Research directed toward optimized implementation of additional risk minimization measures based on drug risk management plan in Japan

Yuka Yasuoka

DP-17405

Department of Clinical Medicine (Pharmaceutical Medicine)

Graduate School of Pharmaceutical Sciences

Kitasato University

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

Abstract

Background

Risk minimization measures are planned and conducted as part of a drug's risk management plan (RMP), and consist of routine activities that are performed for all drugs and additional measures that are implemented as needed based on the characteristics of the drugs and other factors. An additional risk minimization measure is undertaken to minimize the risk associated with a drug; however, the burden associated with the measure might be quite high in some cases. In this thesis, first, the status of implementing additional risk minimization measures in the USA, Europe and Japan was investigated. Subsequently, the status and contents of information materials created for healthcare professionals, which are most commonly implemented as additional risk minimization measures in Japan, was examined. Based on them, future strategies for optimizing the implementation of additional risk minimization measures were discussed.

Methods

In Research 1, the status of implementing additional risk minimization measures for new drugs approved between 2013 and 2017 in the USA, Europe and Japan was investigated based on the information published on the three countries/regions regulatory agencies' website. In Research 2, for new drugs approved in Japan from 2016 to 2018, the status and contents of information materials created for healthcare professionals was investigated based on the RMP and related materials for each drug.

Results

In Research 1, the status of implementation of additional risk minimization measures was 7.6% (15/197 drugs) in the USA, 26.4% (42/159 drugs) in Europe, and 64.8% (92/142 drugs) in Japan. Similar implementation status was shown in 45 new drugs

approved in all three countries/regions, indicating that additional risk minimization activities were implemented for many drugs in Japan. Common additional activities were implemented for only three drugs and for two of these drugs, “teratogenicity” was identified as a safety concern subjected to additional activities.

In Research 2, of the 102 new drug products approved from 2016 to 2018 in Japan, information materials for healthcare professionals were created for 61 drugs (59.8%). The average number of safety concerns described in the RMP of each drug was 8.3, and among these, the average of 71.4% of the safety concerns were the target for the information materials. The average number of pages of the materials was 34.4, and the average number of pages related to the target safety concerns was 13.2 pages (33.7% of the total number of pages of the materials). Most of the materials containing extensive information besides the target safety concerns were proper use guides or similar materials.

Conclusions

While additional risk minimization measures are important activities to minimize risks, they are largely influenced by differences in regulatory thinking, medical systems, and culture among countries/regions. Even considering it, more additional risk minimization measures are conducted in Japan, and risks that truly require attention may be missed in the process. To optimize risk minimization activities , it is necessary to narrow down drugs and associated risks for which additional risk minimization activities are conducted. Regarding the content of the materials, it should be focused on specific risks with concise information to minimize the risks. It is also essential to properly monitor whether those activities have the desired effect while considering their burden on the entire healthcare system.

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Abbreviations

ATC	Anatomical Therapeutic Chemical
EPAR	European Public Assessment Reports
EPPV	Early Post-marketing Phase Vigilance
EU	European Union
FDA	Food and Drug Administration
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
MedDRA	Medical Dictionary for Regulatory Actives
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred Term
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk Management Plan
SD	Standard Deviation
USA	United States of America

1. Introduction

All drugs have both benefits and risks. In the case of an approved drug, based on data obtained in clinical trials, benefits outweigh its potential risks at the population level [1]. At the same time, to ensure drug safety in actual clinical practice, it is necessary to consider factors directly related to the drug as well as various external factors such as medical environments, regulations, and patients and their families [1]. Therefore, measures to monitor the safety of drugs and properly manage them should be considered and implemented. Currently, in many countries, risk management of drug products is based on the concepts laid down in the International Conference on Harmonisation (ICH) E2E Guideline [2]. The important risks posed by a drug are summarized as safety specification and serve as the basis for risk management measures undertaken for a drug [2]. Although the ICH E2E Guideline forms the basis for the measures needed to reduce risk, it does not specify risk minimization activities. This was because the international harmonization of risk minimization activities had been considered especially difficult, as cultures, medical activities, and healthcare systems differ greatly across the world [3].

Risk minimization measures consist of routine activities that are performed for all drugs, and additional measures that are undertaken as needed based on the characteristics of the drug and other factors. Generally, safety concerns about an approved drug can be addressed sufficiently with routine risk minimization measures; when such routine measures are judged insufficient, additional risk minimization activities are planned and implemented for specific risks [4]. An additional risk minimization measure is undertaken to minimize the risk associated with a drug; however, the burden associated with the measure might be quite high in some cases. For example, when conditions for use of a

drug are too strict, drug use may not be feasible even if the benefits exceed the risks at the individual patient level. Furthermore, safety information requiring special attention might be lost and not conveyed if the volume of information to be conveyed is too high. Also, the need for complicated confirmation tasks and expensive testing equipment places a greater burden on healthcare providers. Therefore, although additional risk minimization activities are effective in improving the overall benefit–risk balance of individual drugs, it is also necessary to consider the "burden" imposed on the healthcare system by additional risk minimization activities [3, 5].

In this thesis, the status of implementing additional risk minimization measures was investigated in Japan compared to the USA and Europe, which had implemented them in advance, in Research 1. Subsequently, the status and contents of information materials created for healthcare professionals, which mostly implemented as additional risk minimization measures in Japan was examined, and then discussed how they should be treated in Research 2.

2. Research 1

2-1. Background and objective

In 2001, the ICH began developing a guideline for pharmacovigilance planning, ICH E2E. The ICH is a tripartite forum with representatives from regulatory authorities and the pharmaceutical industry in the European Union (EU), the USA, and Japan. The final document of ICH E2E, which introduced the concept of the Safety Specification, was adopted in November 2004, and the guideline was implemented in December 2004 in the EU, in April 2005 in the USA, and in September 2005 in Japan. Since then, regulatory authorities around the world have increasingly established frameworks for risk management using the concepts introduced in ICH E2E to identify safety issues or concerns. Chapter 3 of ICH E2E deals with the Pharmacovigilance Plan, which describes how the sponsor should identify and characterize further safety issues based on the Safety Specification.

While it forms the basis for the assessment of the need for risk minimization activities, ICH E2E deliberately did not venture into the area of planning risk minimization activities. In view of the inherent difficulties in developing risk minimization activities for regions with vastly different cultures, medical practices, and healthcare systems, this would be the area where harmonization would be especially challenging [3].

As part of a risk management plan, risk minimization activities are carried out to reduce the risk of drugs based on safety concerns. The EU defines risk minimization activities as "interventions intended to prevent or reduce the occurrence of adverse reactions associated with exposure to a drug, or to reduce their severity or impact on a patient, should adverse reactions occur". Routine risk minimization activities normally provide an adequate discourse of the safety concerns of a drug. In exceptional cases, however,

routine risk minimization activities are rather insufficient for some risks, and thus additional risk minimization activities are required to manage the risk and/or improve the risk–benefit balance of a drug [6, 7].

