events and downplayed the benefits of vaccines [11,32]. Because the implementation of immunisation requires not only biological but also social, political, ethical, and economic considerations, multidisciplinary discussions should lead health professionals and the general public to be well informed about vaccines. For example, risk communication is one of the greatest challenges facing any public health authority. In Japan, there is no legal requirement for physicians to communicate the benefits and risks of vaccines to patients. Training programmes to improve physicians' knowledge and communication skills should be provided by the government.

Japan has been a leader in the development of vaccines, such as those for varicella and cellular pertussis, but the aforementioned challenges have stagnated the implementation of newly developed vaccines. We believe our proposals can contribute to a closure of the vaccine gap. The lessons learned so far have helped vaccine policy take a step forward in some respects. The UK experience of the MMR vaccine and its low coverage in urban areas [14] is a good lesson for health care professionals in Japan to improve the public perception of vaccines among Japanese citizens [32]. The Relief System for Injury to Health with Vaccination was introduced in Japan to provide relief in cases of side effects [33]. Routine immunisation is not compulsory but nonetheless high coverage rates have been achieved in Japan [34]. The international community has also contributed to closing the gap. For example, proposals in the EFPIA position paper issued in 2009 [2] had urged the Japanese government to take action to approve bivalent and quadrivalent HPV, and 7-valent PCV vaccines, which were approved in the following years. The notorious exportation [3] and outbreak of measles [35] urged the Japanese government to establish the National Measles Elimination Plan in December 2007. Recent activities among Japanese physicians to establish a strong advisory committee for vaccination policy [24] are encouraging.

5. Conclusions

The present study shows that there is still a large gap between Japan and the UK regarding access to common vaccines and immunisation programmes. The keys to closing this gap include: (1) revision of vaccine regulations, (2) amendment of the vaccine-related laws to secure funding and cooperation between professionals and public health authorities, and (3) improvement in the perception of vaccines among the general public and mass media.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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ORIGINAL REPORT

Safety information in drug labeling: a comparison of the USA, the UK, and Japan

Rumiko Shimazawa and Masayuki Ikeda*

Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

ABSTRACT

Purpose Despite globalization of drug approvals, there is a disparity in drug safety regulations among the USA, Europe, and Japan. We sought to determine differences in safety information on drug labels among the three regions.

Methods This was a cross-sectional study with quantitative survey of safety information on labels of 189 new molecular entities approved in the USA, the UK, and Japan. Outcome measures were the proportions of total safety information (PSI), of contraindications (PCI), and of boxed warnings (PBW) to all information on the label. We identified a boxed warning (BW) on US and Japanese labels through a manual search. These measures were analyzed according to therapeutic indications.

Results On the Japanese labels, PSI was smaller than that on the US and UK labels for cardiovascular diseases. For neoplastic and immunologic diseases, PSI on the Japanese labels was larger than that on the UK labels. For nervous system diseases, PSI on the US labels was larger than that on the UK and the Japanese labels. PCI showed contrasting results with PSI except for neoplastic and immunologic diseases. BWs showed a poorer concordance between the USA and Japan in hematologic and genitourinary diseases than in other therapeutic areas.

Conclusions Substantial differences in safety information exist depending upon outcome measures and therapeutic areas among the US, the UK, and the Japanese labels. This underscores the need for further analyses to determine causes of these differences to optimize drug safety regulations. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—drug labeling; drug toxicity; drug approval; pharmacoepidemiology

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INTRODUCTION

Labeling is an essential communication source to provide important information on drug safety both for patients and healthcare professionals but can fail to ensure optimal prescribing and dispensing of drugs.[1,2] The growing number of new drugs that carry specific risks, such as biologics,[3] may undermine the effectiveness of drug labeling. Overwarning[4] without appropriate context is not helpful, whereas disclosure of risk is important. Exhaustive lists of adverse events induce alert fatigue[5] and lead prescribers to ignore vague, difficult-to-interpret warnings, even for serious risks.[6]

One would expect that labels would not differ significantly among countries given that regulatory authorities evaluate the same scientific data. Different laws and cultures, however, can affect regulatory decisions. Indeed, differences in doses,[7,8] indications,[9,10] and safety[3,11–14] exist among regions. These differences may arise from biological and nonbiological factors. Pharmacokinetics[15] and incidence of side effects,[16] which often show racial differences, are examples of biological factors. Regulatory requirements, evaluation processes, healthcare systems, and the general public's perception are nonbiological factors that might differentially impact the information on labels depending upon regulatory region. Although the significance of various nonbiological factors in drug regulations is widely recognized, these factors have rarely been the focus of systematic research.

