degree of CTE, over 80% of respondents prioritized the post-marketing information in the selection of general adverse reaction information (e.g., PMO studies for re-examination).

5.3.6. Risk management plan

With respect to RMP, we observed significant differences with responses to all the questions according to the degree of CTE. "Know very well" and "know well" accounted for 40.3% (48/119) among respondents with CTE, but only 21.0% (61/290) for those without. In addition, many respondents who knew the published RMP on the Web site had CTE (Table 15).

Table 12 Characteristics of medical institutions and pharmacists (n = 409)

Age	CTE (+) (n = 119) Number of respondents (%)	CTE (-) (n = 290) Number of respondents (%)	*P* value
20s	6 (5.0)	37 (12.8)	< 0.001
30s	34 (28.6)	117 (40.4)	
40s	32 (26.9)	79 (27.2)	
50s	43 (36.1)	40 (13.8)	
Over 60s	4 (3.4)	16 (5.5)	
No response	-	1 (0.3)	
Size of medical institution	**Number of respondents (%)**	**Number of respondents (%)**	
No beds	9 (7.6)	38 (13.1)	NS
Fewer than 100 beds	30 (25.2)	59 (20.3)	
100–199 beds	26 (21.8)	70 (24.1)	
200–299 beds	12 (10.1)	33 (11.4)	
300–399 beds	14 (11.8)	19 (6.6)	
400 or more beds	28 (23.5)	68 (23.5)	
No response	-	3 (1.0)	

Involved activities *)	Number of respondents (multiple selections)
CRC †)	26
Clinical trial office, IRB †) office	48
IP †) management (within medical institution)	80
CRA †)	5
Clinical trial sponsor	4
Regulatory authority	3
Others	7

*) Activities previously conducted by respondents with CTE (multiple selections)

†) IP, investigational product; IRB, institutional review board

P value, Fisher's exact test
NS, not significant
CTE, clinical trial experience

Fig. 7 Use of information materials to investigate adverse reaction information
CTE (+) (n = 119), CTE (-) (n = 290)

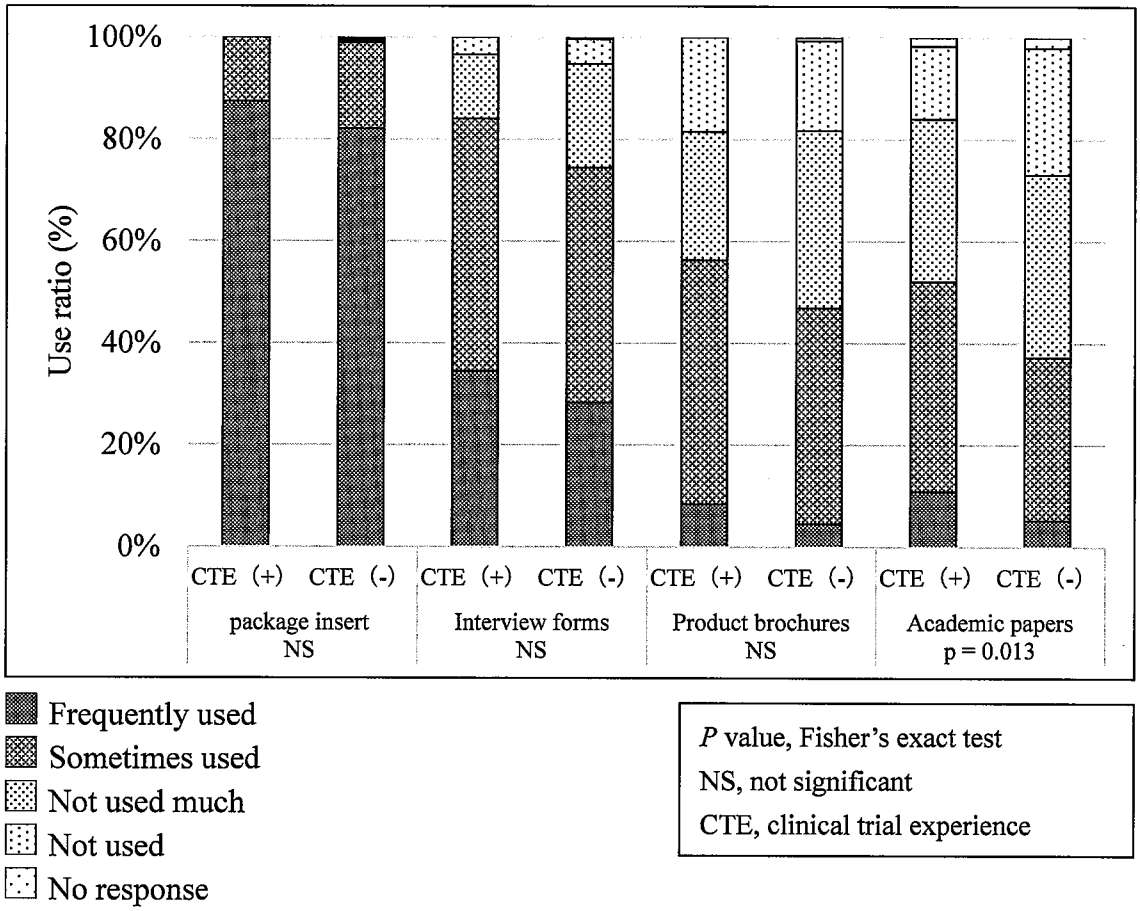


Table 13 Interpretation of the adverse reaction information in the package insert

	CTE (+) (n = 119) Number of respondents (%)	CTE (-) (n = 290) Number of respondents (%)	*P* value
Well described	4 (3.4)	2 (0.7)	0.024
Described such that practice is unaffected	29 (24.4)	103 (35.5)	
Somewhat inadequately described	71 (59.7)	141 (48.6)	
Inadequately described	7 (5.9)	18 (6.2)	
No response	8 (6.7)	26 (9.0)	
Reason (multiple selections)			
a) Frequency of adverse reactions is difficult to understand	49	112	
b) Reporting methods for adverse reactions are not uniform among pharmaceutical companies	35	74	
c) Only the frequency of adverse reactions is stated without the information of sample size	46	86	
d) Information sources for the reports are unclear	59	102	
e) Others	15	20	

P value, Fisher's exact test
NS, not significant
CTE, clinical trial experience

Table 14 Judgement of pharmacists after reviewing safety information in a mock package insert

Table 14-1 Information to be used as a frequency of adverse reaction (multiple selections)

	CTE (+) (n = 119) Number of respondents	CTE (-) (n = 290) Number of respondents
Information at the time of drug approval	48	78
Information from postmarketing studies	70	160
Information from other sources	67	157

Table 14-2 Selection of the most reliable information

	CTE (+) (n = 119) Number of respondents (%)	CTE (-) (n = 290) Number of respondents (%)	*P* value
(i) Information at the time of drug approval	23 (19.3)	25 (8.6)	0.010
(ii) Information from postmarketing studies	54 (45.4)	139 (47.9)	
(iii) Information from other sources	39 (32.8)	118 (40.7)	
Reason for (i)*)			
Frequency was the largest	6	9	
Others	20	17	
Reason for (ii)*)			
Sample size was the largest	49	129	
Others	9	20	
Reason for (iii)*)			
The results of before and after the approval are combined	33	114	
Others	7	8	
No answer	3 (2.5)	8 (2.8)	

*) Multiple selections

P value, Fisher's exact test
NS, not significant
CTE, clinical trial experience

Table 15 Drug RMP

Table 15-1 Knowledge of drug RMP

	CTE (+) (n = 119) Number of respondents (%)	CTE (-) (n = 290) Number of respondents (%)	*P* value
Know very well	5 (4.2)	2 (0.7)	<0.001
Know well	43 (36.1)	59 (20.3)	
Don't know well	37 (31.1)	144 (49.7)	
Know nothing at all	34 (28.6)	84 (29.0)	
No response	-	1 (0.3)	

Table 15-2 Knowledge of the RMP published on the Web site

	CTE (+) (n = 119) Number of respondents (%)	CTE (-) (n = 290) Number of respondents (%)	*P* value
Know	44 (37.0)	60 (20.7)	0.001
Unaware	75 (63.0)	228 (78.6)	
No response	-	2 (0.7)	

P value, Fisher's exact test
NS, not significant
CTE, clinical trial experience

5.4. Discussion

Our objective of this study was to investigate how pharmacists interpreted information of adverse reactions in the package insert and whether it was influenced by their experience of clinical trial related work. When we examined the type of information media used by the respondents regarding adverse reactions, we observed differences in the use of academic papers between those with and without CTE.

