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ORIGINAL RESEARCH

A Comparison of Safety Information in Drug Labeling at the Initial Approval of New Drugs Approved Both in Japan and the United States

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Abstract

Purpose Scientific information in the drug labeling is expected to be the most up-to-date and consistent information across countries where medicine is approved. The objective of the present study is to investigate the consistency of safety-related information on product labeling for novel therapeutics concurrently approved in Japan and the US.

Methods Safety information at the time of initial approval of new drugs approved concurrently both in Japan and the US in the recent 7 years were identified and reviewed for concordance. Factors associated with the discordance were also investigated.

Results Despite the similar medical practices, population health, and regulation in Japan and the US, the level of concordance of safety information found in the drug labeling of 45 new active substances was low (20.4%). The development strategy of the drugs and having the same MAH were significantly associated with the concordance rate. The mean concordance rate among the 9 drugs with Black Box Warning in both countries was also low (32.9%).

Conclusions We found a low level of concordance between Japan and the US even when related to clinically important information raised by Black Box Warnings. The low concordance rate highlighted the need for a greater transparency in decision-making processes about the safety information in a drug labeling by both industry and regulators to take appropriate countermeasures against the discordance.

Keywords Adverse drug reaction · Pharmacovigilance · Pharmacoepidemiology · Labeling · FDA · PMDA

Introduction

Drug labeling is the primary tool to communicate the summary of scientific information that is needed for the safe and effective use of drugs by healthcare professionals [1]. While the formal name of the document and the procedure to prepare the document vary from country to country, its primary role shares some similarity among the US, the EU, and Japan. In the era of global drug development and distribution, safety information is gathered from many regions [2]. Therefore, it is expected that the scientific information in the drug labeling is the most up-to-date and consistent information across countries where the medicine is approved.

International inconsistencies in drug labeling could cause a risk to patients in countries where accurate or up-to-date information is not available; however, studies which have discussed international concordance of the safety information in drug labeling are limited to a comparison in the count of words in the document [3, 4] or a comparison focusing on a specific type of drugs or adverse events [5–8]. In a comparison of drug labeling between Denmark and the US, the low consistency of information related to adverse drug reactions was reported [9]. It was a comparison between the US and a European country, and we took an interest in confirming whether similar patterns are observed in other countries that share core pharmaceutical regulations. In addition, to rule out the possibility that the difference in information available at the time of approval in each country causes inconsistency, a comparison of new drugs approved around the same time in different countries is desirable.

The objective of the present study was to investigate the consistency of safety-related information on product labeling

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at the initial approval of novel therapeutics concurrently approved in Japan and the US.

Materials and Methods

Identification of the Cohort of New Drugs Simultaneously Approved in Japan and the US

We investigated all new active substances (NASs) approved in Japan between 2014 and 2020, which were also approved in the US within 6 months from the date of approval in Japan. A list of all NASs approved in Japan between 2014 and 2020 was collected from the List of Approved Products on the Pharmaceuticals and Medical Devices Agency (PMDA) website [10]. Brand name, generic name, applicant name, and approved date were extracted. Compound name was translated into English using the Japanese Accepted Names for Pharmaceuticals (JAN) Database [11].

Next, we determined the drugs approval status in the US. The generic name in English was used for the search in a database provided by US Food and Drug Administration (FDA), Drugs@FDA [12]. Brand name, generic name, name of marketing authorization holder (MAH), and the initial approval date were extracted, if the drug was listed.

For drugs approved in both countries, the difference of initial approval dates was calculated, and each drug was reviewed whether the drug was approved in both countries simultaneously (defined as within 6 months) or not. Drugs simultaneously approved were included in the study cohort. The drugs included in the study cohort were classified according to their Anatomical Therapeutic Chemical (ATC) classification (Level 1) [13]. First-in-class drugs were classified according to the FDA Center for Drug Evaluation and Research's (CDER) annual report [14–16].