The structure and content of drug labels are based on local guidance. In the USA, the Food and Drug Administration (FDA) issued guidance for requirements on content and format of labeling in 2006.[17] In Europe, detailed presentation of the information in Summaries

*Correspondence to: M. Ikeda, Graduate School of Biomedical Sciences, Nagasaki University, Sakamoto 1-12-4, Nagasaki 852–8523, Japan. E-mail: massie.ikeda@gmail.com

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of Product Characteristics is determined by European Commission guidance.[18] In Japan, the Pharmaceutical Affairs Law defines requirements for the content and format of Japanese drug labeling (*tenpubunsho*).[19] Although these sets of guidance adapt labels to local healthcare circumstances, the extent to which labels follow the recommendations is not known, because such guidance is not legally binding.

Between 1997 and 2005, both in the USA and Europe, 22 drugs were withdrawn from the market because of safety concerns. In 10 of the 22 cases, there was a disparity in regulatory decisions between the FDA and the European Medicines Agency.[20] Differences in regulatory decision making, especially regarding safety, might lead to controversy, such as the debate about cyclooxygenase-2 inhibitors[11] and glitazones.[21,22] However, what accounts for the differences is largely unknown.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities and pharmaceutical industry of the USA, Europe, and Japan to discuss scientific and technical aspects of drug registration. However, harmonization in therapeutic risk management[20] remains to be implemented. Shared knowledge and harmonization of drug safety regulation would help minimize duplication of effort and promote efficient communication of drug safety.

The aim of the present study was to investigate differences in safety information on drug labels among the ICH members and to provide an evidence base for better regulation of drug safety. For quantitative analysis independent of language, we focused on the amount of safety information on labels. We investigated effects of therapeutic indications, approval years, and molecular characteristics of the drug, that is, biological or chemical on the outcome measures.

METHODS

Data sources

This study included new molecular entities (NMEs) and biologics approved in Japan between April 2001 and July 2011, in the USA between May 1976 and July 2011, and in the UK between October 1989 and August 2011. We selected the period for the NMEs approved in Japan as starting from April 2001, because the full set of information including reviews and approval history was available on the Japan Pharmaceutical Information Center website.[23] We excluded any NME not approved in any of the three countries. Drugs with nontherapeutic indications (e.g., vaccines and contrast agents) were excluded. We identified NME drug labels available in September 2011 on the following websites: DailyMed[24] for US Structured Product Labels, the electronic Medicines Compendium[25] for UK Summaries of Product Characteristics, and the Pharmaceuticals and Medical Devices Agency (PMDA)[26] for the Japanese labels (*tenpubunsho*).

We selected the UK as a reference for the European Union countries because the UK, which has a language in common with the USA and provides public pharmaceutical coverage similar to that in Japan, provides a good comparison with the USA and Japan.

Variable definitions, evaluation, and analysis

The outcome measures were the proportions of total safety information (PSI), of contraindications (PCI), and of boxed warnings (PBW, the USA and Japan) to all information on the label. We performed a direct comparison of PSI, PCI, and PBW across the same drug in each therapeutic area among the countries. We defined the measures independent of language. For English, we counted the number of the words and for Japanese, the number of letters in the sections allocated to safety; we then divided that by the total number of the words or letters on the label. For PSI, on the US labels, we included BOXED WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE as safety sections in the old format, issued in 2005 and earlier. In the current format, issued in 2006 and later, we included BOXED WARNINGS, 4 CONTRAINDICATIONS, 5 WARNINGS AND PRECAUTIONS, 6 ADVERSE REACTIONS, 7 DRUG INTERACTIONS, 8 USE IN SPECIFIC POPULATIONS, 10 OVERDOSAGE, and 13 NONCLINICAL TOXICOLOGY. We excluded MEDICATION GUIDE in the old format and PATIENT COUNSELING INFORMATION in the current format from the analysis because information for patients is provided as separate documents in the UK and in Japan. On the UK labels, we included 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicinal products, 4.6 Pregnancy and lactation, 4.7 Effects on ability to drive and use machines, 4.8 Undesirable effects, 4.9 Overdose, and 5.3 Preclinical safety data. In the Japanese labels, we included WARNINGS (equivalent to BOXED WARNINGS in the USA) CONTRAINDICATIONS, and PRECAUTIONS.