Similar to the EU, in Japan, a risk minimization plan is defined as "consolidated individual risk minimization activities conducted to minimize the risk of a medicine and to maintain an appropriate benefit-risk balance". In addition, it says that "the risk minimization activities are classified into two categories; i.e., routine activities conducted for all drugs and additional activities conducted, if necessary, according to the characteristics of the product" [4].

Although creating a document of a risk management plan is not required in the USA, additional risk minimization activities are planned and conducted for some drugs in the USA as in the EU and Japan. The US Food and Drug Administration (FDA) states on its website that "A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks". It also says that "While all medications have labeling that informs health care stakeholders about medication risks, only a few medications require a REMS" [8].

The aim of this research was to investigate the status of implementing additional risk minimization activities in the EU, the USA, and Japan, and to understand these characteristics. We also sought to investigate the characteristics of additional risk minimization activities that are commonly conducted in all three countries/regions with different regulations, medical environments, and cultures.

2-2. Methods

2.1 Drugs Investigated

As pharmaceutical companies in Japan were requested to prepare a risk management plan for new drug applications on and after 1 April, 2013, we investigated new drugs approved from 2013 to 2017 in the EU, the USA, and Japan, although, the EU and the USA had started the regulation earlier. The approved drugs were extracted from the lists of new active substances placed at the end of the review performance reports for the EU, the USA, and Japan published annually by the Center for Innovation in Regulatory Science [9–13]. Furthermore, to equalize the influence by drugs, we identified drugs approved in all three countries/regions, the EU, the USA, and Japan, during this period.

2.2 Implementation of Additional Risk Minimization Activities in the European Union (EU), the USA, and Japan

We accessed the following websites of the regulatory authorities and compiled information about the presence or absence of additional risk minimization activities and their contents for each drug along with the information on its therapeutic indications:

EU: EPAR

(https ://www.ema.europ a.eu/en/medicines)

USA: REMS

(https ://www.acces sdata.fda.gov/scrip ts/cder/rems/index .cfm)

Japan: RMP

(https://www.pmda.go.jp/safety/info-services/drugs/items-information/rmp/0001.html).

In Japan, as “Early Post-marketing Phase Vigilance (EPPV)” is uniformly implemented as an additional risk minimization activity against new drugs, it was excluded from the tabulation. In the USA, “Medication Guide” is sometimes prepared separately from REMS as an explanatory document for patients. Because its content is similar to the explanatory material prepared for patients in the EU and Japan for routine risk minimization activities, we excluded medication guides created separately from REMS from the tabulation. Subsequently, to comprehend the characteristics of drugs where additional risk minimization activities are being implemented, Anatomical Therapeutic Chemical (ATC) Classification was utilized. In addition, safety concerns for additional risk minimization activities were coded by the Medical Dictionary for Regulatory Activities version 21.0, and the number of safety concerns per drug and the major classification by organ were tabulated.

2.3 Additional Risk Minimization Activities Commonly Conducted in the EU, the USA, and Japan

To identify the additional risk minimization activities implemented commonly for drugs regardless of countries/ regions, we compared the implementation of such activities for common drugs approved in the three countries /regions and analyzed the contents of the activities from the viewpoint of whether they intended risk mitigation or risk prevention; the data were analyzed separately for three countries/regions (EU, USA, and Japan) or two countries/ regions (EU and USA, EU and Japan, or USA and Japan).

The following definitions were employed for risk mitigation and risk prevention [5, 14]:

Risk Mitigation: reduction in the severity of an undesirable outcome should it occur (e.g., providing information such as initial symptoms and methods for early detection

of adverse events through explanatory materials).

Risk Prevention: reduction in the frequency of occurrence of an undesirable outcome in a population, population subset, or an individual patient (e.g., a pregnancy program that requires healthcare providers and patients to confirm that the patients are not pregnant in advance of the prescription).

2-3. Results

2-3-1. Drugs Investigated

The number of new drugs approved from 2013 to 2017 was 159 in the EU and 197 in the USA. It was 182 in Japan, and of these, 142 were subjected to risk management plan regulation. Among these drugs, 45 were approved in all three countries/regions.

2-3-2. Implementation of Additional Risk Minimization Activities in the EU, the USA, and Japan

The status of the implementation of additional risk minimization activities for new drugs approved from 2013 to 2017 was 26.4% (42/159 drugs) in the EU, 7.6% (15/197 drugs) in the USA, and 64.8% (92/142 drugs) in Japan. Compared to the EU and the USA, additional risk minimization activities were implemented for many drugs in Japan, although it is on a declining trend (Figure. 1).

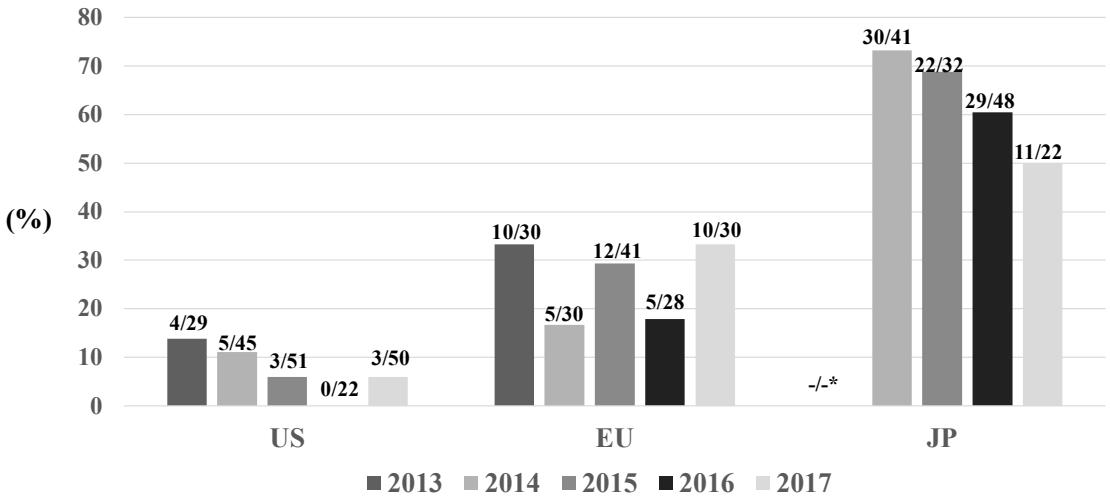

Figure 1. Implementation ratio of additional risk minimization activities in new active substances

The numbers shown in the figure are the number of additional risk minimization activities / number of approval drugs
*In 2013, there were no new drugs targeted for the creation of RMP in Japan

When we examine the 45 new drugs approved in all three countries/regions, the status of implementing additional risk minimization activities was 28.9% (13/45 drugs) in the EU, 13.3% (6/45 drugs) in the USA, and 77.8% (35/45 drugs) in Japan. Similar to the implementation status of all new drugs approved from 2013 to 2017, additional risk minimization activities were implemented for many drugs in Japan compared to the EU and the USA.