Collection of Safety-Related Information in Drug Labeling at the Time of Approval

The drug labeling at the time of approval for each selected NAS in Japan and the US was obtained from the drug information database, SAFE-DI [17] and Drugs@FDA [12], respectively. Safety-related information was defined as safety event terms described in any of the safety-related sections in drug labeling. The safety-related sections for Japanese labeling included WARNINGS, CONTRAINDICATIONS, PRECAUTIONS CONCERNING INDICATIONS, PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION, IMPORTANT PRECAUTIONS, INTERACTIONS, and ADVERSE REACTIONS (Clinically Significant Adverse Reactions and Other Adverse Reactions), and those for the US labeling included BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, and DRUG INSTRUCTIONS.

Concordance Assessment of Safety-Related Information in the Labeling

Each identified item of safety-related information was reviewed for concordance between the two countries. Safety-related term was coded using the Medical Dictionary for Regulatory Activities (MedDRA)/J version 23.0. The safety event terms on labels were firstly coded to MedDRA Low Level Terms, and then concordance was assessed using Preferred Terms (PT). Concordant safety-related information was defined as an exact match of drug-safety-related term between the two countries. Then, we calculated the concordance rate for each NAS by dividing the number of concordant safety-related term by the total number of safety-related information raised in either of the two countries.

Next, we examined factors associated with concordance rate. This study used five groups of explanatory variables, namely (1) development strategy of the NAS [at least 1 multi-regional clinical trial (MRCT) conducted in both Japan and the US/ no MRCT], (2) ATC classification (L/ others), (3) first-in-class (FIC) drug (yes/no), (4) country ahead in approval (Japan/the US), and (5) MAH in each country (same/different). Difference in distribution of concordance rate was analyzed across groups for each variable using the Mann–Whitney U test. The variables with a level of significance $p < 0.1$ were considered to indicate statistical significance. Data were analyzed with StatsDirect (StatsDirect LTD., Cheshire, UK).

Concordance Assessment of Safety-Related Information Raised by Black Boxed Warnings

We also investigated the concordance of black boxed warnings (hereinafter, BBW), called "boxed warning" in the US and "warning" in Japan, which are safety warnings to inform healthcare professionals about fatal or serious adverse reactions [18, 19]. We identified differences in the presence or absence of BBW for each NAS between the two countries. When a BBW was present for a NAS in both countries, the content in the BBW was reviewed and safety-related information was identified, coded, and assessed for concordance as described earlier.

We also reviewed the safety-related information raised by BBW in at least one country and classified its status in the two countries (raised by BBW in Japan only, in the US only or in both countries). In addition, we repeated the same evaluation for those safety issues listed in the Important Medical Event (IME) list [20], which are of particular interest in post-marketing pharmacovigilance activities.

