Research for Effective Pharmacovigilance Activities based on Comparisons of Risk Management Plan between Japan and EU

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Abstract

In recent years, new drugs have increasingly been developed globally, and the number of new drugs that are approved simultaneously in Japan, the US, and Europe has been increasing; it has brought about the situation that less safety information on Japanese patients than before is available for use at the time of the Japanese market launch. Postmarketing safety measures for new drugs in Japan are for this reason becoming more important. Against this background, the risk management plan (RMP) system was introduced in Japan in 2013, to enhance the planning and implementation of pharmacovigilance and risk-minimization activities. This system often requires additional pharmacovigilance activities.

This study was conducted to discuss effective implementation of pharmacovigilance activities aimed at further improving the safety measures implemented for new drugs in Japan. We investigated 49 new active substances approved in 2013 and 2014 in Europe, where the RMP system was introduced earlier than in Japan, for their safety concerns and pharmacovigilance activities of RMPs as well as the main reasons why these pharmacovigilance activities were selected. We also comparatively investigated the safety concerns and pharmacovigilance activities of 20 products that have recently been approved both in Japan and Europe. In Europe, various types of additional pharmacovigilance activities were planned, and whether or not they are implemented depended on the product characteristics and their related safety concerns. The types of safety concerns for which non-clinical studies were most frequently conducted were teratogenicity and drug interactions, those for which clinical trials were conducted were long term use, and those for which non-interventional studies were conducted were medication errors and off-label use. Safety concerns for which additional pharmacovigilance activities were conducted accounted for around 40% of all safety concerns, and for around 30% of all known (identified) safety concerns. In Japan, in contrast, they accounted for 80% of all safety concerns, and 90% of known safety concerns. The only additional pharmacovigilance activities in Japan were postmarketing surveillance studies and postmarketing clinical studies.

In light of these findings, we believe that it would be possible to collect safety information from a wide range of perspectives in Japan as well by researching the safety

concerns that have been identified for an individual drug product through (1) identifying safety concerns by predicting how the drug product will be used in the clinical setting, irrespective of the risks of "specific adverse events," (2) evaluating whether or not additional pharmacovigilance activities are really needed, and not conducting additional pharmacovigilance activities for safety concerns for which additional information can be collected through only routine pharmacovigilance activities, and (3) positioning and conducting nonclinical studies and/or various types of observational studies as additional pharmacovigilance activities. Furthermore, because medical institutions and companies do not have unlimited resources, we believe that the focus of collecting information by conducting additional pharmacovigilance activities needs to be on the detection of unknown risks and the specific conditions of use rather than on collecting additional information about known adverse events.

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Abbreviations

ATC code:	Active substance, anatomical Therapeutic Chemical code
EMA:	European Medicines Agency
ENCePP:	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPAR:	European Public Assessment Report
MedDRA:	Medical Dictionary for Regulatory Activities
PMDA:	Pharmaceuticals Medical Devices Agency
RMP:	Risk Management Plan
SpAE:	Specific Adverse Event

1. Introduction

New drugs used to be approved in Japan after they had already been approved in the West. This was because new drugs that had been discovered in the West were developed first in the West, with clinical studies being initiated and the new drug application being submitted in Japan later[1, 2]. On the other hand, one side benefit of this was that when a drug was launched in Japan, safety information that had already been collected in the West was available to provide more complete information, such as precautions, in the package insert. It was shown, in fact, that fewer safety measures were implemented postmarketing in Japan for new drugs whose market launches trailed those in the West[3]. In recent years, however, new drugs have increasingly been developed globally, and the number of new drugs that are approved simultaneously in Japan, the US, and Europe has therefore been increasing, which has brought about the situation that less safety information than before is available for use at the time of the Japanese market launch. Postmarketing safety measures for new drugs in Japan are for this reason becoming more important.

For a drug product to be used properly and safely in clinical practice, companies and regulatory authorities must provide medical professionals and patients with enough information about the efficacy and safety of the drug product. However, at the time of the market launch of a drug product, only a limited amount of safety information is available. This is because the clinical studies conducted to file a marketing approval application (1) include only a small number of patients compared to the size of the target population; (2) restrict the age, sex, and/or ethnicities of the patients who are enrolled in the clinical studies, the concomitant therapies and drugs that can be used, and also the way in which the drug product can be used; and (3) use short durations of exposure and follow-up[4]. A considerable amount of new safety information is generated postmarketing when a drug product is used in a large number of patients by a large number of physicians in the clinical setting. Therefore, both the company and the regulatory authorities must collect safety and efficacy information postmarketing as well, and assess the risk-benefit balance and implement any required measures based on this new information, and also provide medical professionals in the clinical setting with this information.

As a tool for accomplishing this objective, the risk management plan (RMP) system was introduced in Europe in 2005 and in Japan in 2013, and RMPs are now mandatory for all newly approved drugs. A unique RMP is prepared for each drug product. Companies must submit a draft RMP when filing for approval of a drug product, and, prior to the market launch, the RMP is finalized through discussions with the regulatory authorities. After the market launch, companies must revise the RMP, if necessary, based on assessments of safety information obtained, and continue to clarify and control important risks.

RMPs have three stages: (1) characterization of the safety profile of the drug product, (2) planning of pharmacovigilance activities to increase knowledge about the safety profile of the product, and (3) planning of risk-minimization activities and assessment of the effectiveness of these activities[4]. In stage (1), 'Characterization of the safety profile', all safety concerns are described in detail and classified as 'important identified risks,' 'important potential risks,' or 'missing information'[4]. Identified risks are risks for which a causal relationship to the drug product has been adequately demonstrated in nonclinical studies and that have been confirmed in clinical studies as well, potential risks are risks for which findings have been obtained in nonclinical studies suggesting that the events could be the risks of the drug product but which have not been confirmed in clinical studies, and missing information is information that is needed in the clinical setting but that needs to be obtained from patient populations that were excluded from the clinical studies[5]. Therefore, risks that are classified as potential risks at market launch are sometimes reclassified as identified risks depending on the safety information that is subsequently obtained.

Two types of pharmacovigilance activities are planned and conducted to address these safety concerns: routine activities (such as spontaneous reporting of adverse events) and additional activities (such as interventional/observational studies). Routine pharmacovigilance activities are conducted for all safety concerns. The drug product characteristics and the nature of the safety concerns will dictate whether or not additional pharmacovigilance activities are conducted (Figure 1)[4, 5]. In Europe, additional pharmacovigilance activities contain non-clinical studies, clinical trials, or non-interventional studies (observational studies), in accordance with the Guideline on

Good Pharmacovigilance Practices[4]. In Japan, additional pharmacovigilance activities have, since before the introduction of the RMP system, been classified as "postmarketing surveillance studies" or "postmarketing clinical studies," in accordance with the Japanese GPSP Ministerial Ordinance. While postmarketing surveillance studies are conducted for almost all new drugs, postmarketing clinical studies are rarely conducted.

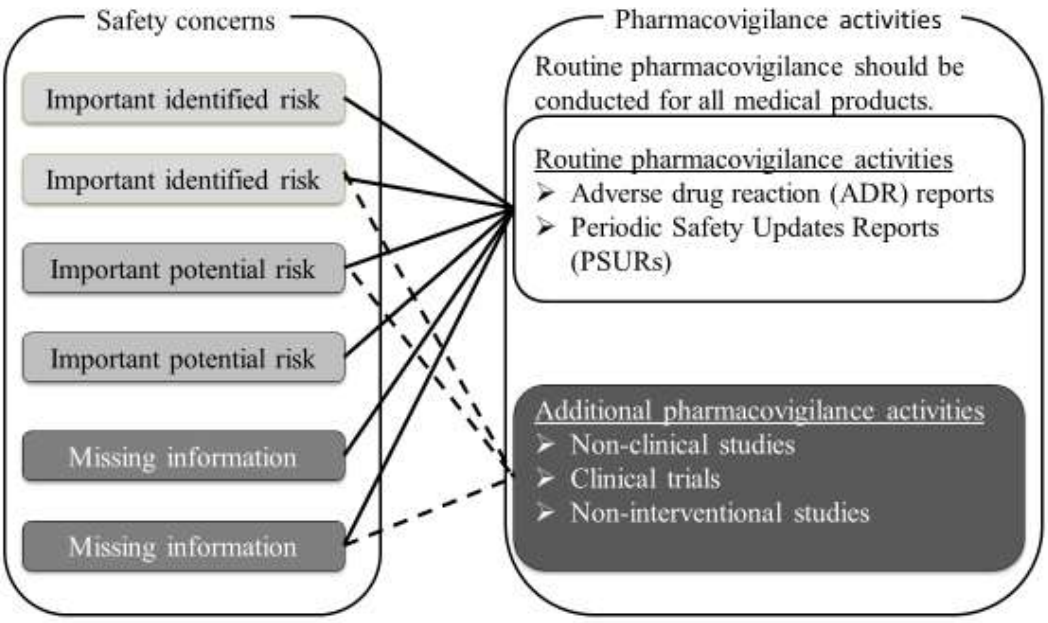

Figure 1: Flow diagram of safety concerns and pharmacovigilance activities in the Risk Management Plan

The research that has been conducted to date[7-11] has identified several problems with the postmarketing surveillance studies that were being conducted in Japan prior to the introduction of the RMP system, such as the complexity of the case report forms and the large number of parameters that needed to be filled out, even though the people primarily responsible for conducting these investigations at medical institutions were physicians who were already extremely busy. These postmarketing surveillance studies therefore placed a considerable burden on these physicians. Another problem was that

the postmarketing surveillance studies did not have clear objectives, and the information that was obtained was therefore not very helpful for formulating safety measures. In other words, even though a tremendous amount of time and expense was being spent by physicians and others at medical institutions completing the case report forms and by companies collecting the case report forms and tabulating and assessing the information obtained, this information was not being utilized. Furthermore, research on the RMPs that have been prepared since the RMP system was introduced[12, 13] has shown that the additional pharmacovigilance activities still depend to a large extent on traditional postmarketing surveillance studies, and that the aforementioned problems have therefore not yet been resolved.

In Japan, RMPs must identify various safety concerns of a new drug, and the information that is needed to assess these safety concerns must be collected and analyzed in a timely fashion. However, no research has been conducted into what kinds of pharmacovigilance activities should be formulated for what specific types of safety concerns. In this study, therefore, we investigated the safety concerns and pharmacovigilance activities of RMPs in Europe, where the RMP system was introduced earlier than in Japan, as well as the main reasons why these pharmacovigilance activities were selected, and also comparatively investigated the safety concerns and pharmacovigilance activities of products that have recently been approved both in Japan and Europe. Based on the results obtained, we discuss the effective implementation of pharmacovigilance activities aimed at further improving the safety measures that are implemented for new drugs in Japan.

2. Part I: Characterization of the Recent Postmarketing Safety Measures in Europe Focusing on Additional Pharmacovigilance Activities

2.1. Part I: Objectives

In 2005, the European Medicines Agency introduced a risk-management system as a means of planning and implementing pharmacovigilance and risk-minimization activities for new drugs in the EU. This has proven to be an effective means of gaining information on safety and of minimizing risks for new drugs postmarketing[14, 15]. Since the issuance of the pharmacovigilance legislation in 2012, pharmacovigilance activities appropriate to the risks have been proactively implemented across the entire life-cycle of drug products[16].

A unique risk-management plan (RMP) is created for each drug product. Companies submit an RMP when filing for approval of a drug product, and the submitted RMP is assessed by the Pharmacovigilance Risk Assessment Committee (PRAC) then approved by the Committee for Medicinal Products for Human Use (CHMP). RMPs are now delivered for all new centrally authorized products[17]. Since March 2014, the EMA has published summaries of the RMPs for all products.

To plan pharmacovigilance activities from which companies and regulatory authorities can obtain practical information to enable the evaluation of the benefit–risk balance of drug products, it is important to understand what pharmacovigilance activities have been implemented for comparable drugs or safety concerns as well as the product characteristics and the pathology of and treatments for the targeted disease. Research has been conducted on the contents of additional risk-minimization activities at approval[18], changes in safety concerns after the acquisition of new information[14], and additional post-approval pharmacovigilance activities implemented[19]. However, no research has comprehensively investigated the additional pharmacovigilance activities for new drug products and associations between these activities and safety concerns since the pharmacovigilance legislation took effect.