We evaluated the judgement of pharmacists on adverse reaction information in a mock package insert, which we created using the package inserts of actual drugs as a reference. The result was that, although nearly half of the respondents put a priority on the rate of adverse reactions obtained postmarketing irrespective of their CTE, the ratio of respondents who preferred the rate at the time of drug approval was high in those with CTE. If the respondent had CTE, they might also take into account the differences in research design and information-gathering environment. With respect to age, respondents with CTE were mostly in their 50s and those without such experience were predominantly in their 30s, so their age might have influenced on the differences. When we asked as a general question as to the preference of safety information on the package insert, respondents, regardless of CTE, adopted the result of postmarketing information, e.g., PMO studies for re-examination.

These two types of investigations, interventional clinical trials and observational studies, are different in nature. Thus, owing to the dissimilarities in the type or frequency

of adverse reactions in the study systems and data collection methods, we are unable to draw any conclusions from a simple consideration of the incidence values. The background of each investigation also has to be considered when making such an evaluation. However, it appeared that postmarketing information (such as PMO studies for re-examination) tended to receive priority. This was because, in postmarketing, the number of cases is large and it is closer to actual clinical conditions.

In this study, we sent a questionnaire to 599 medical institutions registered with the Tokyo Metropolitan Society of Health System Pharmacists, and got responses from pharmacists of only 166 institutions (27.7%). One limitation of this study is that the investigation area was confined to Tokyo. Over 400 pharmacists were responded to our questionnaire, but the population had age bias between with and without CTE. The respondents with CTE were in their 50's and those without it were mainly in their 20's and 30's. Generally, people obtain greater experience with various duties with the increasing age. As a result, factors such as the difference of duties experience and knowledge might have influenced.

Pharmacists should not refer simply to the information in package inserts; they should properly understand such information by recognizing the differences in the implementation environments at the time of clinical trials and postmarketing studies. For example, if there are large discrepancies in the incidence rates of adverse reactions between the time of drug approval and after re-examination, it is necessary to refer the

review reports made at both times. Further, it is important to confirm the backgrounds of the target groups used for the safety information analysis.

Chapter 6

Investigation of the Calculation Method of the Rate of Adverse Reactions Presented in the Package Inserts

6.1. Introduction

The package insert is a public document and the most basic source of medical information in Japan. It is prepared by the manufacturing company based on the Law, and guidelines for preparing the package insert were revised in 1997 [17, 18, 19].

When a new drug gets through the re-examination, usually 8 years after the marketing approval, the package insert is revised to add the safety information collected post-marketing. We understand that the revision of a package insert after the re-examination is an important milestone for the product.

Among various sources of information about drugs, many medical professionals often put priority on the package insert because of its reliability and availability. However, in the revised package insert, no distinction seems to be made between data that was collected before and after approval. Thus, the present study investigated the method of calculating the rate of adverse reactions presented in the package inserts and examined the accuracy of statements related to adverse reactions.

6.2. Method

We examined the package inserts of drug products for which re-examination was completed between January 2009 and December 2014. Then, we investigated the calculation method of frequency of adverse reactions expressed in the package insert based on the information in the package insert and interview form (IF) focusing on "serious adverse reaction" and "other adverse reaction," and classified them as follows:

(i) Rate of the adverse reactions was calculated by simply combing the results of pre-marketing clinical trials and post-marketing observational studies, and this fact is specified in the package insert,

(ii) Rate of the adverse reactions was thought to be calculated by simply combing the results of pre-marketing clinical trials and post-marketing observational studies,

(iii) Rate of the adverse reactions either in the pre-marketing clinical trials or post-marketing observational studies, whichever is greater, was selected and presented,

(iv) The calculation method was unable to determine with the available information.

The number of drug products classified into (i) to (iv) was totaled and analyzed.

6.3. Results

We identified 189 drug products, as in Chapter 2, for which the information about adverse reaction rates was available in both clinical studies for NDA and in PMS studies. The characteristics of those products are shown in Table 16. For the 189 drug products,

calculation methods of the rate of the adverse reactions, which was presented in the package insert, were as follows: (i) 75 drug products (39.7%), (ii) 72 drug products (38.1%), (iii) 15 drug products (7.9%), and (iv) 27 drug products (14.3%; Table 17). We did not observe a major difference between products by domestic companies and those by foreign-affiliated companies, and also among the types of adverse reactions classified by MedDRA SOC.

Table 16 Product characteristics

	189 drug products
Therapeutic group (ATC classification)	
A. alimentary tract and metabolism	23
B. blood and blood-forming organs	10
C. cardiovascular system	20
D. dermatologicals	6
G. genitourinary system and sex hormones	13
H. systemic hormonal preparations, excluding sex hormones and insulins	7
J. anti-infectives for systemic use	27
L. anti-neoplastic and immunomodulating agents	12
M. musculoskeletal system	6
N. nervous system	25
P. anti-parasitic products, insecticides, and repellents	2
R. respiratory system	15
S. sensory organs	7
V. various	16
Completion date of re-examination period	
January–December 2009	47
January–December 2010	47
January–December 2011	32
January–December 2012	23
January–December 2013	22
January–December 2014	18

Table 17 Calculation method of the adverse reaction rate in package inserts (189 drug products)

	Domestic companies (n = 99)	Foreign-affiliated companies (n = 90)	Total
(i)	35	40	75 (39.7%)
(ii)	38	34	72 (38.1%)
(iii)	12	3	15 (7.9%)
(iv)	14	13	27 (14.3%)

(i) Rate of the adverse reactions was calculated by simply combing the results of pre-marketing clinical trials and post-marketing observational studies, and this fact is specified in the package insert,

(ii) Rate of the adverse reactions was thought to be calculated by simply combing the results of pre-marketing clinical trials and post-marketing observational studies,

(iii) Rate of the adverse reactions either in the pre-marketing clinical trials or post-marketing observational studies, whichever is greater, was selected and presented,

(iv) The calculation method was unable to determine with the available information.

6.4. Discussion

It has been reported that safety information collected postmarketing is limited because of underreporting [10, 20]. The results of the study presented in Chapter 2 also indicate that in PMO studies for re-examination, underreporting of adverse reactions does occur, presumably more often in the known or frequent ones. Nevertheless, we found that, for nearly 80% of the products, the rate of adverse reactions were presented in the manner of simply combing the results of pre-marketing clinical trials and post-marketing observational studies. Most of these PMO studies were conducted with a target sample

size of 3,000 patients [5]. Therefore, the number of cases and numerical values related to the adverse reactions were weighted to the information derived from PMO studies, which often showed infrequent adverse reactions. This may lead to the underestimation of the safety information.

Many pharmacists utilize the package insert as a fundamental source of drug information [16]. Also, as presented in Chapter 5, it was indicated that over 80% of respondents frequently used the information in the package insert. Thus, there is a potential risk that medical personnel would take the numerical values presented in the package insert as they are without confirming the data source.

It would be difficult to present all relevant information in the package insert. However, it is important that the data should reflect the source of information; values before and after approval should be presented separately with the information of the study design. One limitation of this study is that we did not investigate all adverse reactions of the 189 drug products.

Chapter 7 Overall Discussion and Conclusion

With the aim of improving postmarketing safety measures in Japan, we conducted the present research focusing on the safety information obtained postmarketing and the system in which that information is collected.

Results of the study in Chapter 2 demonstrated that there exists underreporting of adverse reactions in PMO studies for re-examination, and the incidence rate of adverse reactions obtained in PMO studies is lower than that in clinical trials in most cases. In addition, our findings suggest that one reason for a lower adverse reaction rate in PMO studies was that the number of reports of adverse reactions that had occurred frequently prior to approval decreased postmarketing; in other words, expected and common adverse reactions were likely to be subject to underreporting in PMO studies.

In the studies in Chapter 3 and 4, it was suggested that this decrease of adverse reaction reporting in the postmarketing is partially attributed to insufficient support system within medical institutions at the stage of actual data collection in PMO studies, which brings about unclarity in the case report form preparation process in the PMO studies. Furthermore, result of the study in Chapter 5 indicated that pharmacists actually give priority to the figures of incidence rate of adverse reactions obtained in PMO studies presented in the package insert, which tend to have a lower incidence of adverse reactions. Moreover, in the study of Chapter 6, it was demonstrated that, for package inserts of most drug products investigated, the rate of adverse reactions were presented in the manner of

simply combing the results of pre-marketing clinical trials and post-marketing observational studies. Considering the nature of PMO studies revealed by our studies, this may lead to the underestimation of the safety information.

Findings in the present study suggested that, as with general observational studies, the effect of underreporting of adverse reactions cannot be eliminated in PMO studies conducted to collect information used for re-examination owing to the fragile implementation system at the medical institution as well as the company. At the same time, considering the pharmacists' attitude to the information on the package insert and the manner of calculating the incidence rate of specific adverse reactions presented in the package insert, it can be said that safety information of drug products is not properly communicated and understood.

As a solution, first, to minimize the underreporting of adverse reactions, we believe that the products for which PMO studies are conducted should be selected, and also that survey items should be restricted to important information such as unknown/ severe adverse reactions. Then we can concentrate our resources for PMO studies on selected products and safety issues. At the same time, it is important to strengthen other measures such as medical information database and adverse event report database and to proactively utilize them, which can lessen the burden on medical institutions.