Table 1 List of drugs selected for analysis

#	Year of approval (Japan/US)	Generic name	Brand name	ATC classification	First-in-class drug Yes/No	MAH in each country Same/different
1	2014/2013	Riociguat	ADEMPAS	C	Yes	Same
2	2014/2014	Dapagliflozin Propylene Glycolate Hydrate	FARXIGA	A	No	Same
3	2014/2014	Efinaconazole	JUBLIA	D	No	Different
4	2014/2014	Nivolumab (Genetical Recombination)	OPDIVO	L	No	Different
5	2014/2014	Suvorexant	BELSOMRA	N	Yes	Same
6	2014/2015	Secukinumab (Genetical Recombination)	COSENTYX	L	No	Same
7	2014/2014	Empagliflozin	JARDIANCE	A	No	Same
8	2015/2015	Lenvatinib Mesilate	LENVIMA	L	No	Same
9	2015/2015	Panobinostat Lactate	FARYDAK	L	No	Same
10	2015/2015	Asfotase Alfa (Genetical Recombination)	STRENSIQ	A	No	Same
11	2015/2015	Trabectedin	YONDELIS	L	No	Different
12	2015/2015	Tiotropium Bromide Hydrate, Olodaterol Hydrochloride	STIOLTO RESPIMAT	R	No	Same
13	2016/2015	Evolocumab (Genetical Recombination)	REPATHA	C	No	Different
14	2016/2015	Sebelipase Alfa (Genetical Recombination)	KANUMA	A	Yes	Same
15	2016/2015	Mepolizumab (Genetical Recombination)	NUCALA	R	Yes	Same
16	2016/2015	Osimertinib Mesylate	TAGRISSO	L	No	Same
17	2016/2016	Ixekizumab (Genetical Recombination)	TALTZ	L	No	Same
18	2016/2017	Etelcalcetide Hydrochloride	PARSABIV	H	No	Different
19	2016/2016	Tenofovir Alafenamide Fumarate	VEMLIDY	J	No	Same
20	2017/2017	Naldemedine Tosylate	SYMPROIC	A	No	Same
21	2017/2017	Glecaprevir Hydrate, Pibrentasvir	MAVYRET	J	No	Same
22	2017/2017	Sarilumab (Genetical Recombination)	KEVZARA	L	No	Same
23	2018/2017	Inotuzumab Ozogamicin (Genetical Recombination)	BESPONSA	L	Yes	Same
24	2018/2017	Benralizumab (Genetical Recombination)	FASENRA	R	No	Same
25	2018/2017	Olaparib	LYNPARZA	L	No	Same
26	2018/2018	Migalastat Hydrochloride	GALAFOLD	A	Yes	Same
27	2018/2017	Emicizumab (Genetical Recombination)	HEMLIBRA	B	Yes	Different
28	2018/2017	Semaglutide (Genetical Recombination)	OZEMPIC	A	No	Same
29	2018/2017	Letermovir	PREVYMIS	J	No	Same
30	2018/2018	Lorlatinib	LORBRENA	L	No	Same
31	2018/2018	Gilteritinib Fumarate	XOSPATA	L	No	Same
32	2019/2019	Romosozumab (Genetical Recombination)	EVENITY	M	Yes	Different

Table 1 (continued)

#	Year of approval (Japan/US)	Generic name	Brand name	ATC classification	First-in-class drug Yes/No	MAH in each country Same/different
33	2019/2018	Dacomitinib Hydrate	VIZIMPRO	L	No	Same
34	2019/2019	Risankizumab (Genetical Recombination)	SKYRIZI	L	No	Same
35	2019/2018	Elapegademase (Genetical Recombination)	REVCOVI	L	No	Different
36	2019/2018	Ravulizumab	ULTOMIRIS	L	No	Same
37	2019/2019	Entrectinib	ROZLYTREK	L	No	Different
38	2020/2020	Remimazolam Besilate	BYFAVO	N	No	Different
39	2020/2019	Darolutamide	NUBEQA	L	No	Same
40	2020/2019	Upadacitinib Hydrate	RINVOQ	L	No	Same
41	2020/2019	Lemborexant	DAYVIGO	NA	No	Same
42	2020/2019	Brolucizumab (Genetical Recombination)	BEOVU	S	No	Same
43	2020/2020	Viltolarsen	VILTEPSO	NA	No	Same
44	2020/2019	Trastuzumab Deruxtecan (Genetical Recombination)	ENHERTU	L	No	Same
45	2020/2020	Remdesivir	VEKLURY	NA	Yes	Same