Among the 45 new drugs, drugs classified as "A: Alimentary tract and metabolism", "C: Cardiovascular system", and "L: Antineoplastic and immunomodulating agents" based on the ATC classification were confirmed to have high implementation rates in the three countries/regions (Table 1).

Table 1. Implementation rate of additional risk minimization activities by drug ATC classification.

ATC classification	New Drug Approvals (n)	Additional Risk Minimization Activities [n (%)]		
		EU	US	JP
A Alimentary Tract and Metabolism	6	3 (50.0)	1 (16.7)	5 (83.3)
B Blood and Blood Forming Organs	1	1 (100.0)	0	0
C Cardiovascular System	4	1 (25.0)	2 (50.0)	4 (100.0)
H Systemic Hormonal Preparations (Excl. Sex Hormones and Insulins)	1	0	0	0
J Anti-infectives for Systemic Use	5	0	0	1 (20.0)
L Antineoplastic and Immunomodulating Agents	23	7 (30.4)	3 (13.0)	22 (95.7)
M Musculo-Skeletal System	1	0	0	0
R Respiratory System	1	0	0	1 (100.0)
V Various	3	1 (33.3)	0	2 (66.7)
Total	45	13 (28.9)	6 (13.3)	35 (77.8)

For drugs classified as “A: Alimentary tract and metabolism”, three were for type 2 diabetes mellitus, and the remaining three were for hypophosphatemia, Gaucher’s disease, and lysosome-producing lipase deficiency (see the Appendix 1. for a list of approved common drugs in the EU, the USA, and Japan and the implementation status of additional risk minimization activities). For the 45 new drugs, the average numbers of safety concerns accompanying additional risk minimization activities were 2.8/drug for the EU, 1.3/drug for the USA, and 8.4/ drug for Japan. The average number of safety concerns to be considered for each drug was shown to be larger in Japan than in the EU and the USA (Figure. 2).

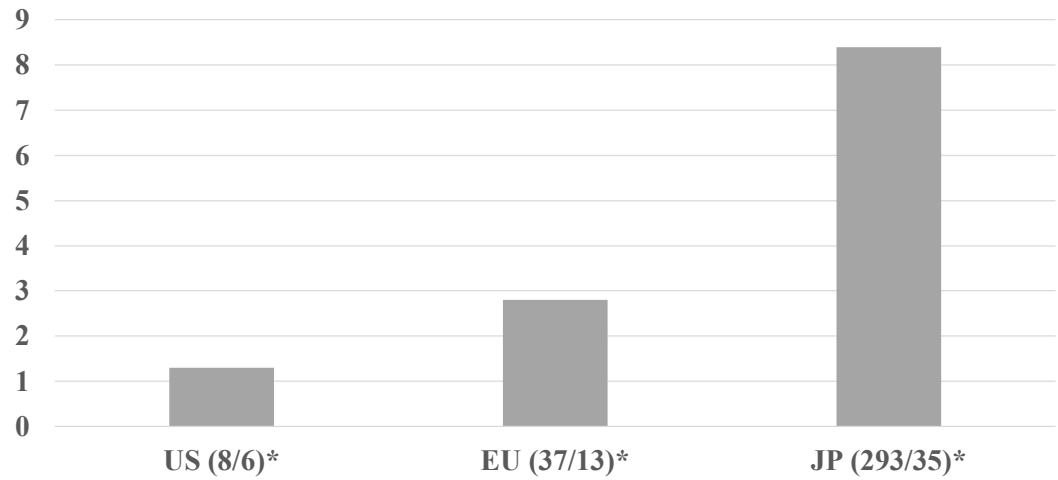

Figure 2. Average number of safety concerns in one drug

*The numbers shown in the figure are the number of safety concerns / number of additional risk minimization activities

Based on the safety concerns classified by the Medical Dictionary for Regulatory Activities System Organ Class, more safety concerns classified as “Blood and lymphatic system disorders” were subjected to additional risk minimization activities in the EU and Japan (Table 2). They included hemocytopenia due to immunosuppression caused by sarilumab, an antirheumatic, and neutropenia and thrombocytopenia caused by pomalidomide, an anticancer drug. In the USA, however, there were no safety concerns classified as “Blood and lymphatic system disorders” for additional risk minimization activities. “Teratogenicity” was the major safety concern subjected to additional risk minimization activities. “Medication errors, product use errors and issues NEC” was only seen in the EU (i.e., this was absent in the USA and Japan).

Table 2. Top 3 Safety Concerns subjected to additional risk minimization activities based on Systemic Organ Class by MedDRA for the 45 new drugs approved in all three countries/region

	EU (37)	US (8)	JP (293)
1	-Blood and lymphatic system disorders (4) -Nervous system disorders (4)	-Congenital, familial, and genetic disorders (3)	-Vascular disorders (25)
2	-Medication errors, product use errors and issues (3) -Endocrine disorders (3) -Immune system disorders (3)	-Gastrointestinal disorders (2)	-Gastrointestinal disorde rs (24) -Blood and lymphatic system disorders (24)
3	-Gastrointestinal disorders (2) -Infections and infestations (2) -Hepatobiliary disorders (2) -Congenital familial and genetic disorders (2) -Metabolism and nutrition disorders (2)	-Cardiac disorders (1) -Psychiatric disorders (1) -Neoplasms benign, malignant, and unspecified (including cyst and polyps) (1)	-Infections and infestations (23)

Numbers in parentheses indicate the number of safety concerns

2-3-3. Additional Risk Minimization Activities Commonly Conducted in the EU, the USA, and Japan

Fourteen drugs had additional risk minimization activities implemented in at least two of the three countries/regions studied (Table 3). By ATC classification, drugs classified as “L: Antineoplastic and immunomodulating agents” accounted for the majority (8/14 drugs).

For safety concerns that are subjected to additional risk minimization activities, teratogenicity for macitentan (pulmonary arterial hypertension) and pomalidomide (multiple myeloma) was confirmed as a common safety concern in all three

countries/regions (Table 4). There are some drugs for which additional risk minimization activities on teratogenicity were conducted in a country: riociguat in the USA, avelumab and apremilast in Japan. For the risk minimization activities implemented in two countries/regions, immune-related adverse events and adverse events associated with myelosuppression caused by anticancer drugs, suicidal behavior caused by drugs for psoriasis, hypersensitivity due to the administration of protein drugs, and caution when handling radiopharmaceuticals were confirmed to be common safety concerns.