In terms of utilization of the package insert, healthcare professionals including pharmacists need to change their mind. We should not be caught up only in the figures

of adverse reaction rates in the package insert, but should verify the data source of the safety information. And, for products with a large discrepancy in the incidence rates of adverse reactions between at the time of approval and upon completion of re-examination, we need to examine the re-examination report and other data sources.

In future, appropriate postmarketing safety measures should be extensively discussed by both healthcare professionals and pharmaceutical companies without being limited to such a conventional method as PMO studies.

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Appendix

Appendix 1

Questionnaire on Implementation of Postmarketing Observational Studies for Re-examination in Medical Institutions (in Japanese)

Appendix 2

Questionnaire on Postmarketing Observational Studies for Re-examination as Observed by Medical Representatives (in Japanese)

Appendix 3

Questionnaire of Hospital Pharmacists on the Use of Safety Information (in Japanese)

Appendix 4

Database for Chapter 2 and Chapter 6

Appendix 1

医療機関における使用成績調査の実施体制に関するアンケート調査

- 回答：薬剤部門の先生に回答をお願いいたします。(1 医療機関 1 回答)

Ⅰ．医療機関の基本情報

Q1． 医療機関の規模を教えてください。

① 病床なし
② 100 床未満
③ 100 床以上 200 床未満
④ 200 床以上 300 床未満
⑤ 300 床以上 400 床未満
⑥ 400 床以上

Q2． 薬剤部門における薬剤師数を教えてください

常　勤（　　）名･･･1 週間の所定労働時間が 32 時間以上の者の人数とする。

非常勤（　　）名･･･1 週間の所定労働時間が 32 時間未満の者の人数とする。

Ⅱ．使用成績調査※への関与【※製造販売後臨床試験（いわゆる第Ⅳ相試験）は除く】

Q3． 医療機関内で使用成績調査業務を主に担当している部門はどこですか？（複数回答可）

□ 医局
□ 薬剤部門
□ 看護部門
□ 事務部門
□ 治験・臨床研究部門
□ その他（　　）

Q4． 薬剤部門として使用成績調査業務に少しでも関与していますか？

① はい　(→**Q5**へ)

② いいえ (→**Q6**へ)

Q5. Q4で「はい」と回答した方にお伺いします。

Q5-1. 次の（ｉ）～（vi）の使用成績調査業務に関与していますか？
また「関与している」場合、どのような調査で関与していますか？（複数回答可）

（ｉ）医師や製薬企業担当者との相談窓口として

① 関与していない

② 関与している

- □ 原則、全ての調査
- □ 全例調査
- □ 調査期間の長い調査
- □ 契約症例数の多い調査
- □ 特別な検査等の実施があるような調査
- □ その他（　　）

（ii）契約手続き

① 関与していない

② 関与している

- □ 原則、全ての調査
- □ 全例調査
- □ 調査期間の長い調査
- □ 契約症例数の多い調査
- □ 特別な検査等の実施があるような調査
- □ その他（　　）

（iii）調査対象者の抽出作業

① 関与していない

② 関与している

- □ 原則、全ての調査
- □ 全例調査
- □ 調査期間の長い調査
- □ 契約症例数の多い調査
- □ 特別な検査等の実施があるような調査
- □ その他（　　）

（ⅳ）症例登録

① 関与していない

② 関与している

- □ 原則、全ての調査
- □ 全例調査
- □ 調査期間の長い調査
- □ 契約症例数の多い調査
- □ 特別な検査等の実施があるような調査
- □ その他（ ）

（ⅴ）調査票の記載（医学的判断を除く部分）

① 関与していない

② 関与している

- □ 原則、全ての調査
- □ 全例調査
- □ 調査期間の長い調査
- □ 契約症例数の多い調査
- □ 特別な検査等の実施があるような調査
- □ その他（ ）

（ⅵ）再調査への対応

① 関与していない

② 関与している

- □ 原則、全ての調査
- □ 全例調査
- □ 調査期間の長い調査
- □ 契約症例数の多い調査
- □ 特別な検査等の実施があるような調査
- □ その他（ ）

Q5-2. 薬剤部門として全例調査に関与した経験はありますか？

経験のある場合、通常の使用成績調査と比べてどの業務が大変でしたか？

① 関与経験なし

② 関与経験あり

どの業務が特に大変でしたか？（複数回答可）

- □ 医師や製薬企業担当者との相談窓口
- □ 契約手続き
- □ 調査対象者の抽出作業
- □ 症例登録
- □ 調査票の記載（医学的判断を除く部分）
- □ 再調査への対応
- □ その他（　　）

Q5-3. 使用成績調査業務に関与することで薬剤部門として研究費の配分等のインセンティブはありますか？

① ない

② ある

どのようなインセンティブがありますか？

→（自由記載：　　）

Q6. Q4で「いいえ」と回答した方にお伺いします。

Q6-1. 今後、薬剤部門で使用成績調査業務に関与する予定はありますか？

① ない

② ある

どのような業務に関与する予定ですか？（複数回答可）

- □ 医師や製薬企業担当者との相談窓口として
- □ 契約手続き
- □ 調査対象者の抽出作業
- □ 症例登録
- □ 調査票の記載（医学的判断を除く部分）
- □ 再調査への対応
- □ その他（　　）

Q7. 使用成績調査に関してご意見、コメント等がございましたら下記にご記入ください。

以上、ご協力ありがとうございました。

ご協力ありがとうございました。
ご協力いただいた医療機関には、後日報告書および薄謝を送付させていただく予定です。
差し支えなければ下記に送付先の住所、名称をご記入いただければ幸いです。

<報告書等の送付先住所>

送付先住所	(郵便番号：　　－　　)
送付先名称	

Appendix 2

医薬情報担当者から見た使用成績調査に関するアンケート調査

2009年4月～2013年12月（過去5年間）で、現在ご所属の会社以外も含む、これまでMRとして担当した使用成績調査に関してご回答をお願い申し上げます。なお、すべての回答は一般的な医療機関に関してのご意見としてお願い申し上げます。

また、企業や個人を特定するものではありませんので、忌憚のないご意見をよろしくお願い申し上げます。

*必須

1. **Q1. 回答者の年齢を教えてください** *

1 つだけマークしてください。

- ◯ 20歳代
- ◯ 30歳代
- ◯ 40歳代
- ◯ 50歳代
- ◯ 60歳代以上

2. **Q2. MRとしてのこれまでの経験年数を教えてください** *

1 つだけマークしてください。

- ◯ 1年未満
- ◯ 1年以上5年未満
- ◯ 5年以上10年未満
- ◯ 10年以上

3. **Q3. 2009年4月～2013年12月（過去5年間・現在の会社以外も含む）で、合計おおよそどの程度の数の使用成績調査を担当されましたか？（実施要綱数として）** *

1 つだけマークしてください。

- ◯ 担当したことがない （Q12に遷移します） 質問 *16* に進んでください。
- ◯ 1調査以上5調査未満
- ◯ 5調査以上10調査未満
- ◯ 10調査以上

4. **Q4. 2009年4月～2013年12月（過去5年間・現在の会社以外も含む）で、医療機関全般における使用成績調査の「スピード」に関して満足していますか？** *

1 つだけマークしてください。

- ◯ 満足している　　質問 *6* に進んでください。
- ◯ やや満足している　　質問 *6* に進んでください。
- ◯ やや不満である　　質問 *5* に進んでください。
- ◯ 不満である　　質問 *5* に進んでください。

Q4で「やや不満」「不満」と回答した方にお伺いします。

5. **Q4-2. 使用成績調査の「スピード」に関してどのような点が不満ですか？**

<複数回答可能>

当てはまるものをすべて選択してください。

- ☐ 治験審査委員会や倫理委員会の審査が必要な場合がある
- ☐ 契約に時間がかかる
- ☐ 対象症例がいてもなかなか症例登録されない
- ☐ 登録されても調査票がなかなか記載されず回収に時間がかかる
- ☐ 修正を依頼したときの作業に時間がかかる
- ☐ 医師のアポイントが取れない
- ☐ その他: _____

6. **Q5. 2009年4月～2013年12月（過去5年間・現在の会社以外も含む）で、医療機関全般における使用成績調査の「質」に関して満足していますか？** *

<複数回答可能>

1 つだけマークしてください。

- ◯ 満足している　　質問 *8* に進んでください。
- ◯ やや満足している　　質問 *8* に進んでください。
- ◯ やや不満である　　質問 *7* に進んでください。
- ◯ 不満である　　質問 *7* に進んでください。

Q5で「やや不満」「不満」と回答した方にお伺いします。

7. **Q5-2. 使用成績調査の「質」に関しどのような点が不満ですか？**

<複数回答可能>

当てはまるものをすべて選択してください。

- [ ] 調査票の記載内容に社内データマネジメント担当者から調査票を返却されるような不備がある
- [ ] 患者基本情報（既往歴・合併症等）に記載漏れがある
- [ ] 使用されているはずの併用薬剤・併用療法に記載漏れがある
- [ ] 発生しているはずの有害事象に記載漏れがある
- [ ] 調査票の修正依頼に応じてくれないことがある
- [ ] 全例調査にも関わらず全例登録されない
- [ ] その他: .....