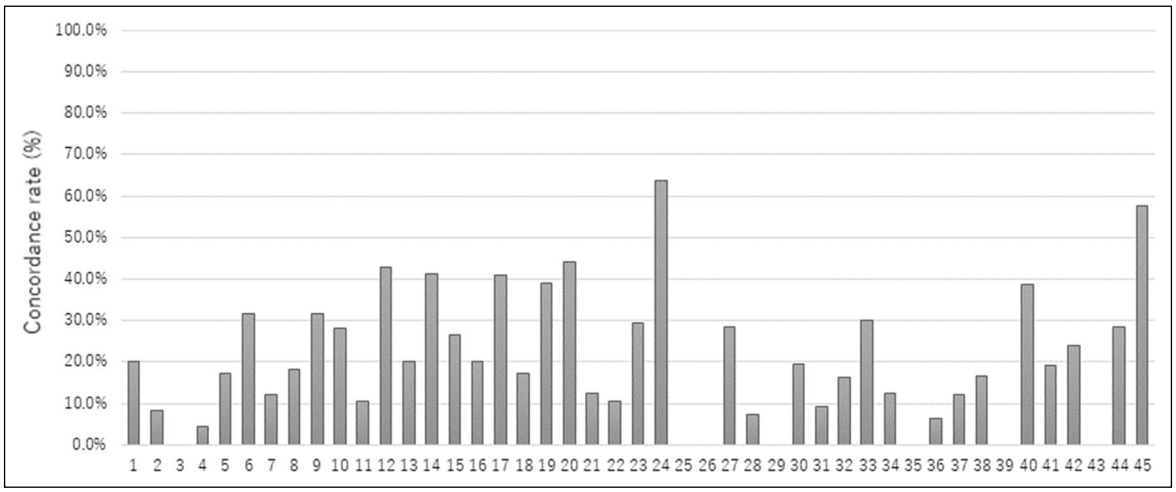

Fig. 1 Concordance rate of safety-related information for 45 drugs. Drug# corresponds to the number provided in Table 1

Results

A total of 271 NASs were approved in Japan between January 1, 2014 and December 31, 2020, and 182 were also approved in the US. Of those, 45 drugs were identified as approved concurrently in both countries and selected for the study cohort (Table 1). ATC category L (antineoplastic and immunomodulating agents) was the most common, accounting for approximately 44.4% (20/45) of all the included drugs. Nine out of 45 drugs were identified as FIC drug. The MAH was same in both countries for 35 out of 45 drugs.

The concordance rate of safety-related information in the 45 drugs is shown in Fig. 1. The mean concordance rate among the 45 drugs, which was defined as the percentage of concordant safety issues to the total number of safety issues raised in either of the two countries, was 20.4% (min–max: 0–63.6%). The box plots of concordance rate for each variable are shown in Fig. 2. The development strategy of the NAS (at least one MRCT conducted in