As a result of the subsequent analysis of the contents of additional risk minimization activities from the viewpoint of risk mitigation or risk prevention, measures to mitigate the risk by providing additional information to healthcare providers and/or patients (risk mitigation) were taken for all drugs for which additional risk minimization activities were commonly implemented in all three countries/regions or in two countries/ regions. In contrast, although measures that aimed to prevent the risk (risk prevention) were implemented for four drugs out of five in the USA, they were performed for only one drug in the EU and for none in Japan (Table 5).

For safety concerns, “teratogenicity” was the subject of additional risk minimization activities commonly set in the EU, the USA, and Japan; access control (risk prevention) was adopted in the EU and the USA for macitentan and in the USA alone for pomalidomide.

Table 3. List of drugs with risk minimization activities in all three counties/region or in two countries/region

3-A. Drugs with additional risk minimization activities in all three countries/region
-Macitentan (pulmonary arterial hypertension) -Panobinostat lactate (multiple myeloma) -Pomalidomide (multiple myeloma)

3-B. Drugs with additional risk minimization activities in two countries/region
The EU and Japan (9 drugs) - Asfotase alfa (low phosphatase disease) - Avelumab (Merkel cell carcinoma) - Daratumumab (multiple myeloma) - Eliglustat tartrate (Gauche disease) - Flutemetamol (18 F) (radiopharmaceutical for β amyloid detection for patients suspected of Alzheimer's disease) - Nivolumab (malignant melanoma, non-small cell lung cancer etc.) - Pembrolizumab (malignant melanoma, non-small cell lung cancer etc.) - Sarilumab (rheumatoid arthritis) - Sebelipase alfa (lysosomal acid lipase deficiency) **The USA and Japan (2 drugs)** - Brodalumab (psoriasis) - Riociguat (pulmonary hypertension) **The EU and the USA (0 drugs)**

Parentheses indicate the indication of the drug

Table 4. Drugs and their safety concerns (MedDRA PT) for which additional risk minimization activities are conducted in all three countries/region

	EU	USA	JAPAN
Macitentan	Anemia Hepatotoxicity Teratogenicity	Teratogenicity	Anemia Hemoglobin decreased Hepatic function abnormal Teratogenicity Blood pressure decreased
Pomalidomide	Teratogenicity Neutropenia Embolism Neuropathy peripheral Infection Thrombocytopenia Tumor lysis syndrome Somnolence	Teratogenicity	Teratogenicity Bone marrow failure Embolism Neuropathy peripheral Infection Tumor lysis syndrome Somnolence Confusional state Fatigue Dizziness Acute kidney injury Cardiac failure Arrhythmia Interstitial lung disease Hypersensitivity Hepatic function abnormal Jaundice Neoplasm malignant
Panobinostat	Medication error	Diarrhea Cardiotoxicity	Electrocardiogram QT prolonged Bone marrow failure Hemorrhages Infection Hepatic function abnormal Renal impairment Diarrhea, Nausea, Vomiting Dehydration Hypotension Orthostatic hypotension Syncope, Loss of consciousness

Table 5. Details of the implementation of additional risk minimization activities based on classification either as risk prevention or risk mitigation by drugs

		EU (n)	USA (n)	JAPAN (n)
EU/USA/JAPAN (3)	Mitigation	3	3	3
	Prevention	1	2	0
EU/JAPAN (9)	Mitigation	9	-	9
	Prevention	0	-	0
USA/JAPAN (2)	Mitigation	-	2	2
	Prevention	-	2	0

Numbers in parentheses indicate the number of drugs

2-4. Discussion

In the present study, we investigated the status of additional risk minimization activities that have been implemented in the EU, the USA, and Japan for drugs recently approved in the three countries/regions. In addition, we elucidated the characteristics of the additional risk minimization commonly carried out in these countries/regions with different regulations, medical environments, and cultures.

As for the status of additional risk minimization activities, in the USA, the number of newly approved drugs for which the additional risk minimization activities were implemented was limited, and there was a tendency to adopt measures to prevent risks such as access control, which would serve as a more reliable strategy for risk management. However, in Japan, although additional risk minimization activities were implemented for more than half of the approved drugs, most strategies were intended to mitigate risks through the provision of additional information to healthcare providers and patients. In

the EU, the number of additional risk minimization activities being implemented and the details regarding these implementations were found to lie between the USA and Japan.

As discussed at the time of the ICH E2E development, differences in regulatory thinking, as well as medical systems, such as the number of healthcare providers per patient and the insurance system, and cultural differences, appear to greatly impact the risk minimization activity [3].

It was revealed in this research that the majority of the ATC classifications of drugs with additional risk minimization activities were “A: Alimentary tract and metabolism”, “C: Cardiovascular system”, and “L: Antineoplastic and immunomodulating agents” in all three countries/regions. The impact of the launch of immunotherapy products called the fourth therapeutic generation, which have different features of side effects and treatments to the conventional therapies, seemed significant in the field of antineoplastic agents. As for drugs classified as “A: Alimentary tract and metabolism”, they were drugs for type 2 diabetes with novel mechanisms of action such as sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists, and some orphan drugs. When the methods to deal with side effects for the novel drugs differ from those for the conventional therapies, additional risk minimization activities may be required to ensure dissemination of information on the treatment.

For the safety concerns subjected to additional risk minimization activities, Japan was confirmed to have a larger average number of safety concerns per drug than the EU and the USA, implying that, while additional risk minimization activities are conducted against “a specific risk” in the EU and the USA, such activities are implemented against “a drug” in Japan.

Among the 45 drugs approved in the EU, the USA, and Japan, “teratogenicity” was confirmed as a common safety concern for two drugs for which additional risk minimization activities were conducted in the three countries/regions. “Teratogenicity” was considered to be a factor/feature of drugs for which risk minimization activities were needed regardless of the differences in regulation, medical environment, and culture. However, because the contents of implementation ranged from access control to provision of information alone even for the same drug, the contents of activities are considered to be influenced by the medical environment and ideas of the country. Furthermore, for example, although additional risk minimization activities are conducted for riociguat in the USA and Japan, teratogenicity is the safety concern for the activity in the USA, but not in Japan. Therefore, “teratogenicity” does not necessarily mean the common safety concern for additional risk minimization activities in all countries/regions.

When the contents of the additional risk minimization activities were classified either as risk prevention or risk mitigation, it was confirmed that most additional risk minimization activities were for risk mitigation in which additional information was provided to healthcare providers and patients. Although risk prevention with access control can certainly prevent risks, it may lead to loss of treatment opportunities. It can also make the process for healthcare providers and companies more complicated and increase the burden on the entire medical system. Therefore, it is reasonable that the number is limited in all countries/region.

There were some limitations to this study. The contents of the additional risk minimization activities such as explanatory materials for healthcare providers were not

evaluated in the present study because we focused on the overall status of additional risk minimization activities among the countries/ regions. If the amount of additional information given to healthcare providers and patients increases excessively, it may complicate their understanding of the risks. It would be a task to evaluate the volume of information and type of contents to enhance the efficacy of explanatory materials, because the most common additional risk minimization activities are materials for healthcare professionals in Japan [16].