In Part I, we investigated the characteristics of the safety concerns for products approved since the pharmacovigilance legislation took effect in the EU and associations between these safety concerns and pharmacovigilance activities, with the aim of

enhancing the planning and implementation of future pharmacovigilance activities in Japan.

2.2. Part I: Methods

2.2.1. Data Source and Data Extraction

We studied 49 of the 67 new active substances approved between January 2013 and December 2014 in the EU for which the European Public Assessment Reports (EPARs) had been posted on the EMA website[20] (we excluded one withdrawn product, one suspended product, eight combination drug products, and eight products for which detailed pharmacovigilance plan information was not included in the EPAR).

For each of the 49 drug products, we extracted the ‘Summary of safety concerns’ and ‘Pharmacovigilance plans’ subsections from the RMP section of the EPAR posted as an initial marketing authorization document on the EMA website[20]. On 1 January 2016, we also downloaded the background information for each of the drug products (active substance, anatomical therapeutic chemical [ATC] code, status, authorization date, and approval details) from the same website and summarized the product characteristic information (product type, therapeutic group, approval details, and the region of first approval worldwide). We confirmed which parts of the pharmacovigilance plans constituted additional pharmacovigilance activities based on the information available in the EPARs and on the clinicaltrials.gov[21] and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) websites[22].

2.2.2. Data Classification

2.2.2.1. Safety Concerns

Safety concerns are classified in the RMP as important identified risks, important potential risks, or missing information. We divided all safety concerns into either ‘specific adverse event’ (SpAE) or ‘context of use.’ We further categorized SpAEs according to Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 system organ classes (SOCs) and categorized the contexts of use into the following categories: use in specific age groups, use during pregnancy/lactation, use in patients with specific comorbidities, use with concomitant medications (including interactions),

abuse/misuse/medication errors, long-term use, use in unstudied ethnicities, and off-label use. Some safety concerns were classified as both SpAE and context of use.

2.2.2.2. Additional Pharmacovigilance Activities

The 'pharmacovigilance plans' subsections listed the study/activity type, title and category, objectives, safety concerns addressed, status, and date for submission of interim or final reports for the additional pharmacovigilance activities. We extracted this information and linked the safety concerns with the additional pharmacovigilance activities based on the information pertaining to the 'safety concerns addressed.'

We categorized all additional pharmacovigilance activities as non-clinical studies (e.g., pharmacology studies, general toxicity studies, toxicokinetic and nonclinical pharmacokinetic studies, reproduction toxicity studies, genotoxicity studies), clinical trials (e.g., human interventional studies such as human pharmacology studies, therapeutic confirmatory studies, and clinical studies in special populations), or non-interventional (observational) studies (e.g., cohort studies, drug-utilization studies). When we could not classify the type of additional pharmacovigilance activity based solely on information from the EPAR, we consulted the clinicaltrials.gov[21] and ENCePP websites[22]. In addition, we further categorized the objectives of clinical trials as either efficacy and safety, safety, or pharmacokinetics and the status of each pharmacovigilance activity as either planned/being planned, ongoing, or completed.

We analyzed associations between the product characteristics and safety concerns, between the product characteristics and additional pharmacovigilance activities, and between safety concerns and additional pharmacovigilance activities.

2.3. Part I: Results

2.3.1. Product Characteristics

Table 2-1 shows the characteristics of the 49 drug products (see also the Appendix 1 for more in-depth details) based on the product type. The most common therapeutic group was 'L' (antineoplastic and immunomodulating agents), comprising 12 antineoplastic agents, three immunosuppressants, one endocrine therapy drug, and one immunostimulant. The next most common was 'A' (alimentary tract and metabolism

Table 2-1 Summary of product characteristics (Part I)

		Small molecules (n = 34)	**Biologicals (n = 15)**	**Total (n = 49)**
Therapeutic group, n (%)	L: Antineoplastic and immunomodulating agents	11 (22.4)	6 (12.2)	17 (34.7)
	A: Alimentary tract and metabolism	4 (8.2)	5 (10.2)	9 (18.4)
	J: Antiinfectives for systemic use	6 (12.2)	0	6 (12.2)
	V: Various	5 (10.2)	0	5 (10.2)
	N: Nervous system	3 (6.1)	0	3 (6.1)
	Other groups	5 (10.2)	4 (8.2)	9 (18.4)
Approval details, n (%)	Orphan indication	9 (18.4)	4 (8.2)	13 (26.5)
	Conditional approval	5 (10.2)	0	5 (10.2)
	Exceptional Circumstance	1 (2.0)	0	1 (2.0)
First approval worldwide, n (%)	Europe	6 (12.2)	3 (6.1)	9 (18.4)
	United States	22 (44.9)	10 (20.4)	32 (65.3)
	Japan	3 (6.1)	1 (2.0)	4 (8.2)
	Rest of the world	3 (6.1)	1 (2.0)	4 (8.2)

drugs), comprising seven diabetes drugs, one constipation drug, and one 'other' drug. In total, 13 of the drugs had orphan indications and five had conditional approval. The most common region of first approval was the USA.

2.3.2. Safety Concerns

In total, 813 safety concerns were recorded for the 49 products studied, with a median of 17 per product (interquartile range [IQR] 13.0–21.0). There was no difference in median number of safety concerns when broken down by product type: small-molecule drugs 17.0 (IQR 13.0–20.8); biologicals 17.0 (IQR 13.0–20.5). When based on approval status, the median number was 19.0 (IQR 17.0–22.0) for orphan drugs, 17.0 (IQR 11.8–20.0) for non-orphan drugs, 20.0 (IQR 19.0–22.0) for drugs with conditional approval, and 17.0 (IQR 11.8–20.3) for those without conditional approval. Figure 2-1 shows the number of safety concerns per product based on the key therapeutic groups. Drugs classified in therapeutic groups L and N had the most safety concerns.

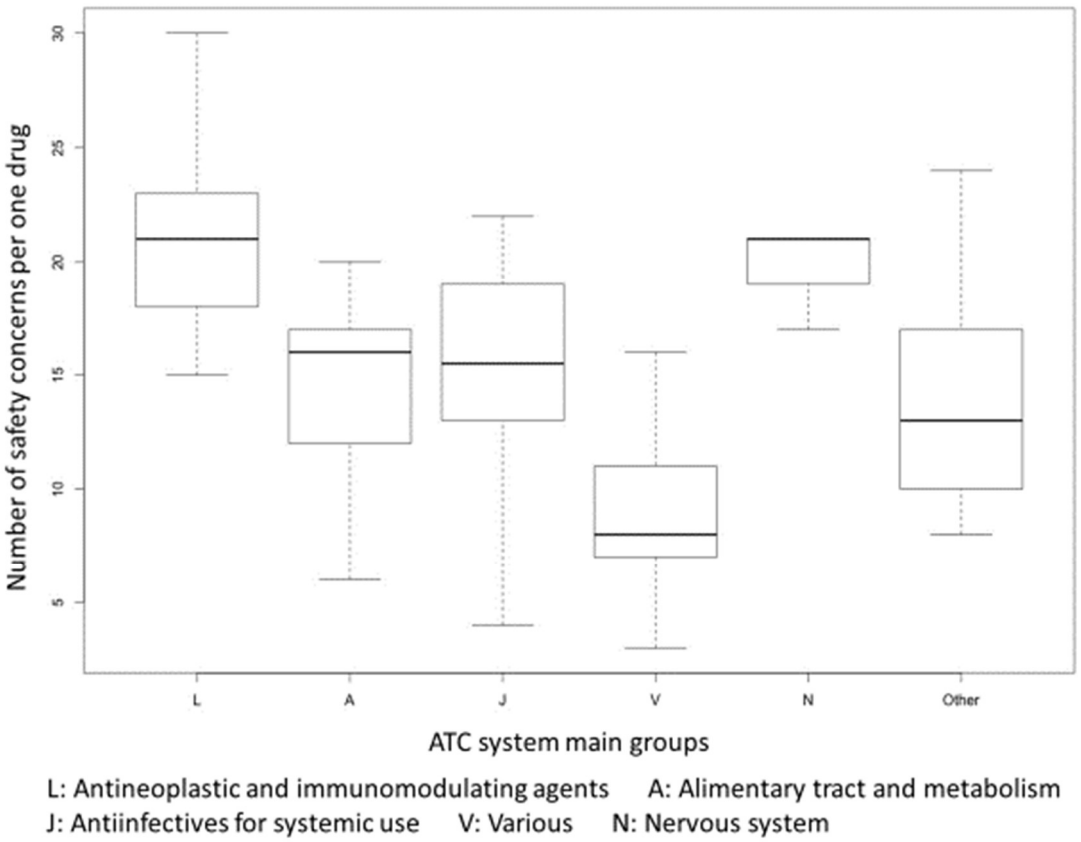

Figure 2-1: Number of safety concerns per product by therapeutic groups

When safety concerns were categorized by type of concern, we found 206 important identified risks, 287 important potential risks, and 320 categorized as missing information. Of the 813 concerns, 426 (52.4%) were SpAEs and 409 (50.3%) were context of use concerns. (Percentages may not add to 100 because some concerns were classified as both SpAE and context of use and 11 safety concerns were not included in either category; Table 2-2.) Almost all identified risks were SpAEs. Two-thirds of the potential risks were SpAEs and one-third were classified as context of use. In contrast, most of the missing information was classified as context of use (Fig. 2-2).

2.3.3. Additional Pharmacovigilance Activities

In total, 300 additional pharmacovigilance activities were planned to address specific safety concerns, including 143 clinical trials (47.7%), 73 non-interventional studies (24.3%), and 72 non-clinical studies (24.0%). Based on product type, the median number of additional pharmacovigilance activities was 5.5 (IQR 3.0–9.0) for small-molecule drugs and 3.0 (IQR 2.0–6.0) for biologicals. Based on approval status, the median number of additional pharmacovigilance activities was 7.0 (IQR 3.0–11.0) for orphan drugs, 4.5 (IQR 2.0–7.0) for non-orphan drugs, 15.0 (IQR 11.0–15.0) for drugs with conditional approval, and 4.0 (IQR 2.0–7.0) for drugs without conditional approval.

Table 2-3 shows the associations between the type and status of additional pharmacovigilance activities. The proportion of additional pharmacovigilance activities that were already or being planned was high for non-interventional studies, and the proportion of ongoing activities was high for clinical trials. The objectives of the 92 clinical trials for which the status was ‘ongoing’ were as follows: efficacy and safety 52 (56.5%); safety 22 (23.9%); pharmacokinetics 16 (17.4%); unknown 2 (2.2%). Meanwhile, the objectives of the 47 clinical trials for which the status was ‘planned/planning’ were as follows: pharmacokinetics 21 (44.7%); efficacy and safety 15 (31.9%); safety 9 (19.1%); and unknown 2 (4.3%).

The median number of additional pharmacovigilance activities per drug product was 5.0 (IQR 3.0–8.0), with at least one additional pharmacovigilance activity conducted for each of the 49 products: non-clinical studies were conducted for 21 products, clinical trials for 40 products, and non-interventional studies for 38 products.

We studied associations between the type of study and the therapeutic group. Therapeutic groups with high proportions of non-clinical studies were groups J (21 of 54 [38.9%]) and L (38 of 131 [29.0%]); those with high proportions of clinical trials were groups N (8 of 15 [53.3%]) and L (69 of 131 [52.7%]). Clinical trials were being conducted as additional pharmacovigilance activities for 57 of the antineoplastic agents in therapeutic group L. We also investigated associations between the additional pharmacovigilance activity status and therapeutic group. Drugs in therapeutic group L had a high proportion of ongoing additional pharmacovigilance activities (68 of 131 [51.9%]).