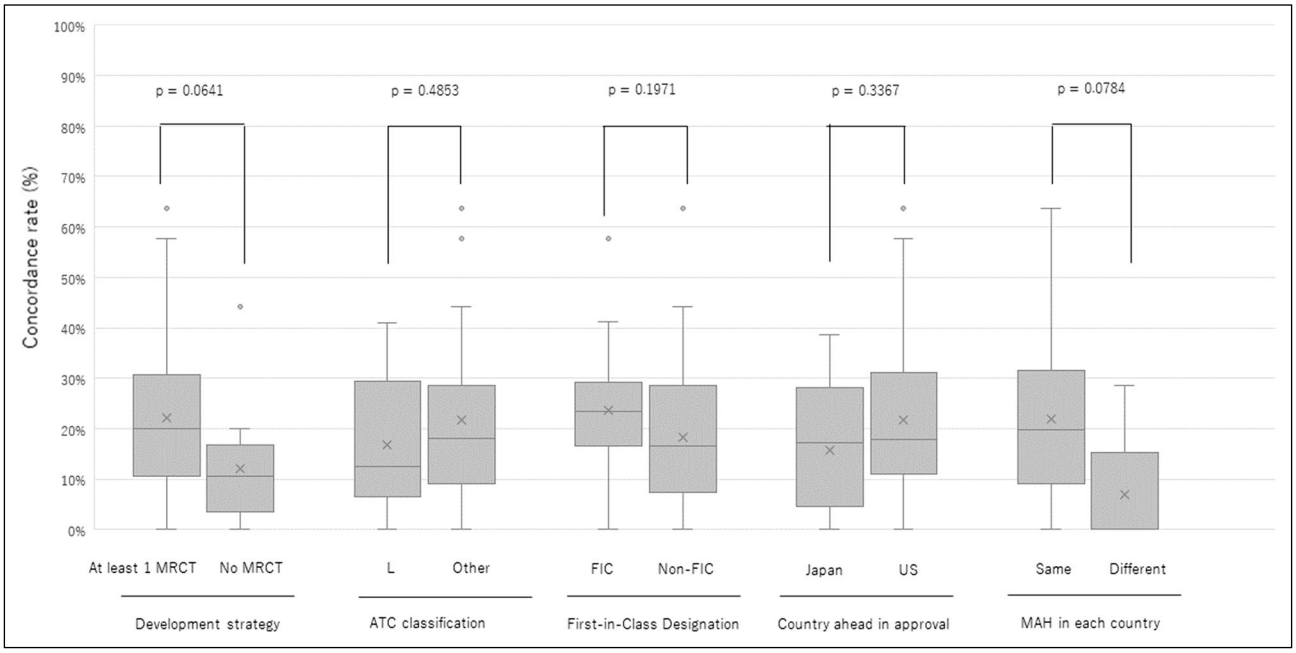

Fig. 2 Distribution of concordance rate across two groups for each variable

Table 2 Number of drugs with concordant outcome in BBW presence/absence

	Labeling in the US	
	With BBW	Without BBW
Labeling in Japan		
With BBW	9	14
Without BBW	5	17

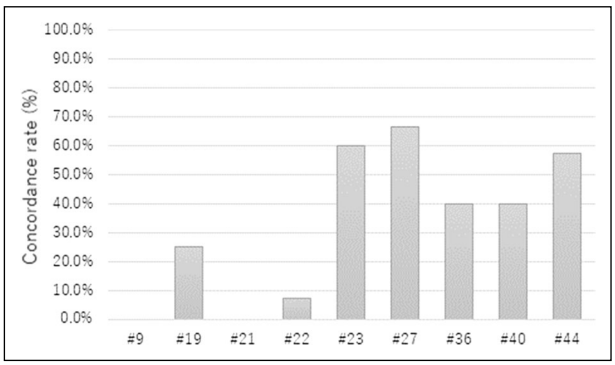

Fig. 3 Concordance rate of safety-related issues for 9 drugs with BBW in both countries. Drug# corresponds to the number provided in Table 1

both Japan and the US) and the difference in MAH (having same MAH) were significantly associated with the higher concordance rate (p = 0.0641 and p = 0.0784, respectively).

Twenty-six (57.8%) out of 45 drugs had concordant outcome in the presence or absence of BBW in both countries, while 19/45 (42.2%) had discordant outcomes (Table 2). The mean concordance rate among the 9 drugs with BBW in both countries was 32.9% (min–max: 0–66.7%) (Fig. 3).

The summary of 81 safety-related information raised by BBW in at least one country and the complete list of issues are shown in Tables 3 and 4, respectively. 15 issues (18.5%) were concurrently included in the BBW. A similar result (9 out of 45 issues, 18.5%) was obtained when limiting the assessment to safety issues listed in the IME list.

Discussion

In this study, we examined the labeling of new drugs approved concurrently both in Japan and the US in the recent 7 years. Although these countries have a similar medical environment and drug regulations, the mean concordance rate of safety-related information among 45 drugs was 20.4%, indicating that inconsistencies in the safety-related information in the drug labeling already existed at the time of initial approval. Our analysis showed that the NAS supported by MRCTs was significantly associated with the higher concordance rate, and this result

Table 3 Summary of 81 safety-related issues raised by BBW in at least one country