Another limitation was that, because this study was focused on additional risk minimization activities, we have not investigated the details of routine risk minimization activities. Additional risk minimization activities are planned and conducted based on the routine risk minimization activities. Investigations of the details of the routine risk minimization activities would help to better understand the difference in medical systems and regulatory thinking among the three countries/regions.

3. Research 2

3-1. Background and objective

In Japan, the Ministry of Health, Labour and Welfare issued the "Risk Management Plan Guidance" in 2012, which have been implemented since 2013, in response to the final recommendation by the Pharmaceutical Administration Review Committee for the verification of drug-induced hepatitis cases and prevention of recurrence in 2010 [4, 15]. This guidance includes risk minimization measures in addition to pharmacovigilance activities, which have already been implemented, as per the concepts from the ICH E2E Guideline [4].

Risk minimization measures includes routine activities that are performed for all drugs, and additional measures that are undertaken as needed based on the characteristics of the drug and other factors. Generally, safety concerns about an approved drug can be addressed sufficiently with routine risk minimization measures; when such routine measures are judged insufficient, additional risk minimization activities are planned and implemented for specific risks [4].

As found in Research 1, more additional risk minimization activities were conducted in Japan than in other countries, and there were many safety concerns that require additional measures. These measures may be considered a "burden" on the entire healthcare system, and risk minimization measures that truly require additional information provision may be missed in the process.

Regarding the types of additional risk minimization activities, Guadamuz et al. (2020) reported that Elements to Assessment of Safe Use, which minimizes risk by restricting the use of drugs in specific ways, accounted for 91.3% of additional risk minimization activities in the USA. Furthermore, they reported that the number of communication plans

had decreased year by year and accounted for 8.8% of the total at the time of reporting [17]. On the other hand in Japan, Sato et al. (2017) reported in terms of the ratio of activity status to the number of safety concerns for drugs, the percentage of materials created for healthcare professionals accounted for 38.3%, followed by information provision by EPPV (27.1%) and materials created for patients (16.8%) [16]. Since EPPV is required to all new approved drugs, the provision of information to healthcare professionals are mostly implemented.

Therefore, in Research 2, we investigated the status and contents of information materials created for healthcare professionals, which are most commonly implemented as additional risk minimization activities in Japan, and discussed how they should be treated.

3-2. Methods

The following study and analysis were conducted for 102 new drugs (pharmaceutical products containing new active ingredients) approved in Japan from 2016 to 2018 [12, 13, 18].

3-2-1. Understanding the status of the creation of information materials for healthcare professionals

The Risk Management Plan (RMP) of the target product was obtained from the website of the Pharmaceuticals and Medical Devices Agency (PMDA), and information on safety concerns and additional risk minimization activities was extracted. In addition, we collected information on the ATC classification of the target product. For each product, we checked the existence or absence of information materials for healthcare professionals as additional risk minimization activities, examined related annual trends, and

summarized the status by ATC classification.

3-2-2. Analysis of the contents of the materials for healthcare professionals

Materials for healthcare professionals were obtained from the PMDA's website [19]. Besides identifying the safety concerns, the name of the material, total number of pages, and information on the pages describing the target safety concerns were investigated. Based on the information obtained, the percentage of the number of safety concerns in the material relative to the safety concerns described in the RMP and the percentage of the pages describing the safety concerns relative to the total number of pages of material developed for healthcare professionals were determined.

3. Study of the characteristics of the materials for healthcare professionals

Information materials for healthcare professionals as additional risk minimization activities are prepared to minimize risks associated with specific safety concerns and are provided to healthcare professionals, in addition to the package insert as a routine risk minimization activity [4]. The European guideline states that materials should be as concise as possible with clear descriptions and concise messages that focus on specific safety concerns and indicate the measures taken to avert and minimize these risks.

Further, the range of information should be limited to the agreed key elements (main matters) and should not include efficacy data, comparison of safety information with that of other drugs, and additional information such as statements which imply that the medicine is well tolerated or that adverse reactions occur with a low frequency [20]. On the other hand, there are no specific guidelines for the contents of materials in Japan [4].

Therefore, it was set the following criteria as desired characteristics of the materials: (1)

safety concerns of interest are narrowed down and (2) contents of the materials are clear and concise. Materials with these characteristics were selected and their contents were confirmed. Regarding (1) safety concerns are narrowed down, since the average number of the target safety concerns per drug in additional risk minimization activities was 2.8 per drug in the EU and 1.3 per drug in the USA, we set the number of safety concerns as 3 or less. With regard to (2) clear and concise content, we judged whether the contents of the target safety concerns are recognizable from the cover page of the material.

3-3. Results

3-3-1. Understanding the creation status of information materials for healthcare professionals

Of the 102 new drug products studied, information materials for healthcare professionals were created 61 drugs (59.8%) as an additional risk minimization activity, and the total number of materials was 70. The proportion of drugs for which materials were created was stable throughout the study period (Figure 3).

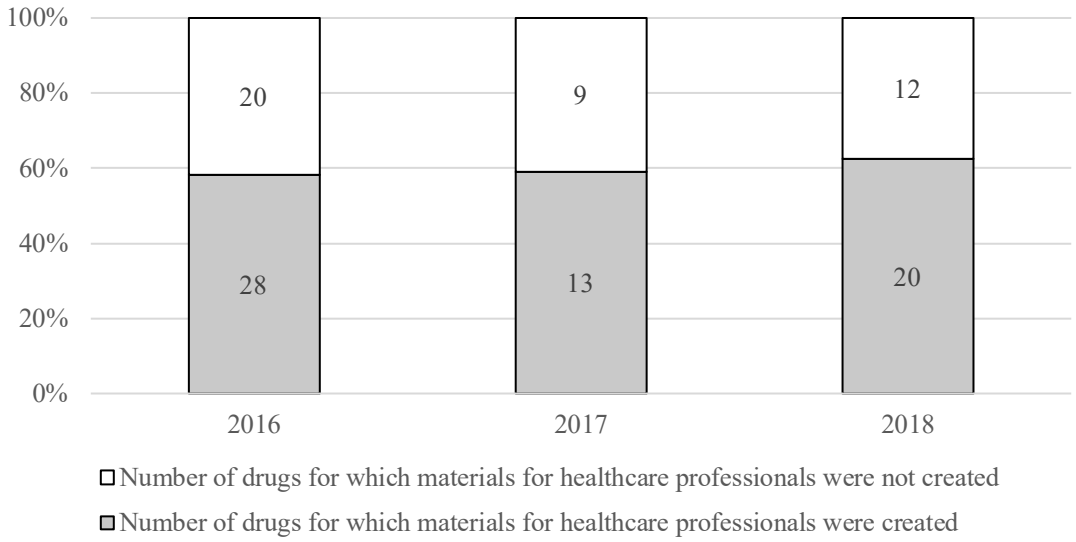

Figure 3. Creation status of materials for healthcare professionals as an additional risk minimization activity

In terms of ATC classification, the proportion of drugs for which materials for healthcare professionals were created as additional risk minimization activities was large for drugs classified as L. Antineoplastic and immunomodulating agents and C. Cardiovascular system (Figure 4).