8. **Q6. 2009年4月～2013年12月（過去5年間・現在の会社以外も含む）で、調査票に記載するように定められている項目について不備があり医師に追記や修正を求めた際に、記載を断られた経験はありますか？** *

1 つだけマークしてください。

- ◯ 断られた経験はない　　質問 *10* に進んでください。
- ◯ 断られた経験がある　　質問 *9* に進んでください。

Q6で「断られた経験がある」と回答した方にお伺いします。

9. **Q6-2. どのような理由で断られましたか？**

<複数回答可能>

当てはまるものをすべて選択してください。

- [ ] 忙しいため
- [ ] カルテ等が手元にないためわからないため
- [ ] 医学的に判断して記載不要と言われたため
- [ ] 主治医ではないため
- [ ] 後にして欲しいと言われそのままになってしまった
- [ ] その他: .....

10. **Q7. 2009年4月～2013年12月（過去5年間・現在の会社以外も含む）で、医師から代わりに調査票の記載するよう指示された経験はありますか？** *

1 つだけマークしてください。

- ◯ ない
- ◯ ある

11. **Q8．2009年4月～2013年12月（過去5年間・現在の会社以外も含む）で、実際に調査票の記載を手伝った経験はありますか？** *

1 つだけマークしてください。

- ◯ ない
- ◯ ある

12. **Q9．2009年4月～2013年12月（過去5年間・現在の会社以外も含む）で、回収した調査票のうち、「得たい情報が十分に記載されている」と感じる調査票はどの程度ありますか？** *

1 つだけマークしてください。

- ◯ 4分の3以上
- ◯ 半分程度
- ◯ 4分の1以下

13. **Q10．2009年4月～2013年12月（過去5年間・現在の会社以外も含む）で、いわゆるアンダーレポーティング（有害事象が発生しているにも関わらず報告がない）と感じた経験はどの程度ありますか？** *

1 つだけマークしてください。

- ◯ アンダーレポーティングの状況を強く感じた経験がある　質問 *14* に進んでください。
- ◯ アンダーレポーティングの状況をやや感じた経験がある　質問 *14* に進んでください。
- ◯ アンダーレポーティングの状況をあまり感じた経験がない　質問 *15* に進んでください。
- ◯ アンダーレポーティングの状況を殆ど感じた経験がない　質問 *15* に進んでください。

Q10でアンダーレポーティングを「強く感じた経験がある」「やや感じた経験がある」と回答をした方にお伺いします。

14. **Q10-2．どのような有害事象が発生した時に「アンダーレポーティングだ（発生しているにも関わらず報告がない）」と感じた経験がありますか？**

<複数回答可能>

当てはまるものをすべて選択してください。

- ☐ 「軽度」な有害事象が発生した時
- ☐ 「重篤」な有害事象が発生した時
- ☐ 「因果関係が不明」な有害事象が発生した時
- ☐ 「既知」の有害事象が発生した時
- ☐ 「未知」の有害事象が発生した時
- ☐ その他: .....

Q11. 一般的な使用成績調査の調査項目について、どの程度情報が記載されていると感じるかをお伺いします。

15. **Q11. 2009年4月～2013年12月（過去5年間・現在の会社以外も含む）で、調査票の各項目について、どの程度記載がされているかお答えください。** *

1 行につき *1* つだけマークしてください。

	十分に記載されている	ある程度記載されている	あまり記載されていない	殆ど記載されていない
患者背景（既往歴・合併症等）	○	○	○	○
本剤の服薬記録	○	○	○	○
併用薬・併用療法	○	○	○	○
一般的な臨床検査値	○	○	○	○
有害事象に関連した臨床検査値	○	○	○	○
一般的な有害事象	○	○	○	○
重点調査項目に該当する有害事象	○	○	○	○

16. **Q12. 今後、使用成績調査の「質の向上」のためには、どのような対策が必要と考えますか？** *

<複数回答可能>

当てはまるものをすべて選択してください。

- ☐ 対照群を設定する等の調査デザイン自体を見直す
- ☐ 医薬情報担当者ではなく、使用成績調査にも開発部門担当者が関与をする
- ☐ 直接閲覧（SDV）をおこなう（サンプリングSDVを含む）
- ☐ 重点項目のみに絞ったシンプルな調査票にする
- ☐ その他: .....

17. **Q13. 使用成績調査に関してご意見等がございましたら下記にご記入ください**

.....

.....

.....

.....

.....

Appendix 3

副作用情報に焦点を当てた添付文書の利用に関するアンケート調査

- 回答：薬剤師の先生に回答をお願いいたします。（薬剤師の先生、個人の回答）

Ⅰ．回答者の基本情報

Q1. 回答者の年齢を教えてください

① 20 歳代
② 30 歳代
③ 40 歳代
④ 50 歳代
⑤ 60 歳代以上

Q2. 現在所属の医療機関の規模を教えてください。

① 病床なし
② 100 床未満
③ 100 床以上 200 床未満
④ 200 床以上 300 床未満
⑤ 300 床以上 400 床未満
⑥ 400 床以上

Q3. 現在の所属先を含み、回答者の業務経験年数を教えてください（複数回答可）

□ 医療機関（　　年）
□ 調剤薬局（　　年）
□ ドラッグ・ストア（　　年）
□ 製薬企業（　　年）
□ その他（　　年）

Q4. 過去に治験・臨床研究の業務に携わった経験はありますか？

① ない
② ある

具体的にどのような業務をおこなったことがありますか？（複数回答可）

□ CRC 業務
□ 治験事務局、IRB 事務局業務
□ 治験薬管理業務（医療機関内）
□ CRA（モニター）業務
□ 治験依頼者の立場としての業務
□ 規制当局としての業務
□ その他（　　）

1/4

Ⅱ．添付文書の利用状況

Q5. 医薬品の副作用を調べる場合、下記の情報源をどの程度利用しますか？

（ｉ）～（ⅳ）の各情報源について利用頻度を①～④の中から選択してください。

（ｉ）添付文書

① 頻繁に利用する　② 時々利用する　③ あまり利用しない　④ ほとんど利用しない

（ⅱ）インタビューフォーム

① 頻繁に利用する　② 時々利用する　③ あまり利用しない　④ ほとんど利用しない

（ⅲ）製品のパンフレット

① 頻繁に利用する　② 時々利用する　③ あまり利用しない　④ ほとんど利用しない

（ⅳ）学術論文

① 頻繁に利用する　② 時々利用する　③ あまり利用しない　④ ほとんど利用しない

Q6. 添付文書内には「副作用」に関する情報は十分に記載されていると思いますか？

① 十分記載されている

② 実務上困らない程度には記載されている

③ 多少記載が不十分である

④ 不十分である

↓

どのような点を不十分だと感じますか？（複数回答可）

□ 副作用の発現頻度の記載が分かりにくいこと

□ 製薬会社間で副作用の記載方法が統一化されていないこと

□ 副作用の発現頻度だけで、母数の記載がないこと

□ 記載の根拠となる情報源が不明確なこと

（承認時までのデータ基にしているのか、市販後のデータを基にしているのかなど）

□ その他（　　）

★ある医薬品の添付文書に次のような記載があったと仮定します。

薬剤Xの添付文書

<副作用>

承認時までの臨床試験70例において、副作用は35例(50.0%)に認められた。主な副作用は、嘔吐17件(24.3%)等であった。

製造販売後の調査2,814例において、副作用は161例(5.7%)に認められた。主な副作用は、嘔吐40件(1.4%)等であった。

(1) 重大な副作用

--- 略 ---

(2) その他の副作用

嘔吐 (2.0%)

(但し、発現頻度は承認時までの臨床試験及び製造販売後調査の結果をあわせて算出した)

Q7. 医師より上記薬剤Xの「嘔吐」の副作用発現頻度について問い合わせがありました。

Q7-1. どの値を副作用の発現頻度として回答しますか？(複数回答可)

□ 承認時の値「17件(24.3%)」

□ 製造販売後の調査の値「嘔吐40件(1.4%)」

□ その他の副作用として記載のあった「嘔吐 (2.0%)」

Q7-2. 薬剤師としてどの値が最も信頼できる値だと考えますか？**一つだけ**選択ください。

また、その理由を教えてください。

① 承認時の値「17件(24.3%)」

その理由(複数回答可)

□ 副作用発現頻度が最も大きかったから

□ その他 (　　)

② 製造販売後の調査の値「嘔吐40件(1.4%)」

その理由(複数回答可)