	All safety-related issues coded	Safety-related issues coded and listed in IME list
Total number	81	45
Number of issues raised by BBW in both counties (%)	15 (18.5%)	9 (20.0%)
Number of issues raised by BBW only in Japan (%)	27 (33.3%)	12 (26.6%)
Number of issues raised by BBW only in the US (%)	39 (48.1)	24 (53.3%)

suggested that the content of the drug labeling in each country may be determined based on the information filed to the regulatory authority, not all the information being available worldwide at the same time. In addition, having different MAHs in two countries were associated with the lower concordance rate, and this suggested that decisions on the labeling were made within one company and may not be shared between companies. We reviewed individual cases with > 50% concordance and 0% of concordance. Among the cases with a concordance rate of 0%, some of the discrepancies occurred because there were no coded terms in one country (#3, #26, and #35), whereas in other cases there was no concordance at all despite the presence of multiple terms in both countries (#25 and #43). We believe that we should pay attention to the latter case of 0% because this suggested inequity in safety information depending on country of residence. Unfortunately, we could not find a pattern in factors associated with concordance rate between the cases with > 50% or 0% of concordance from our study cohort. However, we believe that this finding suggested that inconsistency in safety information was occurring in a disorderly fashion and was a signal that there may be no process to resolve inconsistency in labeling or that it was not working properly.

BBW is the strongest medication-related safety warning in a drug's labeling information and highlights major risks of the drug [21]. Despite the expectations for a higher concordance rate for highest important information, our data showed that concordance remained low (32.9%) even when limiting the analysis to the BBW section. We also investigated the relationship between safety-related information and its status of warnings (raised by BBW in Japan only, in the US only, or in both countries). We did not find any meaningful trends suggesting that specific events were frequently raised in one country, causing the inconsistency. We found similar results when limiting the assessment to IMEs. We found some events raised only in one country in multiple drugs (e.g., "Pneumonia" and "Sepsis" in Japan, "Maternal drugs affecting foetus" in the US); however, the cumulative number was at most 2 and we were not able to conclude any trends due to small sample size.

Our group previously investigated the concordance in decision and timing of safety-related labeling changes after approval in Japan and the US and reported a low level of concordance between countries [22]. In the present study, we revealed that the inconsistency existed from the time of approval even in the cohort of drugs concurrently approved in both countries in the recent 7 years. The Council for International Organizations of Medical Science (CIOMS) working group proposed the concept of Company Core Safety Information (CCSI), which is the core clinical safety information of each product, and recommended that MAHs provide these information in all countries where the drug is marketed, assuming that the majority of information distributed in the product labeling would overlap across countries in their schematic image of CCSI [23]. In contrast, our results showed that most of the information in drug labeling was country specific (Fig. 4).

Some limitations exist in this study. First, we conducted the concordance assessment based on MedDRA PT terminology. MedDRA PT is considered most suitable for the purpose of this study, as this level of terminology reflects a single medical concept that is widely used for reporting in regulatory filings and research [24]. However, small differences in terminology might result in discordant outcome and this could underestimate the level of concordance. Second, the reasons for listing or not listing a safety event in the label are not open to public. We covered all possible factors for which public data were available; however, there could be still underlying causes which were not discussed in this study. Both industry and regulatory authorities may be responsible for this inconsistency, but we were not able to determine this from publicly available information. Greater transparency in decision-making process for the CCSI and drug labeling in each country is desirable to identify the causes of low concordance, and take appropriate countermeasures to ensure the availability of scientific information on a proper use of the drug for all the people, irrespective of the country where they live.