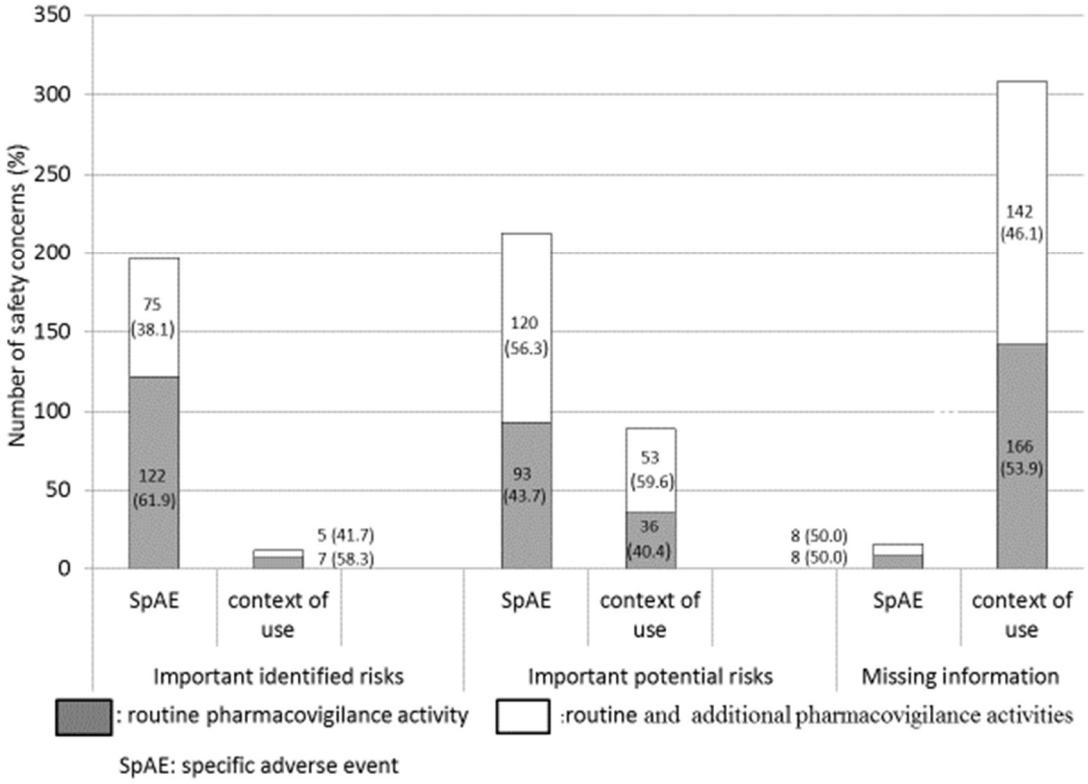

Figure 2-2: Safety concerns by types and how these are intended to be addressed

Table 2-2 Characteristics of safety concerns listed in the Risk Management Plan

	n	(%)
Safety concerns by type		
Important Identified Risks	206	(25.3)
Important Potential Risks	287	(35.3)
Missing Information	320	(39.4)
Nature of safety concerns by specific adverse event[1, 2], n (%)	**426**	**(52.4)**
Gastrointestinal disorders	34	(4.2)
Immune system disorders	33	(4.1)
Vascular disorders	30	(3.7)
Investigations	29	(3.6)
Blood and lymphatic system disorders	27	(3.3)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	25	(3.1)
Infections and infestations	24	(3.0)
Injury, poisoning and procedural complications	24	(3.0)
Others	200	(24.6)
Nature of safety concerns by context of use[2], n (%)	**409**	**(50.3)**
Patients with comorbidities	145	(17.8)
Specific age groups	64	(7.9)
Concomitant medication/ interaction	63	(7.7)
Pregnancy, lactation	47	(5.8)
Off-label use	30	(3.7)
Long-term use	20	(2.5)
Abuse, misuse, medication error	19	(2.3)
Unstudied ethnicity	10	(1.2)
Others	11	(1.4)

1) Specific Adverse events (SpAEs) categorized according to Medical Dictionary for Regulatory Activities (MedDRA)

2) For 11 safety concerns, a combination of one SpAE and one or two contexts of use was specified (e.g., neoplasms + interactions). For 11 safety concerns (pharmacokinetic data), neither was specified. For 20 safety concerns, a combination of two or three contexts (e.g., patients with hepatic impairments + pregnancy) was specified.

Table 2-3 Type and Status of additional pharmacovigilance activities (Part I) [n (%)]

	Planned /Planning	Ongoing	Completed	Unknown	Total
Clinical trial	47 (32.9)	92 (64.3)	3 (2.1)	1 (0.7)	143
Non-interventional study	68 (93.2)	3 (4.1)	0	2 (2.7)	73
Non-clinical study	38 (52.8)	29 (40.3)	4 (5.6)	1 (1.4)	72
Unknown	3 (25.0)	5 (41.7)	2 (16.7)	2 (16.7)	12
Total	156 (52.0)	129 (43.0)	9 (3.0)	6 (2.0)	300

2.3.4. Associations between Safety Concerns and Additional Pharmacovigilance Activities

In total, 300 specific additional pharmacovigilance activities were being implemented for 418 of the safety concerns. Multiple additional activities were being implemented for some safety concerns, and, in some instances, a single additional pharmacovigilance activity was being implemented for multiple safety concerns. The maximum number of additional activities per safety concern was 16 (minimum 0, median 2.0, IQR 0–2.0), whereas the maximum number of safety concerns per additional pharmacovigilance activity was 24 (minimum 1, median 1.0, IQR 1.0–3.0).

2.3.4.1. Frequency of Additional Pharmacovigilance Activities Based on the Type of Safety Concerns

When we investigated the proportions of the type of safety concerns for which additional pharmacovigilance activities were being conducted, we found that the proportion was highest for potential risks (n = 165 [57.5%]), followed by missing information (n = 173 [54.1%]) and identified risks (n = 80 [38.8%]). Figure 2-2 shows whether or not additional pharmacovigilance activities were conducted for each type of concern, with the concerns further classified into SpAEs or context of use. The most common SpAEs for which additional pharmacovigilance activities were being conducted were neoplasms (16 of 25 [64.0%]), blood and lymphatic system disorders (17 of 27 [63.0%]), infections and infestations (15 of 24 [62.5%]), investigations (18 of

29 [62.1%]), and immune system disorders (17 of 33 [51.5%]). The most common context of use concerns for which additional pharmacovigilance activities were being conducted were long-term use (16 of 20 [80.0%]), use with concomitant medications (including interactions) (42 of 63 [66.7%]), abuse/misuse/medication errors (12 of 19 [63.2%]), use in specific age groups (38 of 64 [59.4%]), and off-label use (17 of 30 [56.7%]).

2.3.4.2. Associations between Safety Concerns and Additional Pharmacovigilance Activity Study Type

The median number of safety concerns associated with one study was 1.0 (IQR 1.0–1.0) for non-clinical studies, 1.0 (IQR 1.0–3.8) for clinical trials, and 2.5 (IQR 1.0–7.0) for non-interventional studies.

Figure 2-3 shows associations between the types of safety concerns and the type of additional pharmacovigilance activity. The type of safety concern for which non-clinical studies were most frequently conducted were injury, poisoning, and procedural complications (n = 9 [39.1%]) and use with concomitant medications, including interactions (n = 42 [38.2%]). The most common type of safety concerns for which clinical trials were conducted were blood and lymphatic system disorders (n = 57 [83.8%]), long-term use (n = 35 [68.6%]), and use in unstudied ethnicities (n = 7 [63.6%]). The most common types of safety concerns for which non-interventional studies were conducted were abuse/misuse/medication errors (n = 15 [83.3%]), off-label use (n = 15 [57.7%]), and infections and infestations (n = 20 [57.1%]).

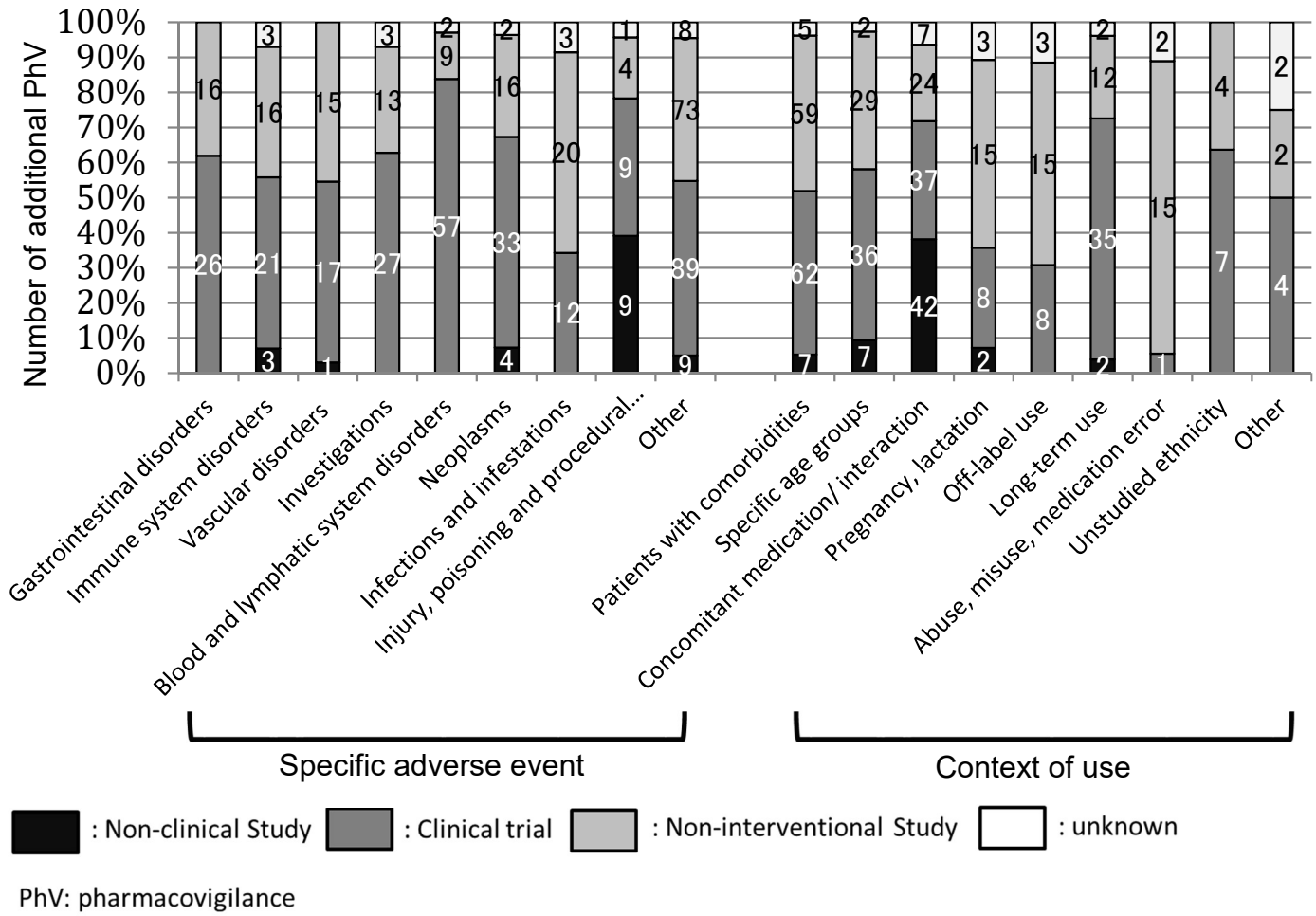

Figure 2-3: Associations between different types of safety concerns and additional pharmacovigilance activities

2.4. Part I: Discussion

The Guideline on Good Pharmacovigilance Practices, module V: Risk Management Systems, issued in 2012[4], states that additional pharmacovigilance activities may or may not be conducted depending on the characteristics of the drug product and the extent to which the safety concerns have been clarified. The present study supports this idea. It was also clear that the additional pharmacovigilance activity study type and/or status differed depending on the therapeutic group and/or the type of safety concerns for the product.

Identified risks were somewhat less common than either potential risks or missing information, and SpAE concerns were more common than context of use concerns. These results are similar to those obtained in a study of 48 new drug products that were approved between November 2005 and December 2009[14].

The number of safety concerns per product was largest for products in therapeutic groups L and N. The number of additional pharmacovigilance activities per product was largest for products in therapeutic groups J, N, and L. These results suggest the therapeutic group affects the safety concerns and pharmacovigilance activities. The median number of safety concerns per product was the same for small-molecule drugs and biologicals. Per product, more additional pharmacovigilance activities were undertaken for small-molecule drugs. Therefore, we cannot say definitively that a product will necessitate more additional pharmacovigilance activities solely because it is a biological. Products that were orphan drugs or had conditional approval had more safety concerns and additional pharmacovigilance activities than those that were not orphan drugs or without conditional approval. This may reflect that orphan drugs and drugs with conditional approval were approved with relatively limited safety information.