□ 調査対象症例数(母数)が最も多かったから

□ その他 (　　)

③ その他の副作用として記載のあった「嘔吐 (2.0%)」

その理由(複数回答可)

□承認時までの臨床試験及び製造販売後調査の結果をあわせた結果だったから

□ その他 (　　)

Q8. 添付文書の副作用情報は、承認時（治験時）までに得られた情報と、市販後の使用成績調査等から得られた情報を基に記載されています。

Q8-1. 添付文書を参照する際、副作用が「治験から得られた情報なのか？」「市販後に得られた情報なのか？」「両者を合わせた情報なのか？」など「データソースの違い」を意識していますか？

① かなり意識している
② ある程度は意識している
③ あまり意識していない
④ まったく意識していない

Q8-2. 一般的に承認時（治験時）までに得られた情報と、市販後に追加された情報（使用成績調査等）の両方の記載があった場合、どちらの情報を優先しますか？

① 承認時までの情報
② 市販後に追加された情報（使用成績調査・自発報告等）

Q9. 医薬品リスク管理計画（RMP：Risk Management Plan）についてお伺いします。

Q9-1. 医薬品リスク管理計画（RMP：Risk Management Plan）についてご存じですか？

① よく知っている
② ある程度は知っている
③ あまり知らない
④ まったく知らない

Q9-2. PMDA（医薬品医療機器総合機構）のホームページにて個別医薬品の「医薬品リスク管理計画書」の公表が開始されましたが、そのことをご存じでしたか？

① 知っていた
② 知らなかった

Q10. 添付文書の副作用情報の記載やRMPに関してご意見等がございましたら下記にご記入ください。

以上、ご協力ありがとうございました。

Appendix 4

ATC	Re-examination mm/yyyy	Trade Name	"ARR-NDA" (%)	"ARR-PMO" (%)	(1) PMOs Only (2) Total Data	"ARR-PMI" (%)	"ARR-NDA" - "ARR-PMO" (%)	Difference of incidence rate of the most common adverse reaction in clinical studies for NDA and that in PMO studies for re-examination (%)	(1) Serious adverse reaction (2)Non-serious adverse reaction	SOC	(D) Domestically-funded enterprises (F) Foreign-affiliated companies	Chapter6 (i) (ii) (iii) (iv)
A	03/2009	Colonel Tablets	8.79	2.2	(1)	-	6.59	1.3	(2)	Skin and subcutaneous tissue disorders	(D)	(ii)
J	03/2009	Zithromac Pediatric Use Tablets	13.12	2.4	(1)	-	10.72	2.37	(2)	Gastrointestinal disorders	(F)	(ii)
A	03/2009	Starsis Tablets	17.8	7	(1)	-	10.8	6.13	(1)	Metabolism and nutrition disorders	(D)	(ii)
J	03/2009	Tarivid Tablets	3.7	2.6	(1)	-	1.1	1	(2)	Gastrointestinal disorders	(D)	(ii)
S	03/2009	Nipranol Eye Solution	8.56	3.94	(1)	-	4.62	1.58	(2)	Eye disorders	(D)	(iv)
S	03/2009	Hypadil Ophthalmic Solution	8.56	8.07	(1)	-	0.49	0.94	(2)	Eye disorders	(D)	(ii)
R	03/2009	Flutide Diskus	6.8	-	(2)	8.81	-	-	-	-	-	-
R	03/2009	Flutide Diskus	25.9	0.9	(1)	-	25	1.8	(2)	General disorders and administration site conditions	(F)	(ii)
A	03/2009	Protecadin Tablets	2.5	-	(2)	-	-	-	-	-	(D)	(ii)
A	03/2009	Polyful Tablets	8.79	2.2	(1)	-	6.59	1.3	(2)	Skin and subcutaneous tissue disorders	(F)	(ii)
D	03/2009	Bonalfa Ointment	4.2	3.3	(1)	-	0.9	0.8	(2)	General disorders and administration site conditions	(D)	(iv)
N	03/2009	Mystan Tablets	48.9	18.3	(1)	-	30.6	30.5	(2)	Nervous system disorders	(D)	(ii)
A	03/2009	Livact Granules	6.4	6.2	(1)	-	0.2	1.79	(2)	Gastrointestinal disorders	(D)	(ii)
R	03/2009	Livostin Nasal Solution	4.3	0.8	(1)	-	3.5	1.84	(2)	Nervous system disorders	(F)	(ii)
H	04/2009	Nasanyl Nasal Spray	79.9	24.8	(1)	-	55.1	35	(2)	Vascular disorders	(F)	(ii)
H	04/2009	Nasanyl Nasal Spray	56.5	15.8	(1)	-	40.7	29.25	(2)	Vascular disorders	-	-
G	06/2009	Estrane Tape	53.8	17.7	(1)	-	36.1	-0.7	(2)	Reproductive system and breast disorders	(D)	(iv)
V	06/2009	Omniscan Intravenous Injection	0.8	0.69	(1)	-	0.11	1.11	(2)	Investigations	(D)	(ii)
D	06/2009	Dovonex Ointment	6.2	4.9	(1)	-	1.3	1.9	(2)	Skin and subcutaneous tissue disorders	(F)	(ii)
V	06/2009	hCRH Injection	29.1	12.6	(1)	-	16.5	8.32	(2)	Vascular disorders	(D)	(iv)
V	06/2009	Pylonic Tablets	1.7	0.2	(1)	-	1.5	0.39	(2)	Investigations	(D)	(ii)
R	06/2009	Hokunalin Tape	12.5	3.69	(1)	-	8.81	3.28	(2)	Nervous system disorders	(F)	(iv)
R	06/2009	Hokunalin Tape	10.2	1.7	(1)	-	8.5	4.67	(2)	Skin and subcutaneous tissue disorders	-	-
V	06/2009	Ubit Tablets	0.7	0.14	(1)	-	0.56	0.27	(2)	Gastrointestinal disorders	(D)	(ii)
N	06/2009	Lullan Tablets	62.2	20.3	(1)	-	41.9	23.1	(2)	Nervous system disorders	(D)	(ii)
A	06/2009	Rocaltrol Injection	40	21.3	(1)	-	18.7	10.2	(1)	Metabolism and nutrition disorders	(D)	(ii)
D	09/2009	Oxarol Ointment	11.9	7.5	(1)	-	4.4	3.2	(2)	Skin and subcutaneous tissue disorders	(F)	(ii)
V	09/2009	Ophthagreen Intravenous Injection	1.8	0.62	(1)	-	1.18	1.75	(2)	Gastrointestinal disorders	(D)	(ii)
G	09/2009	Cabaser Tablets	42.1	19.7	(1)	-	22.4	10.4	(2)	Gastrointestinal disorders	(F)	(ii)
G	09/2009	Cabaser Tablets	24.5	8.2	(1)	-	16.3	11.6	(2)	Gastrointestinal disorders	-	-
G	09/2009	Cabaser Tablets	3.7	3.2	(1)	-	0.5	0.3	(2)	Nervous system disorders	-	-
R	09/2009	Ketas Eye drops	4.9	1.7	(1)	-	3.2	1.4	(2)	Eye disorders	(D)	(iv)
S	09/2009	Detantol Ophthalmic Solution	3.3	4.32	(1)	-	-1.02	0.3	(2)	Eye disorders	(D)	(ii)
H	09/2009	Norditropin Injection	11.9	25.6	(1)	-	-13.7	-	-	-	(F)	(iv)
B	09/2009	Bifil Dialysate	20.6	6.1	(1)	-	14.5	1.4	(2)	General disorders and administration site conditions	(F)	(iv)
V	09/2009	Visipaque Injection	7.1	1.7	(1)	-	5.4	-	-	-	(D)	(iii)
V	09/2009	Proscope Injection	4.43	2.61	(1)	-	1.82	1.04	(2)	Skin and subcutaneous tissue disorders	(D)	(ii)
V	09/2009	Levovist Injection	7.6	1.2	(1)	-	6.4	2.7	(2)	General disorders and administration site conditions	(F)	(iv)