Table 4 List of safety-related events raised by BBW in each country

Issues raised only in Japan	Issues raised in both countries	Issues raised only in the US
Common to all categories		
Death* (2 drugs)	Death*	Death* (2 drugs)
Dyspnea (3 drugs)	Dyspnea	Dyspnea
Fungal infection	Fungal infection	Fungal infection
Viral infection (2 drugs)	Viral infection	Viral infection
Tuberculosis*	Tuberculosis*	Tuberculosis*
Common to 2 categories		
	Opportunistic infection*	Opportunistic infection*
Bacterial infection (2 drugs)		Bacterial infection (2 drugs)
Meningococcal infection		Meningococcal infection
Cough (3 drugs)	Cough	
Pyrexia (4 drugs)	Pyrexia	
Infection (2 cases)	Infection (2 cases)	
Neoplasm malignant*	Neoplasm malignant*	
Interstitial lung disease* (2 cases)	Interstitial lung disease*	
Only for 1 category		
Acute kidney injury*	Embolism*	Arrhythmia*
Acute phase reaction	Hepatitis B*	Arterial thrombosis
Anaphylactic reaction*	Thrombotic microangiopathy*	Candida infection
C-reactive protein increased	Venoocclusive liver disease* (2 cases)	Cardiotoxicity*
Extrapulmonary tuberculosis*		Cerebrovascular accident*
Fatigue		Deep vein thrombosis*
Hemorrhage*		Diarrhea
Headache		Dysphagia
Hepatic function abnormal		Dysphonia
Infusion-related reaction		Dyspnea at rest*
Liver disorder		Hepatic failure*
Nuchal rigidity		Hepatic steatosis
Pneumonia* (2 drugs)		Hepatitis B reactivation*
Rheumatoid arthritis*		Hepatitis fulminant*
Sepsis* (2 drugs)		Hepatomegaly
		Hepatotoxicity*
		Infarction*
		Lactic acidosis*
		Lymphoma*
		Maternal drugs affecting fetus* (2 drugs)
		Medullary thyroid cancer*
		Multiple endocrine neoplasia Type 2
		Myocardial infarction*
		Myocardial ischemia*
		Neck mass
		Pneumocystis jirovecii pneumonia*
		Pneumonitis*
		Pulmonary embolism*
		Respiratory symptom
		Thrombosis*
		Thyroid neoplasm

*Events included in the IME list

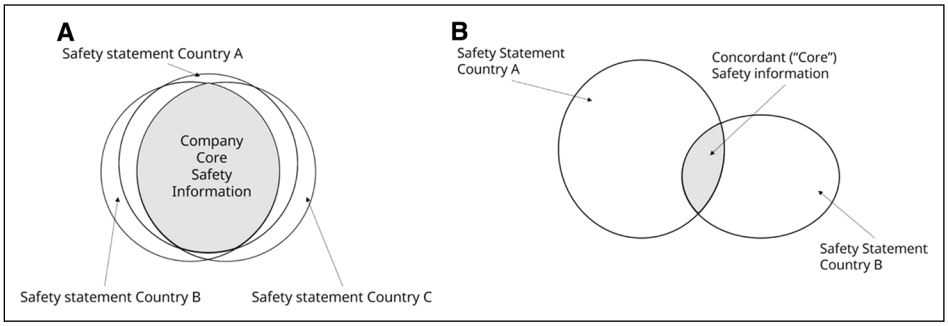

Fig. 4 Schematic image of the core safety information. **A** Diagram of Company Core Safety Information, reprinted from reference [23]; **B** Schematic image of the level of international concordance of safety information on drug labeling from the present research

Conclusion

We studied the international concordance of safety information in drug labeling at the time of drug approval, in a cohort of NASs concurrently approved in Japan and the US. We found a low level of concordance between countries, even when related to clinically important information raised by BBWs. Drug development strategy and having the same MAH were associated with the concordance between countries, and this result suggested that the contents in a drug labeling are decided based primarily on the clinical data submitted to the regulatory authority at the time of drug filing. The low concordance highlighted the need for a greater transparency in the decision-making process on the safety information in a drug labeling by both industry and regulators to take appropriate countermeasures against the discordance.

Author Contributions

All authors contributed to the study conception and design. Data collection and analysis were performed by YH and MN. The first draft of the manuscript was written by YH, and MN commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest

Yuko Hoshino and Mamoru Narukawa declare that they have no conflict of interest.