While most identified risks and potential risks were SpAEs, the majority of the missing information related to context of use concerns. In addition, the proportion of safety concerns for which only routine pharmacovigilance activities were conducted was highest for identified risks. Therefore, it was clear that additional pharmacovigilance activities were conducted less frequently for risks that had already been identified at the time of approval.

Clinical trials were the most common additional pharmacovigilance activities. In particular, more than 60% of the additional pharmacovigilance activities conducted for long-term use were clinical trials. Given these, the fact that a high proportion of ongoing activities were clinical trials suggests that a fairly large number of clinical trials conducted to obtain marketing approval were continued post-approval to collect information on safety in long-term use. Thus, it appears that clinical trials are planned right from the development stage, taking into account pharmacovigilance activities that will be conducted post-approval. Conversely, the status for most of the non-interventional studies was 'planned/being planned,' reflecting the nature of this type of study.

The additional pharmacovigilance activities that were conducted for the majority of abuse/misuse/medication errors and for close to 60% of off-label use were non-interventional studies. These are safety concerns that are encountered only post-approval, which means non-interventional studies appear to be suited to the characteristics of these safety concerns. Close to 40% of the additional pharmacovigilance activities conducted for injury, poisoning, and procedural complications were non-clinical studies. This was a far higher proportion than that for other risks. Furthermore, close to 40% of the additional pharmacovigilance activities conducted for use with concomitant medications (including interactions) were non-clinical studies. These activities also appeared to be well suited to the characteristics of these safety concerns.

These results suggest that whether additional pharmacovigilance activities are conducted or not depends on the characteristics of the therapeutic group and the level of safety concerns for the particular drug. Furthermore, these factors also dictate the type of study when additional pharmacovigilance activities are conducted. Additional pharmacovigilance activities are conducted more frequently for safety concerns for which sufficient clinical data have not been obtained prior to approval, such as potential risks and missing information, than for identified risks.

From the early stages of drug development, companies should consider what kind of safety information will be required in the postmarketing stage based on factors such as the product characteristics and anticipated safety concerns as well as the

pharmacovigilance activities already being conducted for comparable drugs or similar safety concerns. At the same time, pharmacovigilance activity plans should be updated based on accumulating postmarketing information. We believe the present study provides insight to enhance future postmarketing pharmacovigilance activities.

The limitations of our study include that the data were extracted from the EPARs at the time of approval and thus may differ somewhat from the actual RMPs. Furthermore, it may be possible that a clinical trial conducted to address one primary safety concern may also study other safety concerns as a secondary objective; this might influence the number of safety concerns addressed in any particular clinical trial.

2.5. Part I: Conclusions

The necessity for and types of additional pharmacovigilance activities depend on the characteristics and the uncertainty about the safety concerns pertaining to the product. From the early stages of drug development, companies should consider the kind of safety information that will be required in the postmarketing stage and plan pharmacovigilance activities accordingly.

3. Part II: Comparative Analysis of Safety Concerns and Pharmacovigilance Activities in Japan and Europe

3.1. Part II: Objectives

Looking at the pharmacovigilance activities in Europe, where the RMP system was introduced earlier than in Japan, an analysis of the characteristics of the postmarketing safety concerns in Europe, as discussed in Part I, clearly shows that (1) the pharmacovigilance activities are related both to the characteristics and the safety concerns of the individual drug products and (2) additional pharmacovigilance activities are only conducted for around half of the safety concerns. Earlier studies of pharmacovigilance activities in Japan[7-11] have identified several problems with the postmarketing surveillance studies that were being conducted in Japan prior to the introduction of the RMP system, such as the complexity of the case report forms and the large number of parameters that needed to be filled out, even though the people primarily responsible for conducting these investigations at medical institutions were physicians who were already extremely busy. These postmarketing surveillance studies therefore placed a considerable burden on these physicians. Another problem was that the postmarketing surveillance studies did not have clear objectives, and the information that was obtained was therefore not very helpful for formulating safety measures. Furthermore, research on the RMPs that have been prepared since the RMP system was introduced[12, 13] has shown that the additional pharmacovigilance activities still depend to a large extent on traditional postmarketing surveillance studies. Therefore, the approach to pharmacovigilance that has been used in Japan since the time when there was a lag in the approval of new drugs in Japan compared to the West – in other words, since the time when it was possible to use the safety information that had already been collected in the West when the drug was launched in Japan – continues to be used despite the fact that now new drugs are approved in Japan at nearly the same time as in the West.

However, although previous research has identified problems with the postmarketing surveillance studies themselves, no research has been conducted on what kinds of pharmacovigilance activities should be used for what kinds of safety concerns. Therefore, in Part II, we identify and categorize the numbers and types of safety

concerns, the numbers, types, and times of implementation of pharmacovigilance activities for each drug product that has recently been approved in both Japan and Europe, and comparatively analyze the associations between them and discuss methods for effectively implementing pharmacovigilance activities in order to realize a more complete set of new drug safety measures in Japan.

3.2. Part II: Methods

3.2.1. Data Sources and Data Extraction

Of the 49 products discussed in Part I, 20 had been approved in Japan as well by August 2016 for the same indication, and the European data from Part I were therefore used without any modification.

For these 20 products, we obtained the risk management plans listed on the PMDA web site[23)] and extracted the information on the safety concerns and also the pharmacovigilance activities that are being conducted for these safety concerns (titles of the activities, key/target numbers of subjects, key scheduled time points, status of conduction, planned date of report preparation). Early postmarketing phase vigilance activities were excluded from consideration because of the fact that, from a procedural standpoint, they are the same as routine pharmacovigilance activities.

3.2.2. Data Classification

3.2.2.1. Safety concerns

We classified the safety concerns that were listed in the Japanese and European RMPs as identified risks, potential risks, or missing information. In addition, in order to compare the risks in Japan to those in Europe, we classified the safety concerns into the following 3 groups: those that were listed in the same risk category (identified risk/potential risk/missing information) in both the Japanese and the European RMP, those that were listed as risks, but in different risk categories, in the Japanese and European RMPs, and those that were listed in only one of the Japanese and European RMPs. We also classified identified risks as (a) risks that were listed as identified risks only in Japan, (b) risks that were listed as identified risks only in Europe, or (c) risks that were listed as identified risks in both Japan and Europe, and also investigated the

relationships between these risks and the times of approval of each product in both Japan and Europe.

Separately, we classified all the safety concerns as “specific adverse events” (SpAEs) or “context of use concerns.” Context of use concerns were further classified into the following categories in accordance with the previous research[14]: use in specific age groups, use during pregnancy/lactation, use in patients with specific comorbidities, use with concomitant medications (including interactions), abuse/misuse/medication errors, long-term use in unstudied ethnicities, and off-label use. Some safety concerns were classified as both SpAEs and context of use concerns.

3.2.2.2. Additional Pharmacovigilance Activities

Additional pharmacovigilance activities in the European RMPs were classified as non-clinical studies (e.g., pharmacology studies, general toxicity studies, toxicokinetic and nonclinical pharmacokinetic studies, reproduction toxicity studies, genotoxicity studies), clinical trials (e.g., human interventional studies such as human pharmacology studies, therapeutic confirmatory studies, and clinical studies in special populations), or non-interventional (observational) studies (e.g., cohort studies, drug-utilization studies), in accordance with the EMA guidelines[4]. Additional pharmacovigilance activities in the Japanese RMPs were classified as postmarketing surveillance studies or postmarketing clinical studies, in accordance with the Japanese GPSP Ministerial Ordinance. The postmarketing surveillance studies were further classified by whether or not they were all-patient surveillance programs. For both Japan and Europe, the additional pharmacovigilance activities were also classified by status (planned/planning, ongoing, or completed).

Then, for both Japan and Europe, the relationships between the drug characteristics and the safety concerns, the relationships between the drug characteristics and the additional pharmacovigilance activities, and the relationships between the safety concerns and the additional pharmacovigilance activities were analyzed and these relationships in Japan were compared to those in Europe.

3.3. Part II: Results

3.3.1. Product Characteristics

Table 3-1 shows the product backgrounds. The therapeutic group with the most drug products was Group L (antineoplastic and immunomodulating drugs). There were 4 products for which the region of first approval in the world was Japan and 1 product for which it was Europe; almost all of the other products were first approved in the United States. There were 5 products that were designated as orphan drugs in Europe, 7 products designated in Japan, and 3 products designated in both regions (elosulfase alfa, ibrutinib, and pomalidomide). The difference between the international birth date and the date of approval was 136.0 days (interquartile range [IQR]: 60.3-233.8) in Europe and 327.0 days (IQR: 198.0-597.5) in Japan.

3.3.2. Safety concerns

The European and Japanese safety concerns for each drug product are shown in the appendix 2. The total number of safety concerns was 329 in Europe and 197 in Japan. The number of identified risks was 85 in Europe and 105 in Japan, the number of potential risks was 108 in Europe and 55 in Japan, and the number of missing information risks was 136 in Europe and 37 in Japan. Thus, although there was no major difference between Europe and Japan in the number of identified risks, the number of potential risks in Europe was around double as many as that in Japan, and the number of missing information risks in Europe was around 4 times more than that in Japan. There were 103 safety concerns that were listed as risks and also classified into the same category in both Europe and Japan, 192 that were listed as risks only in Europe, and 61 that were listed as risks only in Japan.

Figure 3-1 shows the results of classifying the safety concerns as SpAEs or context of use concerns. Of the 329 concerns in Europe, 177 (53.8%) were SpAEs and 165 (50.2%) were context of use. (Percentages may not add to 100 because some concerns were classified as both SpAE and context of use and 5 safety concerns were not included in either category.) By contrast, of 197concerns in Japan, 148 (75.1%) were SpAEs and 49 (24.9%) were context of use. In addition, the risks associated with context of use included risks that were listed as risks only in Europe (use in unstudied

ethnicities, off-label use). Figure 3-2 shows the results of a comparison of only the risks associated with context of use when these risks are excluded.

The number of safety concerns per product was 11.0 (IQR: 5.8-14.0) in Japan and 17.0 (IQR: 12.8-20.0) in Europe. When the relationship between the number of identified risks and the time of approval of each product was investigated, it was found that the disposition of the 94 identified risks for the 13 products that had been approved at least 180 days earlier in Europe than in Japan was as follows: 34 risks that were listed only in the Japanese RMP (36.2%), 29 risks that were listed only in the European RMP (30.9%), and 31 risks that were listed in both the European and the Japanese RMPs (33.0%). The disposition of the 16 identified risks for the 2 products that were approved at least 180 days earlier in Japan than in Europe was as follows: 12 risks that were listed as risks only in Japan (75.0%), 2 risks that were listed as risks only in Europe (12.5%), and 2 risks that were listed as risks in both Japan and Europe (12.5%). Of the 30 identified risks for the 5 products for which the difference between Japan and Europe in the date of approval was less than 180 days, 9 (30.0%) were listed as risks only in Japan, 4 (13.3%) were listed as risks only in Europe, and 17 (56.7%) were listed as risks both in Japan and in Europe.