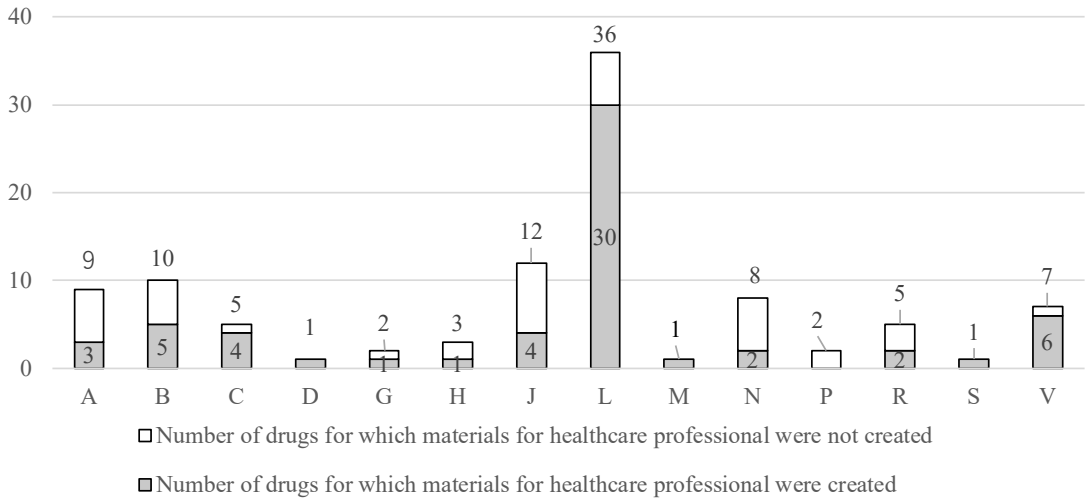

Figure 4. Creation status of materials for healthcare professionals by ATC classification of drugs

A: Alimentary tract and metabolism; B: Blood and blood-forming organ; C: Cardiovascular system; D: Dermatologicals; G: Genito-urinary system and sex hormones; H: Systemic hormonal preparations, excl. sex hormones and insulins; J: Anti-infectives for systemic use; L: Antineoplastic drugs and immunomodulating agents; M: Musculoskeletal system; N: Nervous system; P: Antiparasitic products, insecticides, and repellents; R: Respiratory system; S: Sensory organs; V: Various

2. Analysis of the contents of the materials for healthcare professionals

The number of safety concerns described in the RMP of each drug was 8.3 on average (range: 1–21, standard deviation (SD): 4.8), and among these, the average of 71.4% (range: 0–100, SD: 31.2) of the safety concerns were the target for the information materials for healthcare professionals. This percentage varied greatly depending on the drug, and some materials focused on a specific safety concern, whereas others included almost all safety concerns (Figure 5). In addition, some materials for healthcare professionals were not directly related to any of the safety concerns described in the RMP.

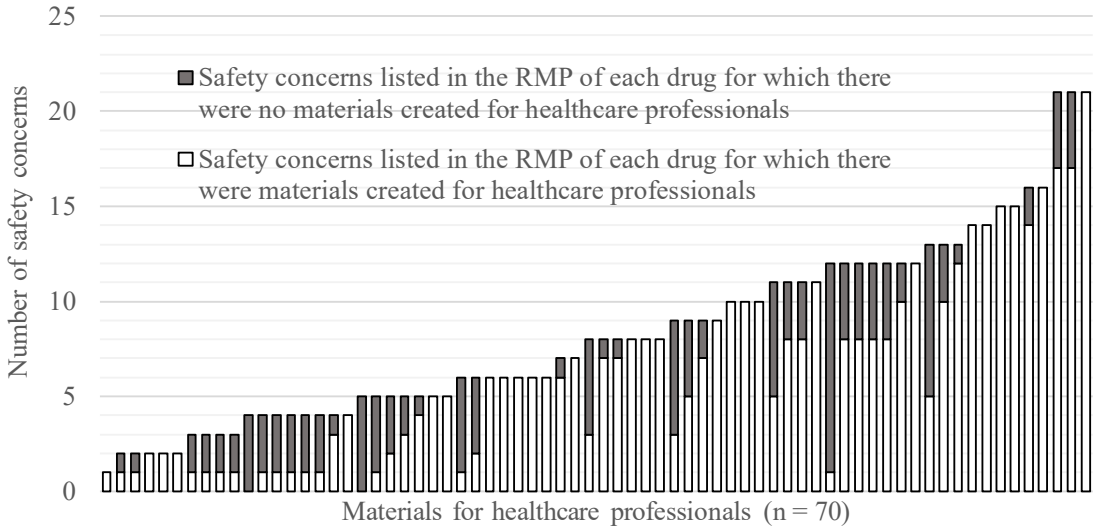

Figure 5. Safety concerns in drug RMPs and ratio of safety concerns for creating healthcare professionals' materials.

The materials are arranged in ascending order of the number of safety concerns listed in the RMP. The numbers of safety concerns included in the materials for healthcare professionals are represented in black, and the numbers of concerns that are not included in the materials as described in the RMP are shown in white.

The average number of pages of materials for healthcare professionals as additional risk minimization activities was 34.4 (SD: 27.4); some materials had only one page and some had as many as 130 pages. Thus, the number of pages varied greatly depending on the material. The average number of pages related to the target safety concerns for materials was 13.2 pages, with an average of 33.7% of the total number of pages of the materials (range: 0–100, SD: 27.7). Some materials contained only specific information related to the target safety concerns while others contained a great deal of other contents (Figure 6). Descriptions other than the target safety concerns included easy-to-understand diagram for preparation and administration of the drug and descriptions of the package insert. In addition, there were some materials that contained no description of the contents of the target safety concerns.