ATC	Re-examination mm/yyyy	Trade Name	"ARR-NDA" (%)	"ARR-PMO" (%)	(1) PMOs Only (2) Total Data	"ARR-PMI" (%)	"ARR-NDA" - "ARR-PMO" (%)	Difference of incidence rate of the most common adverse reaction in clinical studies for NDA and that in PMO studies for re-examination (%)	(1) Serious adverse reaction (2)Non-serious adverse reaction	SOC	(D) Domestically-funded enterprises (F) Foreign-affiliated companies	Chapter6 (i) (ii) (iii) (iv)
V	09/2009	Levovist Injection	4.1	1.7	(1)	-	2.4	1.42	(2)	Gastrointestinal disorders	-	-
H	10/2009	Genotropin TC Injection	9.09	4.13	(1)	-	4.96	0.78	(2)	Renal and urinary disorders	(F)	(iv)
H	10/2009	Genotropin TC Injection	17.8	9.02	(1)	-	8.78	0.06	(2)	Investigations	-	-
A	12/2009	Actos Tablets	26.6	16.3	(1)	23.9	10.3	1.72	(1)	General disorders and administration site conditions	(D)	(iii)
R	12/2009	Accolate Tablets	13.9	4.8	(1)	-	9.1	2.17	(2)	Nervous system disorders	(F)	(ii)
C	12/2009	Adehl Intravenous Injection	37.2	21.4	(1)	-	15.8	10.7	(1)	Cardiac disorders	(D)	(iii)
N	12/2009	Imigran Injection	14.9	7	(1)	-	7.9	2.8	(2)	General disorders and administration site conditions	(F)	(i)
B	12/2009	Opalmon Tablets	9.1	-	(2)	8.33	-	-	-	-	(D)	(ii)
L	12/2009	Zoladex Depot	75	25.3	(1)	-	49.7	51.4	(2)	Vascular disorders	(D)	(i)
M	12/2009	Didronel Tablets	5.9	-	(2)	28.4	-	-	-	-	-	-
M	12/2009	Didronel Tablets	13.3	23	(1)	-	-9.7	2.95	(2)	Gastrointestinal disorders	(D)	(ii)
C	12/2009	Blopress Tablets	24.4	5.2	(1)	25.6	19.2	3.5	(2)	Investigations	(D)	(iii)
M	12/2009	Bonalon Tablets	19.5	12.8	(1)	28.4	6.7	1.7	(2)	Gastrointestinal disorders	(D)	(i)
V	12/2009	Magnescope Intravenous Injection	1.3	0.9	(1)	-	0.4	0.34	(2)	Skin and subcutaneous tissue disorders	(F)	(ii)
C	12/2009	Lipidil Tablets	5.57	16.12	(1)	-	-10.55	14.7	(2)	Investigations	(D)	(i)
S	12/2009	Livostin Eye drops	3.8	2.2	(1)	-	1.6	1.2	(2)	Eye disorders	(F)	(ii)
R	12/2009	Flunase for Pediatric Nasal Spray	8	0.9	(1)	-	7.1	-	-	-	(F)	(ii)
C	03/2010	Artist Tablets	6.2	4.7	(1)	-	1.5	0.8	(2)	Nervous system disorders	(D)	(ii)
C	03/2010	Artist Tablets	40.2	11.1	(1)	-	29.1	7.7	(2)	Nervous system disorders	-	-
A	03/2010	Azuloxa Tablets	0.4	0	(1)	-	0.4	0.2	(2)	General disorders and administration site conditions	(D)	(iv)
N	03/2010	Aricept Tablets	10.5	10.7	(1)	-	-0.2	0.5	(2)	Metabolism and nutrition disorders	(D)	(i)
C	03/2010	Indacin Injection	43.5	48.4	(1)	-	-4.9	-14	(2)	Investigations	(F)	(ii)
C	03/2010	Sunrythm Capsules	2.9	5.4	(1)	-	-2.5	0.2	(2)	Investigations	(D)	(i)
S	03/2010	Zepelin Ophthalmic Solution	2.41	1.17	(1)	-	1.24	1.78	(2)	Eye disorders	(D)	(ii)
A	03/2010	Cerezyme Injection	40	27.3	(1)	87.5	12.7	-	-	-	(F)	(iv)
N	03/2010	Seroquel Tablets	62.5	26.7	(1)	45.2	35.8	18.87	(2)	Psychiatric disorders	(D)	(ii)
H	03/2010	Desmopressin Spray	9.8	0.7	(1)	-	9.1	0.6	(2)	Nervous system disorders	(D)	(ii)
H	03/2010	Desmopressin Injection	44.2	31.3	(1)	-	12.9	11.5	(2)	Vascular disorders	(D)	(ii)
R	03/2010	Baynas Tablets	6.9	2.2	(1)	-	4.7	-	-	-	(D)	(iv)
C	03/2010	Lipitor Tablets	8.7	12	(1)	10.5	-3.3	0.14	(2)	Skin and subcutaneous tissue disorders	(D)	(ii)
C	03/2010	Luprac Tablets	3.43	2.88	(1)	-	0.55	0.72	(2)	Nervous system disorders	(D)	(i)
M	03/2010	Lorcam Tablets	14	5.2	(1)	-	8.8	5.2	(2)	Gastrointestinal disorders	(D)	(i)
N	06/2010	Anapeine10mg/mL Injection	42.2	22.2	(1)	-	20	17.7	(2)	Investigations	(F)	(i)
N	06/2010	Anapeine2mg/mL Injection	42.8	6	(1)	-	36.8	25.7	(2)	Investigations	(F)	(i)
A	06/2010	Amaryl Tablets	16.54	4.28	(1)	21.3	12.26	2.64	(1)	Metabolism and nutrition disorders	(F)	(i)
G	06/2010	Ange Tablets	29.42	12.18	(1)	-	17.24	13.99	(2)	Gastrointestinal disorders	(D)	(i)
A	06/2010	Urso Tablets	24.16	2.44	(1)	-	21.72	6.41	(2)	Gastrointestinal disorders	(D)	(i)
G	06/2010	Ortho 777 Tablets	42	16.9	(1)	-	25.1	17.5	(2)	Gastrointestinal disorders	(D)	(i)

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G	06/2010	Ortho M Tablets	25.4	19.2	(1)	-	6.2	7.7	(2)	Gastrointestinal disorders	(F)	(i)
N	06/2010	Oxycontin Tablets	76.5	37.51	(1)	100	38.99	47.1	(2)	Nervous system disorders	(D)	(iv)
A	06/2010	Omepral Injection	1.3	1.5	(1)	-	-0.2	0.4	(2)	Gastrointestinal disorders	(F)	(ii)
B	06/2010	Clivarine Dialysate	2.95	4.22	(1)	-	-1.27	1.1	(2)	Skin and subcutaneous tissue disorders	(F)	(i)
C	06/2010	Shinbit Injection	8.8	22.2	(1)	-	-13.4	-0.8	(1)	Cardiac disorders	(F)	(i)
G	06/2010	Synphase Tablets	34	20.4	(1)	-	13.6	8.25	(2)	Reproductive system and breast disorders	(D)	(i)
J	06/2010	Tamiflu Capsules	27.5	-	(2)	0	-	-	-	-	(F)	(i)
J	06/2010	Tamiflu Dry Syrup	50	5.7	(1)	-	44.3	22.9	(2)	Gastrointestinal disorders	(F)	(i)
G	06/2010	Triquilar Tablets	50.9	11.4	(1)	-	39.5	26	(2)	Gastrointestinal disorders	(F)	(i)
D	06/2010	Fiblast Spray	1.51	3.66	(1)	0	-2.15	0.73	(2)	General disorders and administration site conditions	(D)	(i)
A	06/2010	Fulstan Tablets	11.9	19.8	(1)	-	-7.9	-9.2	(1)	Metabolism and nutrition disorders	(D)	(i)
N	10/2010	Evoxac Capsules	30.9	23.9	(1)	-	7	3.89	(2)	Gastrointestinal disorders	(D)	(ii)
L	10/2010	Sumiferon Injection	95	89.1	(1)	100	5.9	21.6	(2)	General disorders and administration site conditions	(D)	(i)
L	10/2010	Cellcept Capsules	78.3	56.3	(1)	-	22	34.9	(2)	Investigations	(F)	(i)
C	10/2010	Diovan Tablets	21.6	7.6	(1)	-	14	1.7	(2)	Nervous system disorders	(F)	(i)
G	10/2010	Viagra Tablets	41.4	5.27	(1)	46.4	36.13	7.72	(2)	Vascular disorders	(F)	(i)
A	10/2010	Humalog N Injection	84.9	10.7	(1)	-	74.2	30.2	(2)	General disorders and administration site conditions	(F)	(iv)
A	10/2010	Humalog Injection	29	25.8	(1)	-	3.2	0.7	(1)	Metabolism and nutrition disorders	(F)	(iv)
A	10/2010	Humalog Mix Injection	4.9	15.7	(1)	-	-10.8	-14.3	(1)	Metabolism and nutrition disorders	(F)	(iv)
D	10/2010	Protopic Ointment	66.6	30.4	(1)	81	36.2	32.5	(2)	General disorders and administration site conditions	(D)	(i)
A	12/2010	Argi-U Granule Granules	12.5	8.1	(1)	-	4.4	5	(2)	Investigations	(F)	(i)
B	12/2010	Argi-U Injection Injection	0	5.6	(1)	-	-5.6	0	(2)	General disorders and administration site conditions	(F)	(iv)
L	12/2010	Intron A Injection	100	-	(2)	100	-	-	-	-	(F)	(i)
V	12/2010	Cholebine Tablets	22.6	14.9	(1)	-	7.7	8.5	(2)	Gastrointestinal disorders	(D)	(i)
A	12/2010	Novo Rapid Injection	43.8	-	(2)	65.6	-	-	-	-	(F)	(ii)
L	12/2010	Leuplin Injection	27.9	17.1	(1)	-	10.8	4.71	(2)	Skin and subcutaneous tissue disorders	(D)	(iii)
L	12/2010	Leuplin Injection	96.8	19.1	(1)	-	77.7	71.9	(2)	Vascular disorders	-	-
J	12/2010	Targocid Injection	22.9	15.3	(1)	30.4	7.6	6.9	(2)	Investigations	(F)	(i)
J	12/2010	Targocid Injection	19.4	15.4	(1)	17.6	4	6.5	(2)	Investigations	-	-
R	03/2011	Qvar Aerosol	6.6	4.7	(1)	-	1.9	1	(2)	Respiratory, thoracic and mediastinal disorders	(D)	(ii)
R	03/2011	Qvar Aerosol	11.2	2.5	(1)	-	8.7	2.6	(2)	Investigations	-	-
J	03/2011	Klaricid Tablets	3.33	0.76	(1)	-	2.57	0.65	(2)	Gastrointestinal disorders	(F)	(i)
J	03/2011	Klaricid Tablets	2.08	0.89	(1)	-	1.19	0.81	(2)	Gastrointestinal disorders	-	-
J	03/2011	Klaricid Tablets	33.3	39	(1)	-	-5.7	8.1	(1)	Hepatobiliary disorders	-	-
H	03/2011	Sandostatin Injection	90.9	40.7	(1)	26.7	50.2	20.3	(2)	General disorders and administration site conditions	(F)	(i)
H	03/2011	Sandostatin Injection	50	9.1	(1)	-	40.9	50	(2)	Hepatobiliary disorders	-	-
N	03/2011	Zomig RM	23.4	5.5	(1)	-	17.9	3.24	(2)	General disorders and administration site conditions	(F)	(i)
N	03/2011	Zomig Tablets	26.5	5.5	(1)	-	21	2.2	(2)	Gastrointestinal disorders	(F)	(i)