Table 3-1: Summary of product characteristics (Part II)

		Small molecules (n =16)	**Biologicals (n = 4)**	**Total (n = 20)**
Therapeutic group, n (%)	L: Antineoplastic and immunomodulating agents	6 (30.0)	1 (5.0)	7 (35.0)
	A: Alimentary tract and metabolism	3 (15.0)	3 (15.0)	6 (30.0)
	J: Antiinfectives for systemic use	4 (20.0)	0	4 (20.0)
	V: Various	1 (5.0)	0	1 (5.0)
	N: Nervous system	0	0	0
	Other groups	2 (10.0)	0	2 (10.0)
Approval details, n (%)	Orphan indication (Europe)	3 (15.0)	2 (10.0)	5 (25.0)
	Conditional approval (Europe)	0	0	0
	Exceptional Circumstance (Europe)	0	0	0
	Orphan indication (Japan)	6 (30.0)	1 (5.0)	7 (35.0)
	Priority review (Japan)	4 (20.0)	1 (5.0)	5 (25.0)
First approval worldwide, n (%)	Europe	1 (5.0)	0	1 (5.0)
	United States	10 (50.0)	3 (15.0)	13 (65.0)
	Japan	3 (15.0)	1 (5.0)	4 (20.0)
	Canada	2 (10.0)	0	2 (10.0)

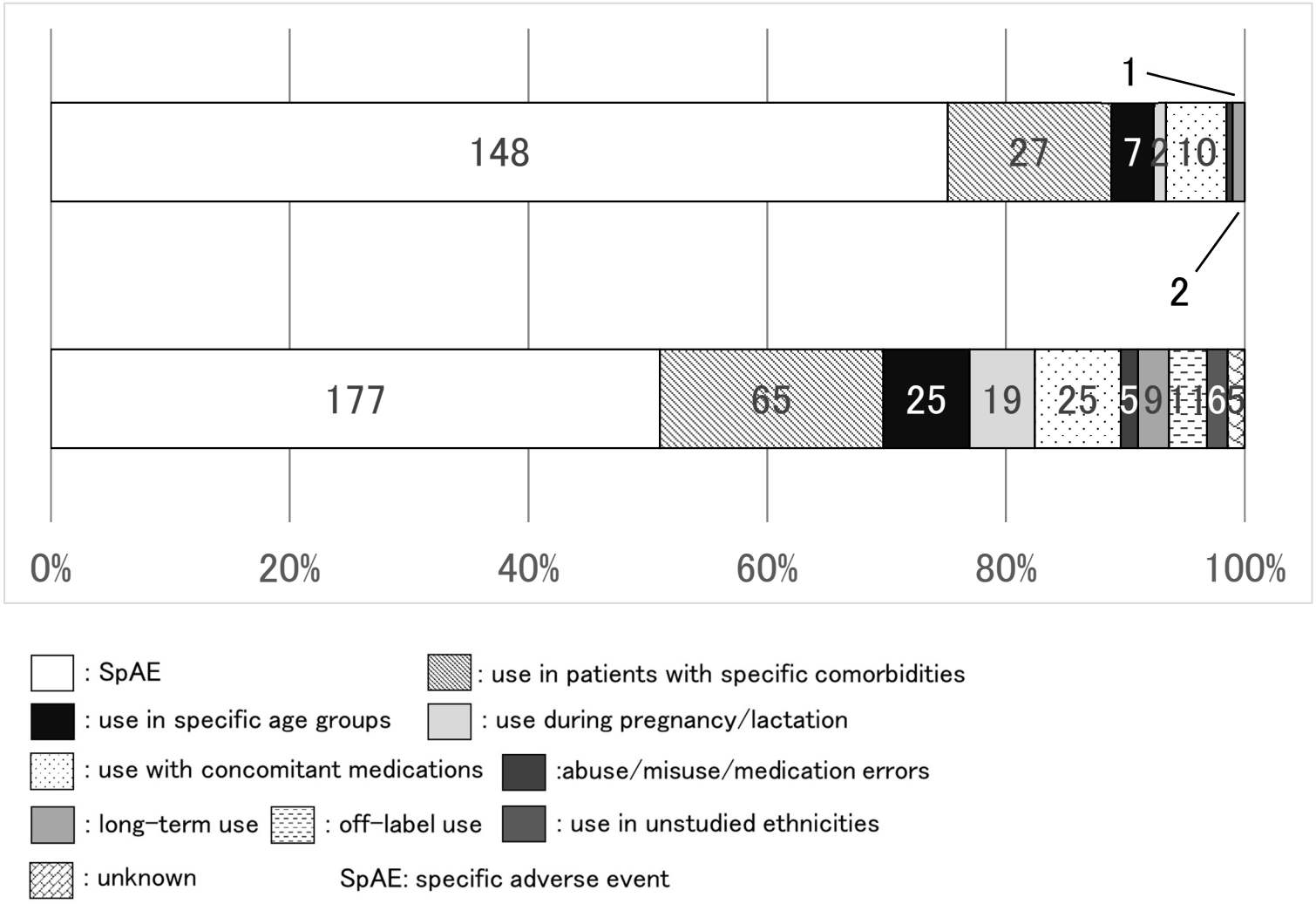

Figure 3-1: Classification of the safety concerns as SpAEs or context of use

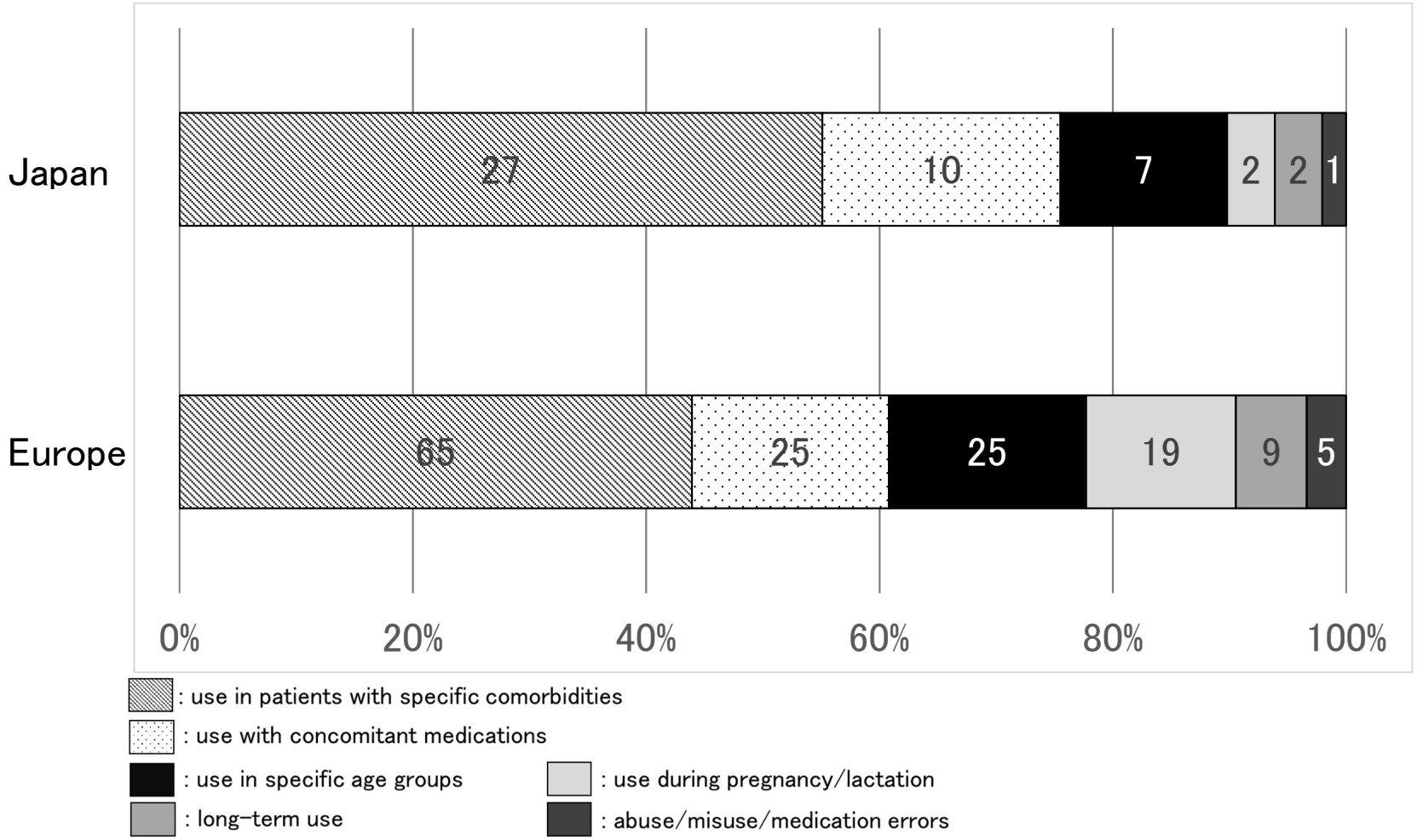

Figure 3-2: Classification of the safety concerns as context of use (excluded specific adverse events and risks only in Europe (use in unstudied ethnicities, off-label use)

3.3.3. Additional Pharmacovigilance Activities

The total number of additional pharmacovigilance activities was 47 in Japan and 123 in Europe. Table 3-2 shows a comparison of the types and statuses of the additional pharmacovigilance activities in Japan and Europe. The most common additional pharmacovigilance activities in Europe were clinical trials, and the next were non-interventional studies. Although the non-interventional studies included drug utilization studies and cohort studies conducted using patient registries, there was only a single study for which it was clearly stated that a database was being used. The only additional pharmacovigilance activities in Japan were postmarketing surveillance studies and postmarketing clinical studies; there were 11 cases where the term of an ongoing clinical study was extended and the patients transitioned to a postmarketing clinical study.

The number of additional pharmacovigilance activities per product was 5.0 (IQR: 3.0-8.0) in Europe and 2.0 (IQR: 1.0-3.0) in Japan. In Europe, there were no products for which nonclinical studies, clinical trials, and non-interventional studies were all conducted: there were 12 products for which nonclinical studies were conducted, 15 products for which clinical trials were conducted, and 14 products for which non-interventional studies were conducted. In Japan, postmarketing surveillance studies were conducted for all products, and there were 12 products for which postmarketing clinical studies were conducted.

In Japan, there were 8 products for which the conduction of a postmarketing surveillance study in all patients (all-patient surveillance) was required as a condition of approval. When we examined the additional pharmacovigilance activities in Europe for these 8 products, we found that 23 nonclinical studies were conducted for 6 of these products, 27 clinical trials were conducted for 5 of these products (19 of which, covering all 5 products, were extensions of clinical trials), and 8 non-interventional studies were conducted for 6 products.

Table 3-2: Type and Status of additional pharmacovigilance activities (Part II) [n (%)]

	Planned /Planning	**Ongoing**	**Completed**	**Unknown**	**Total**
EU					
Clinical trial	19 (29.7)	42 (65.6)	2 (3.1)	1 (1.6)	64
Non-interventional study	23 (100.0)	0	0	0	23
Non-clinical study	15 (45.5)	18 (54.5)	0	0	33
Unknown	1 (33.3)	2 (66.7)	0	0	3
Total	58 (47.2)	62 (50.4)	2 (1.6)	1 (0.8)	123
Japan					
Postmarketing clinical study	8 (42.1)	11 (57.9)	0	0	19
Postmarketing surveillance study	28 (100.0)	0	0	0	28
Total	36 (76.6)	11 (23.4)	0	0	47

3.3.4. Associations between Safety Concerns and Additional Pharmacovigilance Activities

In Europe, additional pharmacovigilance activities were conducted for 146 out of a total of 329 safety concerns (44.4%). In Japan, additional pharmacovigilance activities were conducted for 169 out of a total of 197 safety concerns (85.8%). Figure 3-3 shows the relationships between the categories of safety concerns and the presence or absence of additional pharmacovigilance activities. The proportion of identified risks for which additional pharmacovigilance activities were conducted was around 30% (23 of 85) in Europe, compared to around 90% (97 of 105) in Japan.