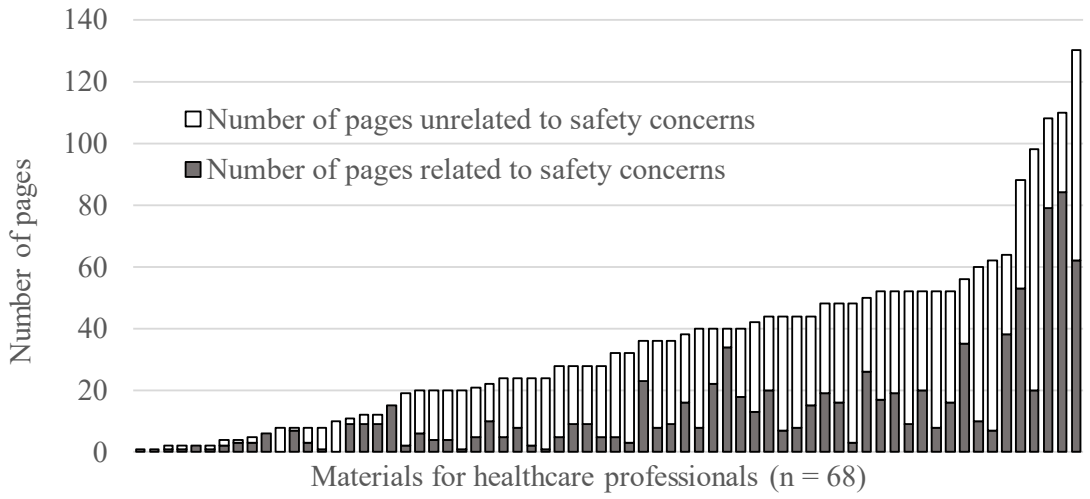

Figure 6. Number of pages of materials for healthcare professionals and percentage of safety concern-related pages

The number of pages relating to safety concerns pertaining to additional risk minimization activities is shown in black, and the number of other pages is shown in white, starting with materials with a small number of pages. The number does not include the two materials not available on the PMDA website.

3. Study of the characteristics of the materials for healthcare professionals

Ten materials created for nine drugs met the criteria of (1) the number of safety concerns being three or less and (2) safety concerns could be recognized from the cover page of the material (Table 6). Four materials were related to adverse events (1–4 in Table 6), three materials were related to the effect on laboratory tests (5–7 in Table 6), two materials were related to patient selection (same products, #8 and 9 in Table 6), and one material was related to medication dispensing-related errors (10 in Table 6).

Table 6. List of information materials meeting the criteria for desired characteristics of the material

	Generic name	Indications	Number of safety specification (SS) described in RMP	SS for use in creating materials for healthcare professionals	Name of the material	Number of material pages	Number of SS-related pages	Percentage of SS in materials (%)
1	Blinatumomab (genetic recombination)	Recurrent or refractory B-cell acute lymphocytic leukemia	6	*Neurological events *Cytokine release syndrome (CRS)	Proper Use Guide	32	6	18.8
2	Baloxavir marboxil	Influenza A or B influenza virus infection	4	Mental and neurological symptoms	For healthcare professionals (precautions to be undertaken for influenza patients)	1	1	100.0
3	Letermovir	Inhibition of sitemegalovirus infection in allogeneic hematopoietic stem cell transplant patients	3	*Reproductive toxicity	Request for proper use of medicine when administering to pregnant women or women who might be pregnant and women who might become	5	3	60.0
4	Palbociclib	Inoperable or recurrent breast cancer	5	*Interstitial lung diseases	Sensitive side effects of IBRANCE capsules and their countermeasures	11	9	81.8
5	Damoctocog Alfa Pegol (genetic recombination)	Inhibition of bleeding tendency in patients with blood coagulation Factor VIII deficiency	4	*Dose error caused by the measurement method of blood coagulation factor VIII activity	Recommended activated partial thromboplastin time reagent suitable for measuring plasma blood coagulation VIII factor activity after intravenous administration of Jivi	2	1	50.0
6	Lonoctocog alfa (genetic recombination)	Inhibition of bleeding tendency in patients with blood coagulation Factor VIII deficiency	3	*Dose errors caused by the measurement method of factor VIII activity	Precautions for measurements of factor VIII activity during intravenous administration of Afstyla	4	3	75.0
7	Daratumumab (genetic recombination)	Multiple myeloma	6	*Interference with indirect Coohms test (positive for indirect Coohms test)	Materials for the Blood Transfusion Testing Department (Notes on Blood Transfusions)	1	1	100.0
8	Migalastat hydrochloride	Fabry's disease with GLA gene mutation responsive to Migalastat	4	*Administration to patients with GLA gene mutations nonresponsive to Migalastat	A guidebook for selecting patients for treatment by GALAFOLD capsules	12	9	75.0
9	Migalastat hydrochloride	Fabry's disease with GLA gene mutation responsive to Migalastat	4	*Administration to patients with GLA gene mutations nonresponsive to Migalastat	List of GLA gene mutations responsive to GALAFOLD	8	7	87.5
10	Florbetapir (18F)	Visualization of amyloid beta plaque in the brain of patients with cognitive dysfunction and suspected of having Alzheimer's disease	2	*Mistake in the formulations for different amounts of radioactivity in medical institutions	Instructions for the purpose of preventing errors	6	6	100.0
	SS: safety specification							

Most of the materials were focused on specific safety concerns and provided clear explanations and concise messages that indicated the measures to be taken to avoid and minimize these risks. For example, in the material for baloxavir marboxil (warning to influenza patients), features and cases of fall deaths that are considered related to abnormal behavior and measures to prevent such accidents are summarized in one page. In addition, to make them easy to recognize, bold font and boxed characters were used in the material. On the other hand, a guide for the appropriate use of blinatumomab (genetic recombination) contains extensive information besides safety concerns such as dosage and method of administration and dosage adjustment of the drug, and an overview of clinical trials (Table 7).

Table 7. Table of contents for issues related and unrelated to the safety concerns in "Proper Use Guide" for blinatumomab (genetic recombination)

Table of contents for issues related to the safety concerns
*Significant adverse reactions and countermeasures (neurological events, cytokine release syndrome [CRS]) *Adjustment of the dose due to side effects
Table of contents for issues not related to the safety concerns
*Confirmation of the patient to be treated with the drug *In administrating drugs (dosage and administration, schedule of administration) *Preparation method and precautions in administrating *Precautions before and during administering *Q&A *Overview of clinical trials *Safety information (major adverse events in clinical trials in Japan and overseas)

3-4. Discussion

We investigated the actual conditions of information materials for healthcare professionals as additional risk minimization activities in the RMP. It was found that information materials for healthcare professionals were frequently created for newly approved drugs in Japan. In terms of the therapeutic area of the drugs, the proportions were large for antineoplastic and immunomodulating drugs, and drugs for cardiovascular system. The reason for this was considered the relatively high safety risk associated with these drugs.

Regarding the number of safety concerns targeted in the healthcare professional materials and the ratio of them among those described in the RMP, both varied widely depending on the drug. Some materials covered all safety concerns described in the RMP, while others focused on specifically one or two of the safety concerns. The contents of the material also varied from those that focused on the target safety concerns to those that also contained other information. With regard to the information unrelated to the safety concerns, there were materials containing an easy-to-understand diagram for the preparation and administration of the drug and descriptions of the package insert. Many of these materials, called “proper use guide” or had similar names, covered necessary information required for drug administration in clinical practice.