References

1. Prescription Drug Labeling Resources. https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources. Accessed 8 Apr 2021.
2. Shenoy P. Multi-regional clinical trials and global drug development. Perspect Clin Res. 2016;7(2):62–7.
3. Shimazawa R, Ikeda M. Safety information in drug labeling: a comparison of the USA, the UK, and Japan. Pharmacoepidemiol Drug Saf. 2013;22(3):306–18. https://doi.org/10.1002/pds.3408.
4. Alshammari TM, Devadasu VR, Rathnam RP. Comparison of the safety information on drug labels in three developed countries: the USA, UK and Canada. Saudi Pharmaceut J. 2017;25:1103–7.
5. Warrer P, Aagaard L, Hansen EH. Comparison of pregnancy and lactation labeling for attention-deficit hyperactivity disorder drugs marketed in Australia, the USA, Denmark, and the UK. Drug Saf. 2014;37(10):805–13. https://doi.org/10.1007/s40264-014-0215-2.
6. Polinski JM, Kesselheim AS, Seeger JD, Connolly JG, Choudhry NK, Shrank WH. A cross-national comparison of 17 countries' insulin glargine drug labels. Pharmacoepidemiol Drug Saf. 2015;24(2):159–65. https://doi.org/10.1002/pds.3704.
7. Nevin RL, Byrd AM. Neuropsychiatric adverse reactions to mefloquine: a systematic comparison of prescribing and patient safety guidance in the US, UK, Ireland, Australia, New Zealand, and Canada. Neurol Ther. 2016;5(1):69–83. https://doi.org/10.1007/s40120-016-0045-5.
8. Sieluk J, Palasik B, dosReis S, Doshi P. ADHD medications and cardiovascular adverse events in children and adolescents: cross-national comparison of risk communication in drug labeling. Pharmacoepidemiol Drug Saf. 2017;26(3):274–84. https://doi.org/10.1002/pds.4164.
9. Eriksson R, Aagaard L, Jensen LJ, et al. Discrepancies in listed adverse drug reactions in pharmaceutical product information supplied by the regulatory authorities in Denmark and the USA. Pharma Res Per. 2014;2(3):e00038. https://doi.org/10.1002/prp2.38.
10. List of Approved Products. Pharmaceuticals and Medical Devices Agency. https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html. Accessed 24 Aug 2020.
11. Japanese Accepted Names for Pharmaceuticals (JAN). https://jpdb.nihs.go.jp/jan/index.aspx. Accessed 24 Aug 2020.
12. Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed 24 Aug 2020.
13. WHO Collaborating Center for Drug Statistics Methodology ATC/DDD Index. https://www.whocc.no/atc_ddd_index/. Accessed 24 Aug 2020.
14. New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products. https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molec

ular-entities-and-new-therapeutic-biological-products. Accessed 11 Dec 2020.
15. U.S. Food and Drug Administration Center for Drug Evaluation and Research. Novel new drugs 2014 summary. Accessed Jan 2015.
16. U.S. Food and Drug Administration Center for Drug Evaluation and Research. Novel new drugs 2013 summary. Accessed Jan 2014.
17. SAFE-DI. https://www.safe-di.jp/. Accessed 11 Dec 2020.
18. U.S. Food and Drug Administration. Guidance for industry: warnings and precautions, contraindications, and boxed warning sections of labeling for human prescription drug and biological products—content and format. 2011 Oct 11 https://www.fda.gov/downloads/drugs/guidances/ucm075096.pdf. Accessed 8 Apr 2021.
19. Notification: PSEHB No. 0608/1: Information on Contents and Presentation of Package Inserts for Prescription Drugs. http://wwwhourei.mhlw.go.jp/hourei/index.html. Accessed 08 Jun 2017
20. IME list.
21. Panagiotou OA, Contopoulos-Ioannidis DG, Papanikolaou PN, Ntzani EE, Ioannidis JP. Different black box warning labeling for same-class drugs. J Gen Intern Med. 2011;26(6):603–10. https://doi.org/10.1007/s11606-011-1633-9.
22. Hoshino Y, Narukawa M. Comparison of decision and timing of safety related labeling changes for new drugs approved both in Japan and the United States. Pharmacoepidemiol Drug Saf. 2021;30:561–72.
23. CIOMS. Guidelines for preparing core clinical-safety information on drugs. Report of CIOMS Working Group III and V. 1999.
24. Vision for MedDRA. https://www.meddra.org/about-meddra/vision. Accessed 8 Apr 2021.