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We identified a boxed warning (BW) on the US and the Japanese labels through a manual search. To assess whether the content in the US BWs was incorporated in the Japanese ones, we formed three categories[13]: no difference, slight difference, and relevant difference. We measured the proportion of the number of labels with a BW (PwB) to that of all labels.

We analyzed the outcome measures according to the approval date and Anatomical Therapeutic Chemical (ATC) system,[27] which classifies drugs by the organ or system on which they act and their therapeutic, pharmacological, and chemical properties. We obtained dates of approval from the following websites: Drugs@FDA,[28] electronic Medicines Compendium,[25] and Japan Pharmaceutical Information Center.[23] We also stratified the results by the nature of the drug substance, that is, biologics or nonbiologics.[29]

Statistical analysis

We performed descriptive statistics on the outcome measures. Data are presented as mean and standard deviation (SD). We examined differences between the means of multiple groups by one-way analysis of variance followed by a Scheffé's post hoc test to determine which means differed, with the level of significance set at the $p < .05$ level. We used Student's unpaired t-test to compare the means of two groups. We used the Mann–Whitney U test to compare the data between the two groups. A p-value $< .05$ was regarded as statistically significant. Dr. SPSS 2 for Windows statistical software was used for all statistical analyses.

RESULTS

A total of 189 NMEs were approved in the USA, the UK, and Japan between May 1976 and July 2011, October 1989 and August 2011, and April 2001 and July 2011, respectively. The US labels contained more words than the UK labels, both on the whole label (7812 [3558] vs 5161 [2580]; $p < .001$ mean [SD]) and in the safety sections (3813 [2030] vs 2424 [1333]; $p < .001$), although the number of the words in contraindications was similar (55 [75] vs 49 [54]; $p = 0.2$).

Proportion of total safety information

Table 1 shows that labels for antineoplastic and immunomodulating agents (code L) were most represented, 40 (21%), of NMEs among the 189 surveyed, followed by those for the nervous system (code N), 32 (17%), and those for general anti-infectives (code J), 30 (16%). Mean PSI on the total labels was similar among the countries. PSI in each therapeutic area was generally similar across the countries except for the labels for the cardiovascular system (code C), antineoplastic and immunomodulating agents, and the nervous system. On the labels for the cardiovascular system, PSI on the Japanese labels (40 [7]; mean % [SD]) was significantly smaller than that on the US (52 [5]) and the UK (51 [6]) labels. On the labels for general anti-infectives, PSI on the UK labels (47 [12]) was larger than that on the US (42 [12]) and the Japanese (42 [11]) labels, although marginally insignificant. On the labels for antineoplastic and immunomodulating agents, PSI on the Japanese labels (56 [9]) was significantly larger than that on the UK (47 [9]) labels. On the labels for the nervous system, PSI on the US labels (58 [11]) was significantly larger than that on the UK (50 [11]) and the Japanese (45 [8]) labels. Figure 1 shows a direct comparison of PSI across the same drug in each therapeutic area among the countries. Table 2 shows changes in PSI over the years in the three countries. No obvious trend was observed in any of the countries. Table 3 shows changes in the absolute number of the words or letters of total safety information and those of all information on the labels classified by year of approval. No obvious trend was observed in any of the countries.

Proportion of contraindications

The PCI (Table 4 and Figure 2) shows clear differences to PSI. Mean PCI on the total labels was the smallest on the US labels. On 38 US labels, PCI was 0%, which means that there was no description in the CONTRAINDICATIONS section. On all of the corresponding 38 labels in the UK and in Japan, hypersensitivity and infusion reactions to the drug were described in the CONTRAINDICATIONS section. On the 38 US labels with 0% PCI, description on hypersensitivity and infusion reactions were incorporated into the WARNINGS AND PRECAUTIONS section.

The PCI on the Japanese labels was the largest on the labels for the alimentary tract and metabolism (code A), genitourinary system and sex hormones (code G), and antineoplastic and immunomodulating agents (code L). PCI in each therapeutic area remained similar between the USA and the UK.