Additional risk minimization activities are to be conducted, in addition to routine risk minimization activities as needed, to cope with specific safety concerns considering factors such as the characteristics of the drug [4]. Accordingly, as in the EU and the USA, it is considered preferable to create materials that specialize in particular safety concerns that require additional measures. This study investigated into the contents of the materials by identifying materials for which the number of target safety concerns was narrowed down, and the target safety concerns were identifiable from the cover page of the material. Most of the identified materials were specialized in the target safety concerns, and their message was concise. On the other hand, many materials not pertinent to the criteria for desired characteristics of the materials had a name of “proper use guide” or similar ones. These materials were composed mainly of general information to promote appropriate use of the drugs. Therefore, it was considered that the additional risk minimization activities were conducted for the drug itself rather than for the individual safety concerns.

A limitation of this study was that it mainly focused on materials for healthcare professionals among several additional risk minimization activities and did not cover activities such as distribution control for drug products and information materials for patients.

4. Overall Discussion

The result of Research 1 showed that only drugs with a risk of teratogenicity or a new mechanism of action had additional risk minimization activities commonly in more than one country/region, which could be understood as medication-derived factors. At the same time, it was assumed that the contents of additional risk minimization activities were influenced by the medical environment and how the countries/regions think. Through the combined experience of implementing additional risk minimization activities and establishing their evaluation methods, we anticipate that additional risk minimization activities will be harmonized more effectively among the countries/regions with a different culture, medical service, and medical system in the future.

Through this research, it was revealed that more additional risk minimization activities are conducted in Japan than in other countries, and also there are many safety concerns that require additional measures. Although additional risk minimization activities are effective for improving the benefit-risk balance of drugs, the result suggested that these measures may be too much and considered as “burden” on the entire healthcare system, and also risk minimization measures that truly require attention among healthcare professionals may be missed in the process in Japan. Therefore, we thought it is necessary to narrow down drugs and associated risks for which additional risk minimization activities are conducted. Furthermore, against this background, in Research 2, we investigated the information materials for healthcare professionals, which are most commonly implemented as additional risk minimization activities in Japan. As a result, it was shown that both the number of the target safety concerns in the healthcare professional materials and the ratio of them among those described in the RMP varied widely depending on the drug. Some materials covered all safety concerns described in

the RMP, while others focused on specifically one or two of the safety concerns. The contents of the material also varied from those that focused on the target safety concerns to those that also contained other information.

Basically, additional risk minimization activities should be undertaken only when routine risk minimization activities alone are inadequate to manage the risk [4]. In healthcare settings, many drugs are used concurrently. Under such circumstances, additional risk minimization activities are undertaken for nearly 80% of the new drugs in Japan; many of these activities are distribution of information materials for healthcare professionals, which are intended to encourage appropriate use of the drug instead of focusing on specific safety concerns. Thus, it would be difficult to attract adequate attention of healthcare professionals, which may lead to failure in implementing the activities efficiently. The content of the information materials should be focused on specific risks and must accurately and concisely convey the information necessary to minimize the risks.

It is also important to evaluate the effectiveness of additional risk minimization activities whether those activities have the desired effect and whether it is overloading the healthcare system [3, 4, 6, 21], but it is difficult to accurately evaluate the effectiveness of materials such as “proper use guide”, because there are a large number of safety concerns to be covered and contents other than the safety concerns are also included in the materials. Further, considering the burden on healthcare professionals, pharmaceutical companies, and regulatory authorities in the situation where a large number of new drugs are subject to the additional risk minimization activity under the RMP, evaluation of the effectiveness of the information materials is a huge task and not realistic.

In Japan, “proper use guide” and similar materials are commonly used in clinical

practice and are highly convenient. Therefore, it would be more appropriate to separate the materials intended for proper use of drugs from those focusing on safety concerns that require additional measures. One option would be to classify those materials as part of routine risk minimization activities or to establish another framework within the additional risk minimization activities.

5. Conclusion

While additional risk minimization measures are important activities to minimize risks, they are largely influenced by differences in regulatory thinking, medical systems and culture among countries/regions. Even considering it, more additional risk minimization measures are conducted in Japan, and they might be considered as “burden” on the entire healthcare system; risk minimization measures that truly require attention among healthcare professionals may be missed in the process. To optimize these activities in Japan, it is necessary to narrow down drugs and associated risks for which additional risk minimization activities are conducted. Regarding the content of the information materials, it should be focused on specific risks and must accurately and concisely convey the information necessary to minimize the risks. In healthcare settings, it is essential to properly monitor whether those activities have the desired effect and whether it is overloading the healthcare system.

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Appendix

Appendix Table 1. The list of approved common drugs in EU, USA and Japan and the implementation status of additional risk minimization measures

ATC classification	Generic name	EU	US	JP
A Alimentary Tract and Metabolism	Asfotase alfa (genetical recombination)	Y		Y
	Canagliflozin hydrate			Y
	Dulaglutide (genetical recombination)		Y	
	Eliglustat tartrate	Y		Y
	Empagliflozin			Y
	Sebelipase alfa	Y		Y
B Blood and Blood Forming Organs	Selexipag	Y		
C Cardiovascular System	Alirocumab			Y
	Evolocumab			Y
	Macitentan	Y	Y	Y
	Riociguat		Y	Y
H Systemic Hormonal Preparations (Excl. Sex Hormones and Insulins)	Etelcalcetide hydrochloride			
J Anti-infectives for Systemic Use	Bezlotoxumab (genetical recombination)			
	Daclatasvir			Y
	Dolutegravir sodium			
	Glecaprevir hydrate/ Pibrentasvir			
	Sofosbuvir			
L Antineoplastic and Immunomodulating Agents	Alectinib hydrochloride			Y
	Apremilast			Y
	Avelumab (genetical recombination)	Y		Y
	Brodalumab		Y	Y
	Ceritinib			Y
	Dabrafenib mesilate			Y
	Daratumumab (genetical recombination)	Y		Y
	ELOTUZUMAB			Y
	Ibrutinib			Y
	Idarucizumab			Y
	Ixekizumab			Y
	Lenvatinib mesilate			Y
	Nintedanib ethanesulfonate			Y
	Nivolumab (genetical recombination)	Y		Y
	Osimertinib mesilate			Y
	Palbociclib			
	Panobinostat lactate	Y	Y	Y
	Pembrolizumab	Y		Y
	Pomalidomide	Y	Y	Y
	Ramucirumab (genetical recombination)			Y
	Sarilumab (genetical recombination)	Y		Y
	Secukinumab（genetical recombination）			Y
	Trametinib dimethyl sulfoxide			Y
M Musculo-Skeletal System	Nusinersen sodium			
R Respiratory System	Mepolizumab			Y
V Various	Flutemetamol (18F)	Y		Y
	Ixazomib citrate			Y
	Radium （223Ra） dichloride			