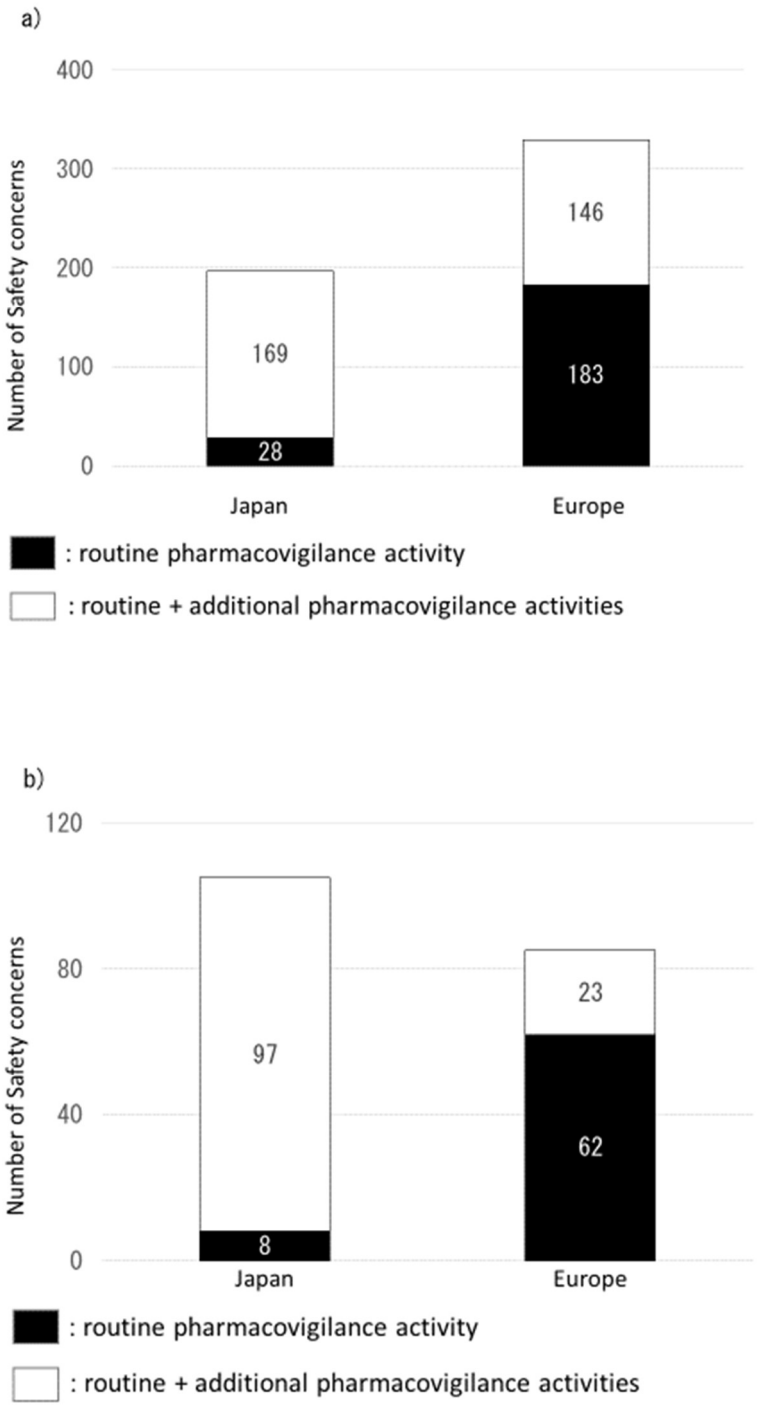

Figure 3-3: Safety concerns by types and how these are intended to be addressed:
a) Overall b) Identified risks

3.4. Part II: Discussion

Comparison of the safety concerns and pharmacovigilance activities listed in the RMPs of products that have been approved in both Europe and Japan showed that the safety concerns were not necessarily the same in Europe and Japan, and that the total number of safety concerns in Europe was around 1.5 times as many as that in Japan. Although the number of identified risks was somewhat larger in Japan, the number of potential risks in Europe was twice as many as that in Japan, and the number of missing information in Europe was around 4 times as many as that in Japan. Although safety concerns that are classified as potential risks or missing information in the early postmarketing phase are occasionally reclassified as identified risks because safety concerns are revised based on the assessment of safety information obtained postmarketing, examination of the proportion of identified risks that were classified as identified risks only in Japan found no significant difference in this proportion between products that were put on the market at least half a year earlier in Europe and products that were put on the market in Europe and Japan at the same time (in each case, the proportion was around 30%). It therefore does not appear that the differences in safety concerns that exist between Japan and Europe may be attributed to differences in the timing of the market launch.

Comparison of the safety concerns in Japan and Europe found that the proportion of SpAEs was higher in Japan. Furthermore, when context of use concerns were compared, excluding those that were listed only in Europe, it was found that the proportions of special age group and pregnancy/lactation concerns were higher in Europe, and the proportions of use in patients with specific comorbidities and use with concomitant medications concerns were higher in Japan. These findings suggested that while in Japan the focus is on specific adverse events (identified or potential risks) that have been elucidated to a certain extent by the time the product is approved, in Europe the focus is on collecting extensively the information that will be needed in the clinical setting.

Comparison of the additional pharmacovigilance activities in Japan and Europe showed that, reflecting the regulatory systems of each region, in Europe a variety of activities such as nonclinical studies, clinical trials, and non-interventional studies were conducted, and in Japan postmarketing clinical studies and postmarketing surveillance

studies were conducted. When Japan was compared to Europe in the median number of additional pharmacovigilance activities per product, it was found that smaller number of additional pharmacovigilance activities per product was conducted in Japan. It was noteworthy that postmarketing surveillance studies were conducted for all products in Japan, demonstrating that Japan has more of a one-size-fits-all approach to pharmacovigilance activities.

The European guidelines[4] state that additional pharmacovigilance activities may or may not be needed depending on the extent to which the safety concerns have been elucidated. In Japan, the "Drug Product Risk Management Plan Guideline" [6] that was enacted in 2013 states that the necessity of conducting additional pharmacovigilance activities should be examined by referencing the ICH Harmonised Tripartite Guideline Pharmacovigilance Planning E2E[5]. In Europe, in fact, safety concerns for which additional pharmacovigilance activities were conducted accounted for around 40% of all safety concerns, and for around 30% of all known (identified) safety concerns. In Japan, in contrast, they accounted for 80% of all safety concerns, and 90% of known safety concerns. This clearly shows that, in Japan, additional pharmacovigilance activities are used for the collection of additional information about known adverse events.

These findings show that although the objectives of the RMPs in Japan and Europe are the same, the approaches to pharmacovigilance that are used in the two regions are different, and whereas pharmacovigilance in Japan involves the conduction of largely standardized additional pharmacovigilance activities that are focused on obtaining information about known, specific adverse events, pharmacovigilance in Europe appears to be focused more on collecting a wide range of information that is needed in the clinical setting, and that in Europe routine pharmacovigilance activities and a variety of additional pharmacovigilance activities are used on more of a case-by-case basis.

In light of these findings, we believe that it would be possible to collect safety information from a wide range of perspectives in Japan as well by researching the safety concerns that have been identified for an individual drug product through (1) identifying safety concerns by predicting how the drug product will be used in the clinical setting, irrespective of the risks of "specific adverse events," (2) evaluating whether or not additional pharmacovigilance activities are really needed, and not conducting additional

pharmacovigilance activities for safety concerns for which additional information can be collected through only routine pharmacovigilance activities, and (3) positioning and conducting nonclinical studies and/or various types of observational studies as additional pharmacovigilance activities. Because the simultaneous global development of drug products is becoming increasingly common, research would also be needed on the international harmonization of safety concerns and pharmacovigilance activities, as well.

4. Overall Discussion

The purpose of a risk management plan is to ensure safety of the drug product after the market launch by assessing the benefits and risks of the drug and implementing necessary safety measures based on these assessments. In Japan, the traditional framework of the re-examination system, the re-evaluation system, and the adverse drug reaction/infection reporting system, which are the foundation of Japan's postmarketing safety measures, have been used to this end. The findings of our study show that, in Japan, additional pharmacovigilance activities are still dependent on postmarketing surveillance studies, as they were before the introduction of the RMP system. The results of our study also clearly show that the focus of additional pharmacovigilance activities in Japan is on collecting additional information about known adverse events.

Because of the fact that the amount of safety information that has been obtained by the time of the market launch of a drug product is limited, and that there are differences in, for example, the use of concomitant medications in the clinical setting between the West and Japan, one important safety measure is the collection and assessment of more information on known adverse events. However, given that the number of new drugs that are being launched in Japan at nearly the same time as in the West is increasing and that the RMP system has been introduced, and given that the safety measures of risk management plans include not only the collection and assessment of safety information, but also the use of the assessed information to minimize the risks in the clinical setting, we believe that the implementation of risk minimization activities based on information about known adverse events that has already been obtained should be positioned as a more important safety measure than the collection of further information about these events. Furthermore, because medical institutions and companies do not have unlimited resources, we believe that the focus of collecting information by conducting additional pharmacovigilance activities needs to be on the detection of unknown risks and the specific conditions of use rather than on collecting additional information about known adverse events, and risk minimization activities need to be further improved by using combinations of additional pharmacovigilance activities based on these principles to more efficiently collect a wide range of information.

Both in the clinical setting and in companies, new drug RMPs are conducted in parallel with the RMPs of drug products that are already being used. The introduction of new approaches to additional pharmacovigilance activities may cause confusion, and we believe that a greater level of efficiency should be realized in stages. It has been reported that any meaningful safety information was obtained in around 40% of the additional pharmacovigilance activities (postmarketing surveillance studies) but the majority of safety actions taken based on the information were just the revisions to the frequency figures of the adverse drug reactions already listed in package inserts[8]. Therefore, we believe that a good first step towards improving pharmacovigilance in Japan would be to stop using stereotypical postmarketing surveillance studies to obtain information about safety concerns for which it appears that information could be collected by routine pharmacovigilance activities (spontaneous reporting of adverse drug reactions) alone. Instead, it would probably be more practical to use these resources to conduct additional pharmacovigilance activities that have as their central focus the detection of unknown risks and/or specific context of use safety concerns.

In addition, although various medical databases that can be utilized for pharmacoepidemiology research have been prepared in recent years, and steps have been taken to utilize database research as one type of additional pharmacovigilance activity[24], we found only a single study that clearly specified the use of a database as an additional pharmacovigilance activity in Europe in the present research. In the future, with the development of available databases, it is hoped that safety concerns for which the collection/assessment of safety information by such database research is suitable will be identified and higher quality safety measures are expected to be implemented. However, database research will not be applicable to all safety concerns, and the methods that are appropriate to the safety concerns of each individual product should be investigated.

The limitations of our study include the fact that the data on the European RMPs were extracted from the EPARs at the time of approval and thus may differ from the actual RMPs. However, because it was based on the information provided in the review reports by the regulatory authorities, it is believed that there are no major differences.

Advances in the elucidation of disease thanks to scientific progress is resulting in the marketing of new drugs with a wide variety of mechanisms of action, and this has been accompanied by an increasing need for a wide variety of safety measures to be implemented in a timely fashion. Moreover, because the resources that are available to companies and medical practitioners for implementing postmarketing safety measures have certain limits, instead of allocating these resources in a one-size-fits-all manner to pharmacovigilance activities that focus on risks in general, including the risks that are already known, it will be necessary to use different combinations of a variety of pharmacovigilance activities, depending on the individual characteristics and safety concerns of each drug product, to focus on the detection and assessment of unknown risks and on the collection of information about specific context of use risks.

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6. Acknowledgement

I would like to express my sincerest thanks to Professor Mamoru Narukawa for his invaluable guidance, numerous helpful suggestions, and kind words of encouragement. For this dissertation, I would like to thank the review committee members of my thesis: Dr. Yuji Yoshiyama, Dr. Hiroshi Homma, and Dr. Hajime Matsubara for their time, interest and helpful comments. I am also thankful to Mr. Masayuki Kaneko for his insightful advice and constant encouragement, and Ms. Akane Takayama for her support on numerous occasions. I am also grateful to Ms. Takako Nakata for all her help in preparing this dissertation, and also to all my supervisors and colleagues at Pharmaceuticals and Medical Devices Agency for their kind words of encouragement.
Finally, I would like to thank my family. Without their support, I would not have been able to move to Tokyo and to find such a phenomenal research institute.