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N	03/2011	Zomig RM/Tablets	42	5.5	(1)	-	36.5	10.43	(2)	General disorders and administration site conditions	(F)	(i)
D	03/2011	Dalacin Lotion	8.1	1.8	(1)	2.99	6.3	-	-	-	(D)	(iv)
J	03/2011	Viramune Tablets	87.5	58.7	(1)	67.7	28.8	56	(2)	Skin and subcutaneous tissue disorders	(F)	(ii)
G	03/2011	Marvelon Tablets	25.5	24.1	(1)	-	1.4	6.2	(2)	Gastrointestinal disorders	(F)	(i)
N	03/2011	Myocalm Oral solution	36.2	34.7	(1)	-	1.5	7.3	(2)	Gastrointestinal disorders	(F)	(iii)
V	03/2011	Radicut Injection	4.57	11.1	(1)	10.3	-6.53	-1.32	(1)	Hepatobiliary disorders	(D)	(i)
M	07/2011	Actonel2.5mg Tablets	32.2	12.6	(1)	31.5	19.6	2.7	(2)	Gastrointestinal disorders	(D)	(iii)
R	07/2011	Alesion Dry Syrup	7.51	0.84	(1)	-	6.67	2.81	(2)	Nervous system disorders	(F)	(ii)
J	07/2011	Invirase Tablets	45	48	(1)	-	-3	11.06	(2)	Investigations	(F)	(i)
B	07/2011	Berinert Intravenous Injection	0	2.6	(1)	-	-2.6	0	(2)	General disorders and administration site conditions	(F)	(iv)
R	09/2011	Allegra Tablets	16.1	1.6	(1)	8.2	14.5	-	-	-	(F)	(i)
J	09/2011	Epivir Tablets	71.4	42.7	(1)	-	28.7	33.18	(2)	Blood and lymphatic system disorders	(F)	(ii)
A	09/2011	Empecid Troche	8	-	(2)	0	-	-	-	-	(F)	(iv)
J	09/2011	Combivir Combination Tablets	71.4	50.1	(1)	-	21.3	-	-	-	(F)	(ii)
C	09/2011	Zione Injection	16.7	10.3	(1)	-	6.4	4	(2)	General disorders and administration site conditions	(D)	(i)
L	09/2011	Sumiferon Injection	83.3	-	(2)	91.1	-	-	-	-	-	-
V	09/2011	Bothdel Oral solution	17.8	0.9	(1)	-	16.9	7.3	(2)	Gastrointestinal disorders	(D)	(iv)
V	09/2011	Magsent Injection	71.8	21.3	(1)	-	50.5	45.6	(2)	General disorders and administration site conditions	(D)	(i)
N	09/2011	Relpax Tablets	28.4	7.09	(1)	-	21.31	3.39	(2)	Nervous system disorders	(F)	(i)
A	12/2011	Ambisome Intravenous Injection	92.4	59.4	(1)	92.3	33	18.7	(2)	Gastrointestinal disorders	(D)	(i)
L	12/2011	Iressa Tablets	95.5	56.2	(1)	-	39.3	47.7	(2)	Skin and subcutaneous tissue disorders	(F)	(i)
J	12/2011	Omegacin Intravenous Injection	2.7	12.2	(1)	-	-9.5	0.53	(2)	Skin and subcutaneous tissue disorders	(D)	(ii)
J	12/2011	Zerit Capsules	63.8	56.4	(1)	-	7.4	20.5	(2)	Investigations	(F)	(ii)
J	12/2011	Norvir Oral solution	73.7	48.7	(1)	-	25	26.2	(2)	Gastrointestinal disorders	(F)	(i)
C	12/2011	Blopress Tablets	48.2	11.6	(1)	-	36.6	9.84	(2)	Investigations	-	-
J	12/2011	Relenza Inhalation	17.2	1.3	(1)	0	15.9	2.06	(2)	Investigations	(F)	(ii)
J	12/2011	Relenza Inhalation	2.1	1.7	(1)	-	0.4	0.56	(2)	Gastrointestinal disorders	-	-
L	12/2011	Remicade Intravenous Injection	87.3	24.6	(1)	-	62.7	23.2	(2)	Respiratory, thoracic and mediastinal disorders	(D)	(i)
B	12/2011	Flolan Injection	77.1	36.3	(1)	-	40.8	33.4	(2)	Nervous system disorders	(F)	(i)
B	03/2012	Activacin Injection	48.5	21.7	(1)	41.4	26.8	17	(1)	Nervous system disorders	(D)	(ii)
J	03/2012	Epzicom Combination Tablets	68.8	32.4	(1)	-	36.4	14.98	(2)	Nervous system disorders	(F)	(ii)
N	03/2012	Oxinorm Powder	63	21	(1)	-	42	11	(2)	Gastrointestinal disorders	(D)	(iv)
C	03/2012	Sotacor Tablets	21.2	11.5	(1)	-	9.7	5.2	(1)	Cardiac disorders	(F)	(ii)
J	03/2012	Pasil Intravenous Injection	3.4	8.33	(1)	-	-4.93	0.47	(2)	Gastrointestinal disorders	(D)	(ii)
J	03/2012	Pasil Intravenous Injection	16.9	12.96	(1)	-	3.94	0.47	(2)	Gastrointestinal disorders	-	-
M	03/2012	Fosamac Tablets	13.1	7.8	(1)	-	5.3	1.3	(2)	Gastrointestinal disorders	(F)	(i)
V	03/2012	Phosblock Tablets	66.8	-	(2)	50.6	-	-	-	-	(D)	(i)
B	03/2012	Pletaal Tablets	8.7	6.3	(1)	-	2.4	-0.2	(2)	Nervous system disorders	(D)	(iii)