Appendix 1: List of 49 drug products in Part I

Medicine Name	Common name	Therapeutic area	EMA authorization date
Krystexxa	pegloticase	Gout	08-Jan-13
Amyvid	florbetapir (18F)	Radionuclide Imaging	14-Jan-13
Tresiba	insulin degludec	Diabetes Mellitus	21-Jan-13
Lyxumia	lixisenatide	Diabetes Mellitus, Type 2	01-Feb-13
Jetrea	ocriplasmin	Retinal Diseases	13-Mar-13
Spedra	avanafil	Erectile Dysfunction	21-Jun-13
Xtandi	enzalutamide	Prostatic Neoplasms	21-Jun-13
Erivedge	vismodegib	Carcinoma, Basal Cell	12-Jul-13
Imnovid	pomalidomide	Multiple Myeloma	05-Aug-13
Tafinlar	dabrafenib	Melanoma	26-Aug-13
Vipidia	alogliptin benzoate	Diabetes Mellitus, Type 2	19-Sep-13
Giotrif	Afatinib	Carcinoma, Non-Small-Cell Lung	25-Sep-13
NovoEight	turoctocog alfa	Hemophilia A	13-Nov-13
Xofigo	radium Ra223 dichloride	Prostatic Neoplasms	13-Nov-13
Invokana	canagliflozin	Diabetes Mellitus, Type 2	15-Nov-13
Kadcyla	trastuzumab emtansine	Breast Neoplasms	15-Nov-13
Brintellix	vortioxetine	Depressive Disorder, Major	18-Dec-13
Tivicay	dolutegravir	HIV Infections	16-Jan-14
Sovaldi	sofosbuvir	Hepatitis C, Chronic	16-Jan-14
Tecfidera	dimethyl fumarate	Multiple Sclerosis	30-Jan-14
Neuraceq	florbetaben(18F)	Radionuclide Imaging Alzheimer Disease	20-Feb-14
Sirturo	bedaquiline	Tuberculosis, Multidrug-Resistant	05-Mar-14
Eperzan	albiglutide	Diabetes Mellitus, Type 2	21-Mar-14
Cometriq	cabozantinib	Thyroid Neoplasms	21-Mar-14
Latuda	lurasidone	Schizophrenia	21-Mar-14
Adempas	riociguat	Hypertension, Pulmonary	27-Mar-14
Vimizim	elosulfase alfa	Mucopolysaccharidosis IV	28-Apr-14
Deltyba	delamanid	Tuberculosis, Multidrug-Resistant	28-Apr-14

Incruse	umeclidinium bromide	Pulmonary Disease, Chronic Obstructive	28-Apr-14
Olysio	simeprevir	Hepatitis C, Chronic	14-May-14
Jardiance	empagliflozin	Diabetes Mellitus, Type 2	22-May-14
Entyvio	vedolizumab	Colitis, Ulcerative Crohn Disease	22-May-14
Sylvant	siltuximab	Giant Lymph Node Hyperplasia	22-May-14
Mekinist	trametinib	Melanoma	30-Jun-14
Plegridy	peginterferon beta-1a	Multiple Sclerosis	18-Jul-14
Gazyvaro	obinutuzumab	Leukemia, Lymphocytic, Chronic, B-Cell	23-Jul-14
Nuwiq	simoctocog alfa (rFVIII)	Hemophilia A	24-Jul-14
Translarna	ataluren	Muscular Dystrophy, Duchenne	31-Jul-14
Daklinza	daclatasvir	Hepatitis C, Chronic	22-Aug-14
Vizamyl	flutemetamol (18F)	Radionuclide Imaging Alzheimer Disease	22-Aug-14
Zydelig	idelalisib	Lymphoma, Non-Hodgkin Leukemia, Lymphocytic, Chronic, B-Cell	18-Sep-14
Imbruvica	ibrutinib	Lymphoma, Mantle-Cell	21-Oct-14
Lymphoseek	tilmanocept	Radionuclide Imaging	19-Nov-14
Trulicity	dulaglutide	Diabetes Mellitus, Type 2	21-Nov-14
Vargatef	nintedanib	Carcinoma, Non-Small-Cell Lung	21-Nov-14
Moventig	naloxegol	Constipation	08-Dec-14
Lynparza	olaparib	Ovarian Neoplasms	16-Dec-14
Cyramza	ramucirumab	Stomach Neoplasms	19-Dec-14
Scenesse	afamelanotide	Protoporphyria, Erythropoietic	22-Dec-14

Appendix 2: Safety concerns of 20 drug products in Part II

		Europe		Japan	
		Safety concerns	authorization date	Safety concerns	authorization date
alogliptin	identified risk	Hypersensitivity reactions, Pancreatitis	2013/9/19	Rhabdomyolysis, Hepatotoxicity・Jaundice, Interstitial pneumonia, Acute pancreatitis, Angioedemas, Intestinal obstruction, Hypoglycaemia , Stevens Johnson syndrome / Erythema multiforme	2010/4/16
	potential risk	Gastrointestinal disorders, Hepatotoxicity, Infections, Peripheral necrotic skin lesions		Malignant tumor, Infections	
	missing information	Children and adolescents, Malignancies, Patients with concurrent CV disease, Patients with severe hepatic impairment, Patients with severe renal impairment or End-Stage Renal disease (ESRD) requiring dialysis, Pregnant and/or breastfeeding women		Patients with severe hepatic impairment Use in very elderly patients, Patients with concurrent CV disease, Patients with severe renal impairment	
canagliflozin	identified risk	Balanitis or balanoposthitis, Hypoglycaemia in combination with insulin or glucose-independent insulin secretagogues, Urinary tract infections,	2013/11/15	Ketoacidosis / Blood ketone body increased, Genital infection, Frequency of urination and polyuria, Volume depletion, Hypoglycaemia , Urinary tract	2014/7/4

	Volume depletion, Vulvovaginal candidiasis	infections
potential risk	Hypoglycaemia in the absence of insulin or glucose-independent, Insulin secretagogues, Off-label use for weight loss, Clinical consequences of increased haematocrit, Bone fractures, Renal impairment/Renal failure, Photosensitivity	Malignant tumor, Fractures, Renal impairment, Weight loss
missing information	Long-term cardiovascular safety in patients, Use in nursing mothers, Use in paediatric patients between 10 and 18 years of age, Use in patients with congestive heart failure defined as NYHA class IV, Use in patients with severe hepatic impairment, Use in patients with severe renal impairment (eGFR<30mG/min/1.73m2), Use in pregnancy, Use in very elderly patients (≥ 85 years)	Hypoglycaemia in the absence of insulin or glucose-independent, Use in patients with severe hepatic impairment, Use in very elderly patients, Patients with concurrent CV disease, Use in patients with renal impairment

dabrafenib	identified risk	Cutaneous SCC (cuSCC; cutaneous squamous cell carcinomas), Hypersensitivity, New primary melanoma, Non-cutaneous secondary/recurrent malignancies, Palmar-Plantar Erythrodysesthesia Syndrome (PPES), Pancreatitis, Pre-renal and Intrinsic Renal failure, Pyrexia, Uveitis	2013/8/26	Hepatic impairment, Eye disorders, Cardiac impairment, Pyrexia, Cutaneous SCC (cuSCC; cutaneous squamous cell carcinomas), Non-cutaneous secondary/recurrent malignancies	2016/3/28
	potential risk	Drug-drug interactions, Hyperglycaemia, Increased risk for Grade 3 or 4 AEs, SAEs or dose adjustments in elderly population (≥65 years), Non-specific cardiac toxicity, Off-label use in resectable/resected melanoma (adjuvant treatment), non-melanoma tumours harbouring a BRAFV600-mutation, in combination with other anti-cancer agents, or when non-validated tests are used, Paediatric effects, Photosensitivity, Potential for QT Prolongation, Testicular Toxicity		Potential for QT Prolongation, Deep vein thrombosis / Pulmonary embolism, Testicular Toxicity, Cerebrovascular disorder, Pancreatitis	

	missing information	Developmental toxicity and risks in breast-feeding, Long-term treatment, Rare adverse reactions, Risks in patients with ECOG 2-4, Safety in patients with moderate to severe hepatic impairment, Safety in patients with severe renal impairment, Use in Non-White population, Use in patients with baseline QTc ≥480 msec; history of acute coronary syndrome (including unstable angina), coronary angioplasty, stenting or cardiac arrhythmias (except sinus arrhythmia) within the past 24 weeks; and abnormal cardiac valve morphology (moderately abnormal or worse), Use in patients with reduce cardiac function or symptomatic NYHA Class II, III, or IV heart failure (NYHA functional classification system)		Safety in patients with hepatic impairment	
daclatasvir dihydrochloride	identified risk	-	2014/8/22	Hepatitis B reactivation, Hepatic impairment, Interstitial pneumonia, Thrombocytopenias, Erythema multiforme	2014/7/4

	potential risk	CYP3A inhibitors and inducers; P-gp i-inhibitors, inducers, and substrates; OATP1B1, OATP1B3, and BCRP substrates, Development of Drug Resistance, Embryo-fetal Development Toxicity, Hematologic Toxicity, Hepatic Toxicity		Hematologic Toxicity	
	missing information	Children and Adolescents (<18 years of age), HBV/HCV, Hepatic Impairment and Decompensated Liver Disease, HIV/HCV, Liver Transplant, Pregnancy and Lactation, Subjects aged > 65 years, Subjects co-medicated with interacting agents dosed at either 30 mg/day or 90 mg/day, Subjects of African origin;		-	
dolutegravir	identified risk	Drug Interactions, Drug resistance, Hepatobiliary disorders, Hypersensitivity reactions	2014/1/16	Hepatic impairment, Increased occurrence of IRIS, Hypersensitivity reactions	2014/3/24
	potential risk	GI Intolerance and erosions, Increased occurrence of IRIS, Lipase elevations (Grade 3 and 4), Muscoskeletal events/ elevated CPK elevations, Phototoxicity, Psychiatric disorders, Renal disorders,		Muscoskeletal events, Drug Interactions	

		Serious rash (DAIDS Grade 3 or 4)			
	missing information	Affinity of DTG to melanocortin receptors, Long term safety data, Use in patients with severe hepatic impairment, Use in pregnancy/ breastfeeding, Use in the elderly		Long term safety data, Use in Japanese patients with HIV, Use in pregnancy/ breastfeeding	
dulaglutide	identified risk	Acute pancreatitis, Gastrointestinal events, Hypoglycaemia	2014/11/21	Gastrointestinal events, Injection site reactions, Hypoglycaemia	2015/7/3
	potential risk	Cardiovascular effects, Hypersensitivity, Medication errors (more than one injection per week), Pancreatic malignancy, Thyroid C-cell tumours		Hyperglycaemia (Use in patients treated insulin), Hypersensitivity reactions, Acute pancreatitis, Thyroid C-cell tumours, Cardiovascular disorder, Intestinal obstruction, Pancreatic malignancy、Intestinal obstruction	
	missing information	Confirmation of memory deficits in directly dosed immature rats, Use in children and adolescents <18 years of age, Use in patients aged ≥75 years, Use in patients with congestive heart failure, Use		Concomitant use with insulin, Use in patients with hepatic impairment, Use in elderly patients , Use in patients with renal failure	

		in patients with hepatic impairment, Use in patients with severe renal failure, Use in pregnant and/or breastfeeding women			
empagliflozin	identified risk	Genital infection, Hypoglycaemia (with insulin and/or sulphonylurea), Urinary tract infection, Volume depletion	2014/5/22	Hypoglycaemia, Ketoacidosis / Blood ketone body increased, Genital infection, Frequency of urination and polyuria, Volume depletion, Urinary tract infection	2014/12/26
	potential risk	Bone fracture, Liver injury, Off-label use (e.g. for weight loss in non-T2DM patients), Renal impairment, Urinary tract carcinogenicity		Malignant tumor, Fractures, Renal impairment, Weight loss	
	missing information	Clinical impact of dyslipidaemia, Concomitant use with GLP-1 analogues, Elderly patients, Long-term safety (particularly cardiovascular), Missing long-term safety information on melanoma, Paediatric patients, Pregnancy/breast-feeding, Use in patients with severe hepatic impairment		Concomitant use with GLP-1 analogues Use in patients with hepatic impairment, Use in elderly patients , Patients with concurrent CV disease, Use in patients with renal impairment	
enzalutamide	identified risk	Falls, Hallucination, Hypertension, Interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19, Interactions with strong	2013/6/21	Interactions with medicinal products that are substrates of CYP2C8, Thrombocytopenias, Seizures	2014/3/24

		inhibitors or inducers of CYP2C8, Neutrophil count decreased, Non-pathologic fracture, Seizures			
	potential risk	Cognitive/memory impairment		Neuropsychiatric disorders	
	missing information	Patients of non-White race, Patients with brain metastases or with baseline factors predisposing for seizure, Patients with ECOG PS ≥ 2, Patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate, Patients with moderate or severe hepatic impairment, Patients with severe cardiovascular disease, Patients with severe renal impairment, Reproduction/fertility		-	
ibrutinib	identified risk	Haemorrhage, Leukostasis	2014/10/21	Interactions with CYP3A inhibitors, Hypersensitivity, Infections, Use in patients with hepatic impairment, Hepatic impairment, Interstitial pneumonia, Eye disorders, Marrow depression, Tumour lysis syndrome,	2016/3/28

				Haemorrhage, Secondary malignancy, Cardiac arrhythmia	
	potential risk	Anaemia, Cardiac arrhythmia, Drug-drug interaction, Eye disorders, Hypersensitivity, Hypertension, Infections, Neutropenia, Other malignancies, Renal failure, Severe GI disorders, Teratogenicity, Thrombocytopenia, Tumour lysis syndrome		Leukostasis, Stevens Johnson syndrome	
	missing information	Long term use (>2 years), Off-label use in paediatric patients, Use during breastfeeding, Use in patients with severe cardiac disease, Use in patients with severe hepatic impairment, Use in patients with severe renal impairment		-	
insulin degludec	identified risk	Hypoglycaemia, Immunogenicity-related events (allergic reactions)	2013/1/21	Allergic reactions, Injection site reactions, Hypoglycaemia	2012/9/28

	potential risk	Immunological events – formation of neutralising insulin antibodies, Medication errors due to mix-up between basal and bolus insulin, Medication errors due to mix-up between the different concentrations of Tresiba		Immunological events – formation of neutralising insulin antibodies, Medication errors due to mix-up between basal and bolus insulin	
	missing information	Children and adolescents < 18 years, Co-administration with GLP-1, Elderly patients (>75 years) with T1DM, Hepatic impairment, Moderate and severe renal impairment, Pregnant and lactating women		Children < 5 years, Hepatic impairment, Elderly patients, Patients with concurrent CV disease, Renal impairment, Pregnant and lactating women	
nintedanib	identified risk	Bleeding, Diarrhoea, Hypertension, Liver enzyme elevations and hyperbilirubinaemia, Neutropenia, Perforation (gastro-intestinal and non-gastro-intestinal), Sepsis, Venous thromboembolism	2014/11/21	Diarrhoea / Nausea, Hepatic impairment, Thrombocytopenias, Thromboembolism, Gastrointestinal perforation	2015/7/3
	potential risk	Arterial thromboembolism, Cardiac failure, Hepatic failure, QT prolongation, Treatment in pregnant women and teratogenicity		Osteonecrosis of jaw, Interstitial pneumonia, Severe skin reactions, Haemorrhage, Impaired wound healing, Patients with severe hepatic impairment (Child–Pugh B or C)	

	missing information	In vitro inhibitory potential on OAT1 and OAT3, Treatment of breastfeeding women, Treatment of patients weighing < 50 kg, Treatment of patients with healing wounds, Treatment of patients with hepatic impairment, Treatment of patients with renal impairment, Treatment of subpopulations with co-morbid CNS conditions such as dementia, depression, brain metastasis, or with co-morbid conditions such as arthritis and osteoporosis		-	
pomalidomide	identified risk	Infection, Neutropenia, Peripheral neuropathy, Somnolence, Teratogenicity, Thrombocytopenia and bleeding, Thromboembolic events, Tumour lysis syndrome	2013/8/5	Hypersensitivity reactions, Infection, Hepatic impairment・Jaundice, Interstitial pneumonia, Acute kidney failure, Somnolence・Sensorium decreased・Confusion・Fatigue・Dizziness, Thromboembolism, Marrow depression, Teratogenicity, Tumour lysis syndrome, Cardiac failure, Cardiac arrhythmia, Peripheral neuropathies	2015/3/26
	potential risk	Cardiac arrhythmia, Cardiac failure, Off-label use, QT interactions		Secondary malignancy	

		(prolongation), Renal failure, Second primary malignancies, Second primary malignancies, Severe skin reactions, Thyroid disorders			
	missing information	Interaction with oral contraceptives, Interactions with drugs affecting and metabolised by cytochrome P450 1A2, 3A4/5 and P-glycoprotein, Paediatric use, Use during breast-feeding, Use in patients of different racial origin, Use in patients with hepatic impairment, Use in patients with renal impairment		Use in patients with hepatic impairment, Use in patients with renal impairment	
radium Ra223 dichloride	identified risk	Bone marrow toxicity leading to reduction in formed elements in blood	2013/11/13	Marrow depression	2016/3/28
	potential risk	Bone sarcoma, Late bone marrow toxicity, Myelodysplastic syndrome/Acute myeloid leukaemia (MDS/AML), Off-label administration of repeated courses of treatment, or other administration of doses in excess of those recommended in the product information, Off-label use in women and children, Osteonecrosis of the jaw, Secondary malignancies (other than		Secondary malignancy	

		MDS/AML and bone sarcoma)			
	missing information	Clinical safety in non-white ethnic groups, Clinical safety in patients receiving calcium supplementation, phosphates or vitamin D, Clinical safety in patients receiving chemotherapy, Clinical safety in patients receiving external beam radiation therapy to bone or prostate, Clinical safety in patients with inflammatory bowel disease, Developmental toxicity due to off-label use in children, Reproductive toxicity due to off-label use in women, Reproductive toxicity in men with metastatic CRPC		-	
ramucirumab	identified risk	Arterial thromboembolic events, Bleeding/Haemorrhagic events, Congestive heart failure, Fistula formation, GI perforation, Hypertension, Impaired	2014/12/19	Infusion-related reaction, Ischemic heart disease, Reversible posterior leukoencephalopathy syndrome, Neutropenia, Hypertension,	2015/3/26

		wound healing, Infusion-related reaction, Liver failure / liver injury, Neutropenia, Proteinuria		Haemorrhage, Gastrointestinal perforation, Embolism venous, Impaired wound healing, Proteinuria / Nephrotic syndrome, Embolism arterial, Fistula	
	potential risk	Abdominal pain, Anaemia, Reproductive and developmental toxicity, Reversible Posterior Leukoencephalopathy Syndrome, VTE (Venous thromboembolic event)		Liver failure, Interstitial pneumonia	
	missing information	Carcinogenicity, Genotoxicity		-	
recombinant human n-acetylgalactosamine-6-sulfatase (rhgalns) (elosulfase alfa)	identified risk	Infusion reactions (including anaphylaxis and severe allergic reactions)	2014/4/28	Infusion reactions (including anaphylaxis and severe allergic reactions)	2014/12/26
	potential risk	Immunogenicity, Medication Errors, Spinal/Cervical Cord Compression (including laxity and unmasking myelopathic symptoms)		Immunogenicity	
	missing information	Limitations of the safety database, Safety in patients with hepatic impairments, safety in patients with renal impairments, safety in patients with cardiac		Use in children	

		impairments, and safety in pregnancy and lactation			
riociguat	identified risk	Hypotension, Serious haemoptysis/pulmonary Haemorrhage, Upper gastrointestinal motility disorders, Worsening of pulmonary venous occlusive disease	2014/3/27	Upper gastrointestinal motility disorders, Hypotension, Worsening of pulmonary venous occlusive disease	2014/1/17
	potential risk	Bleeding, Bone changes and fractures, Concomitant smoking (induction of CYP1A1), Embryo–foetal toxicity, Medication error, Off-label use in patients aged < 18 years, Renal failure, Treatment of patients with pre-existing atrial fibrillation		Concomitant smoking, Haemoptysis・Pulmonary haemorrhage, Concomitant use with CYP1A1 inhibitors	
	missing information	Long-term safety in clinical practice, Patients aged < 18 years, Patients with chronic thromboembolic pulmonary hypertension (CTEPH) or pulmonary arterial hypertension (PAH) in World Health Organisation (WHO) functional class IV, Patients with creatinine clearance < 30 mL/min or on dialysis, Patients with		Patients with hepatic impairment, Patients with renal impairment, Long-term safety in clinical practice, Patients with systolic blood pressure < 95 mmHg at baseline, Concomitant use with CYP3A inhibitors, CYP1A1 inhibitors or P-gp/BCRP inhibitors	

		severe hepatic impairment (Child–Pugh C), Patients with systolic blood pressure < 95 mmHg at baseline, Patients with uncontrolled hypertension, Pregnancy and lactation			
simeprevir	identified risk	Photosensitivity conditions, Rash	2014/5/14	Hepatitis B reactivation, Hepatic impairment, Photosensitivity conditions, Hyperbilirubinaemia, Cerebral haemorrhage, Sepsis	2013/9/27
	potential risk	Development of drug resistance		Erythema multiforme, Neutropenias, Anaemia	
	missing information	Drug-drug interactions, OLYSIO + medicinal products other than peginterferon alfa and ribavirin, Use in children and adolescents (≥3 to <18 years), Use in elderly patients (>65 years), Use in HCV/HBV co-infection, Use in organ transplant patients, Use in patients previously treated with a HCV protease inhibitor or other direct-acting antivirals, Use in patients with GFR <30		-	

		mL/min/1.73 m2, Use in patients with moderate or severe hepatic impairment or decompensated liver disease, Use in pregnant or breast-feeding women			
sofosbuvir	identified risk	-	2014/1/16	Hepatitis B reactivation, Hypertension, Cerebrovascular disorder	2015/3/26
	potential risk	Drug-drug interaction with potent intestinal Pgp inducers		Safety in patients with severe renal impairment or end-stage renal disease, Anaemia	
	missing information	Safety in children, Safety in patients with severe renal impairment or end-stage renal disease, Safety in pregnant or breastfeeding women		-	
trametinib	identified risk	Diarrhoea, Haemorrhagic events, Hepatic events (AST, ALT, increased), Hypersensitivity, Hypertension, Left ventricular systolic dysfunction (e.g., LVEF decreased and left ventricular dysfunction), Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial	2014/6/30	Rhabdomyolysis, Hepatic impairment, Eye disorders, Cardiac impairment, Pyrexia	2016/3/28

	detachment), Oedema events (e.g. oedema peripheral), Pneumonitis, Rhabdomyolysis, Skin toxicities (e.g., rash, dermatitis acneiform,)	
potential risk	Developmental toxicity, Hepatic failure, Impaired female fertility, Off-label use: in resectable/resected melanoma (adjuvant treatment), in nonmelanoma tumours harbouring a BRAF V600- mutation, melanoma tumours negative for BRAF V600-mutation, in patients with tumour progression during prior treatment with BRAF inhibitor therapy, use in combination with other anti-cancer agents, or when non-validated tests are used	Interstitial pneumonia, Impaired female fertility, Deep vein thrombosis・Pulmonary embolism , Renal impairment , Cerebrovascular disorder, Developmental toxicity

missing information	Drug-drug interactions (i.e., Enzymes responsible for the hydrolytic cleavage of trametinib, Potential for saturation of P-gp and BCRP, Whether trametinib is a substrate of OATP1B1 and OATP1B3 and whether trametinib is an inhibitor of OCT2, OAT1, or OAT3), Long-term treatment (>12 months), Pregnancy and risks in breast-feeding, Risks in patients with ECOG 2-4, Safety in elderly (>65 years) patients, Safety in patients with baseline QTc ≥480 msec QT prolongation, recent (within 6 months) acute coronary syndrome including unstable angina, coronary angioplasty , stenting or cardiac arrhythmias (except sinus arrhythmia), treatment refractory hypertension (blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy), Safety in patients with history of pneumonitis or interstitial lung disease, Safety in patients with history of retinal	Safety in patients with hepatic impairment

		vein occlusion or central serous retinopathy (reclassified as Retinal Pigment Epithelial Detachment, RPED), Safety in patients with moderate to severe hepatic impairment, Safety in patients with severe renal impairment, Use in Non-White population, Use in paediatric population (children less than 18 years), Use in patients with reduced cardiac function or symptomatic Class II, III, or IV heart failure (NYHA functional classification system)			
umeclidinium	identified risk	-	2014/4/28	Cardiovascular disorder	2015/3/26

bromide	potential risk	Bladder outflow obstruction and urinary retention, Cardio and Cerebrovascular Disorders, Lower Respiratory Tract Infection (incl. pneumonia), Narrow angle glaucoma, Paradoxical brochospasm (which may be life threatening)	-
	missing information	Interaction with other medicines, Safety in long-term use, Safety in pregnancy and lactation, Safety in severe hepatic impairment	-