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B	03/2012	Pletaal Tablets	26.3	22.2	(1)	52.5	4.1	8.3	(2)	Nervous system disorders	-	-
C	03/2012	Brevibloc Injection	18.9	2.5	(1)	-	16.4	-31.5	(1)	Vascular disorders	(D)	(iii)
C	03/2012	Brevibloc Injection	57.5	3.9	(1)	-	53.6	46.7	(1)	Vascular disorders	-	-
S	03/2012	Mikelan Ophthalmic Solution	12.2	-	(2)	3.2	-	-	-	-	(D)	(iii)
N	03/2012	Rilutek Tablets	82	28.4	(1)	68.8	53.6	-	-	-	(F)	(i)
J	06/2012	Itrizole Oral solution	35.2	10.7	(1)	-	24.5	6.8	(2)	Gastrointestinal disorders	(F)	(ii)
J	06/2012	Sword Tablets	4.46	1.01	(1)	-	3.45	2.21	(2)	Investigations	(D)	(i)
V	06/2012	Ceredist Tablets	9.22	8.6	(1)	-	0.62	1.59	(2)	Gastrointestinal disorders	(D)	(iii)
V	06/2012	Ceredist Tablets	9.22	4.8	(1)	-	4.42	1.59	(2)	Gastrointestinal disorders	-	-
L	06/2012	IA-call Injection	99	41.2	(1)	-	57.8	75.5	(2)	Metabolism and nutrition disorders	(D)	(ii)
G	06/2012	L' estrogel Gel	59.4	6.3	(1)	-	53.1	34.1	(2)	Reproductive system and breast disorders	(D)	(i)
G	10/2012	Divigel Ointment	55	4.9	(1)	-	50.1	23.4	(2)	Reproductive system and breast disorders	(D)	(i)
H	10/2012	Humatrope Injection	6.9	5.3	(1)	-	1.6	3.43	(2)	General disorders and administration site conditions	(F)	(ii)
H	10/2012	Humatrope Injection	5.5	9.3	(1)	-	-3.8	1.2	(2)	Musculoskeletal and connective tissue disorders	-	-
H	10/2012	Humatrope Injection	54.3	16.5	(1)	-	37.8	21.7	(2)	Investigations	-	-
H	10/2012	Humatrope Injection	59	12.9	(1)	-	46.1	18.2	(2)	Musculoskeletal and connective tissue disorders	-	-
P	10/2012	Mephaquin Tablets	42.9	35.2	(1)	-	7.7	4.1	(2)	Gastrointestinal disorders	(D)	(iv)
C	12/2012	Calblock Tablets	14.4	3.5	(1)	-	10.9	2.37	(2)	Investigations	(D)	(ii)
J	12/2012	Zyvox Tablets	55	16.8	(1)	-	38.2	8.3	(1)	Blood and lymphatic system disorders	(F)	(ii)
B	12/2012	Domer Tablets	60	23.4	(1)	-	36.6	16.4	(2)	Nervous system disorders	(D)	(i)
J	12/2012	Valtrex Tablets	16.1	3.3	(1)	-	12.8	2.3	(2)	Nervous system disorders	(F)	(ii)
R	04/2013	Allegra OD Tablets	8.2	0.69	(1)	0	7.51	3.02	(2)	Nervous system disorders	(F)	(i)
L	04/2013	Imunomax-γ Injection	94.8	74.3	(1)	-	20.5	27.9	(2)	General disorders and administration site conditions	(D)	(ii)
L	04/2013	Imunomax-γ Injection	52	37	(1)	-	15	21	(2)	General disorders and administration site conditions	-	-
J	04/2013	Aimmugen Injection	6	1	(1)	-	5	2.5	(2)	General disorders and administration site conditions	(D)	(iv)
B	04/2013	Epogin Injection	9.9	19	(1)	-	-9.1	-	-	-	(F)	(i)
L	04/2013	Zetbulin Intravenous Injection	86	78.7	(1)	-	7.3	10.7	(2)	General disorders and administration site conditions	(D)	(ii)
A	04/2013	Pariet Tablets	12.1	-	(2)	27.6	-	-	-	-	(D)	(i)
N	04/2013	Maxalt Tablets	18.6	4.22	(1)	-	14.38	6.75	(2)	Nervous system disorders	(D)	(i)
J	04/2013	Meropen Injection	44.2	14.3	(1)	-	29.9	24.3	(2)	Investigations	(D)	(i)
J	04/2013	Meropen Injection	16.6	10.8	(1)	-	5.8	4.6	(2)	Investigations	-	-
C	04/2013	Livalo Tablets	22.2	5.4	(1)	29.3	16.8	5.08	(2)	Investigations	(D)	(i)
N	06/2013	Concerta Tablets	80.6	38.2	(1)	-	42.4	14.2	(2)	Metabolism and nutrition disorders	(F)	(iv)
N	06/2013	Salagen Tablets	57.9	31.8	(1)	-	26.1	15.2	(2)	Skin and subcutaneous tissue disorders	(D)	(i)
N	06/2013	Salagen Tablets	76.8	37.9	(1)	-	38.9	19.7	(2)	Skin and subcutaneous tissue disorders	-	-
C	06/2013	Nu-lotan Tablets	10	4.3	(1)	-	5.7	1.6	(2)	Nervous system disorders	(F)	(i)
C	06/2013	Nu-lotan Tablets	17.2	5.1	(1)	-	12.1	4.11	(2)	Nervous system disorders	-	-
J	06/2013	Funguard Injection	31.3	28.5	(1)	-	2.8	3	(2)	Vascular disorders	(D)	(i)

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J	06/2013	Funguard Injection	30	22	(1)	-	8	5	(1)	Immune system disorders	-	-
L	06/2013	Betaferon Subcutaneus Injection	91.5	66.9	(1)	-	24.6	46.1	(2)	General disorders and administration site conditions	(F)	(ii)
J	09/2013	Copegus Tablets	100	-	(2)	100	-	-	-	-	(F)	(ii)
J	09/2013	Prodif Intravenous Injection	22.5	5.31	(1)	-	17.19	3.1	(2)	Skin and subcutaneous tissue disorders	(F)	(i)
L	09/2013	Pegasys Subcutaneus Injection	99.6	-	(2)	100	-	-	-	-	(F)	(ii)
C	09/2013	Onoact Injection	15.6	7.2	(1)	-	8.4	7.2	(1)	Vascular disorders	(D)	(ii)
C	09/2013	Onoact Injection	27.6	8.9	(1)	-	18.7	9.8	(1)	Vascular disorders	-	-
N	12/2013	Paxil Tablets	68.5	22.4	(1)	63.7	46.1	17.6	(2)	Nervous system disorders	(F)	(i)
C	12/2013	Olmetec Tablets	11.4	3.9	(1)	-	7.5	2.59	(2)	Nervous system disorders	(D)	(ii)
J	12/2013	Zithromac Tablets	50	18.61	(1)	-	31.39	-	-	-	(F)	(iii)
R	12/2013	Singulair Tablets	8.8	2.4	(1)	0	6.4	-	-	-	(F)	(i)
N	12/2013	Bi sifrol Tablets	71.8	-	(2)	44.8	-	-	-	-	(F)	(ii)
M	03/2014	Actonel17.5mg Tablets	24.9	7.1	(1)	-	17.8	4	(2)	Gastrointestinal disorders	(D)	(i)
A	03/2014	Irribow Tablets	28.1	-	(2)	27.7	-	-	-	-	(D)	(i)
R	03/2014	Claritin Dry Syrup	10.5	1.6	(1)	-	8.9	5.7	(2)	Nervous system disorders	(F)	(ii)
H	03/2014	Genotropin TC Injection	63	12.8	(1)	-	50.2	15.07	(2)	General disorders and administration site conditions	-	-
R	03/2014	Thiola Tablets	21.2	6	(1)	-	15.2	12.1	(2)	Gastrointestinal disorders	(F)	(ii)
V	03/2014	GHRP Injection	32.6	0	(1)	-	32.6	15.4	(2)	General disorders and administration site conditions	(D)	(i)
J	03/2014	Synercid Injection	46.2	10	(1)	-	36.2	33.4	(2)	General disorders and administration site conditions	(F)	(iii)
N	03/2014	Trerief Tablets	46.7	11.4	(1)	60.7	35.3	7.5	(2)	Nervous system disorders	(D)	(ii)
N	03/2014	Precedex Intravenous Injection	36	14.8	(1)	14.3	21.2	8.3	(1)	Vascular disorders	(D)	(ii)
C	06/2014	Adenoscan Injection	61.7	15.9	(1)	-	45.8	24.4	(2)	Gastrointestinal disorders	(D)	(ii)
R	06/2014	Cleanal Tablets	7.7	1.5	(1)	-	6.2	-	-	-	(D)	(iv)
N	06/2014	Depromel Tablets	43	20.4	(1)	78.9	22.6	4.5	(2)	Gastrointestinal disorders	(D)	(ii)
N	06/2014	Depromel Tablets	82.6	18.2	(1)	78.9	64.4	39.2	(2)	Nervous system disorders	-	-
C	06/2014	Preminent Tablets	9.6	9	(1)	-	0.6	0.88	(2)	Nervous system disorders	(F)	(i)
G	06/2014	Mirena Intrauterine releasing	88.8	56	(1)	-	32.8	30.3	(2)	Reproductive system and breast disorders	(F)	(i)
A	06/2014	Lantus Injection	11.1	2.3	(1)	-	8.8	2.4	(2)	Eye disorders	(F)	(i)
G	06/2014	Levitra Tablets	28.15	2.5	(1)	-	25.65	14.41	(2)	Vascular disorders	(F)	(i)
S	09/2014	Ozex Ophthalmic Solution	2.42	0.49	(1)	-	1.93	0.93	(2)	Eye disorders	(D)	(iii)
P	09/2014	Stromectol Tablets	2	6.1	(1)	-	-4.1	-	-	-	(F)	(ii)
N	09/2014	Loxonin pap	8.5	2.9	(1)	-	5.6	1.6	(2)	Skin and subcutaneous tissue disorders	(D)	(iii)