Figure 2 shows a direct comparison of PCI across the same drug in each therapeutic area. The prominently high PCI (9.92%) on the Japanese label in Figure 2G indicates the combination of ethinylestradiol/drospirenone. In the USA, this label has a BW, but not in Japan. The content of the US BW is incorporated into

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Table 1. Proportion of total safety information to all information on the label classified according to ATC code

ATC code	A ($n=20$)	B ($n=10$)	C ($n=10$)	D ($n=3$)	G ($n=10$)	H ($n=5$)	J ($n=30$)	L ($n=40$)	M ($n=5$)	N ($n=32$)	P ($n=1$)	R ($n=10$)	S ($n=7$)	V ($n=6$)	All ($n=189$)
USA	41 [7]	47 [8]	52 [5]	56 [11]	45 [7]	36 [11]	42 [12]	52 [7]	47 [10]	58 [11]§	63	44 [7]	51 [13]	49 [11]	48 [10]
UK	41 [9]	43 [12]	51 [6]	54 [8]	50 [8]	42 [5]	47 [12]	47 [9]	43 [8]	50 [11]	60	39 [8]	48 [10]	51 [13]	47 [10]
Japan	44 [11]	46 [7]	40 [7]*	41 [9]	47 [13]	42 [7]	42 [11]	56 [9]‡	47 [12]	45 [8]	46	36 [8]	41 [8]	50 [8]	46 [11]
p-value	0.52	0.66	<.001	0.18	0.58	0.34	0.04†	<.001	0.74	<.001		0.05	0.26	0.97	0.09

Abbreviations: ATC, Anatomical Therapeutic Chemical; A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; D, dermatologicals; G, genitourinary system and sex hormones; H, systemic hormonal preparations, excluding sex hormones; J, general anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; P, antiparasitic products; R, respiratory system; S, sensory organs; V, various.
Values are means % [standard deviations].
*Smaller than the USA and the UK.
†Analysis of variance indicates p-value = .04, but a Scheffe's post hoc test does not show significant differences between the means.
‡Larger than the UK.
§Larger than the UK and Japan.

CONTRAINDICATIONS and other safety sections on the Japanese label. Table 5 shows changes in PCI over the years in the three countries. No obvious trend was observed in any of the countries except the UK PCI in 1994 and earlier, which was larger than that in the later years.

Labels with a boxed warning

When we studied PwB according to the ATC classification system (Table 6), we found results similar to those of PSI (Table 1). On the labels for the cardiovascular system (code C), PwB on the Japanese labels (20%) was smaller than that on the USA (50%). On the labels for antineoplastic and immunomodulating agents (code L), PwB on the Japanese labels (95%) was larger than that on the US (58%) labels. On the labels for the nervous system (code N), PwB on the US labels (41%) was larger than that on the Japanese (25%). Concordance of the presence or the absence of a BW on the label between the USA and Japan—in other words, the sum of labels with a BW both in the USA and in Japan and those without a BW either in the USA or in Japan—was 71% on the total labels. In each therapeutic area, the concordance was 60% or more except on the labels for blood and blood-forming organs (code B) (50%) and the genitourinary system and sex hormones (code G) (40%). Figure 3 shows a direct comparison of PBW between the USA and Japan across the same drug in each therapeutic area.

In regard to the content in BWs, of the 48 labels with a BW both in the USA and Japan, nine (19%) showed no difference, whereas 12 (25%) showed a slight difference. Of the 27 labels (56%) that showed relevant differences, 25 were related to diseases, one to a drug interaction, and the other to a laboratory test. Most of the contents in BWs on the US and the Japanese labels were incorporated into 4.3 Contraindications and 4.4 Special warnings and precautions for use on the UK labels.

Table 7 shows changes in PwB over the years in the countries. No obvious trend was observed in the USA. PwB on the Japanese labels approved in 2009 and later was smaller than that on the labels approved in 2008 and before, with the exception of 2002.

Differences in proportion of total safety information, contraindications, and a boxed warning between biologics and nonbiologics

Out of the 189 NMEs, 34 were biologics. Table 8 shows effects of the nature of the drug substance on PSI and PCI. PSI was larger in nonbiologics (48 [8]) than in biologics (41[9]) on the UK labels, whereas

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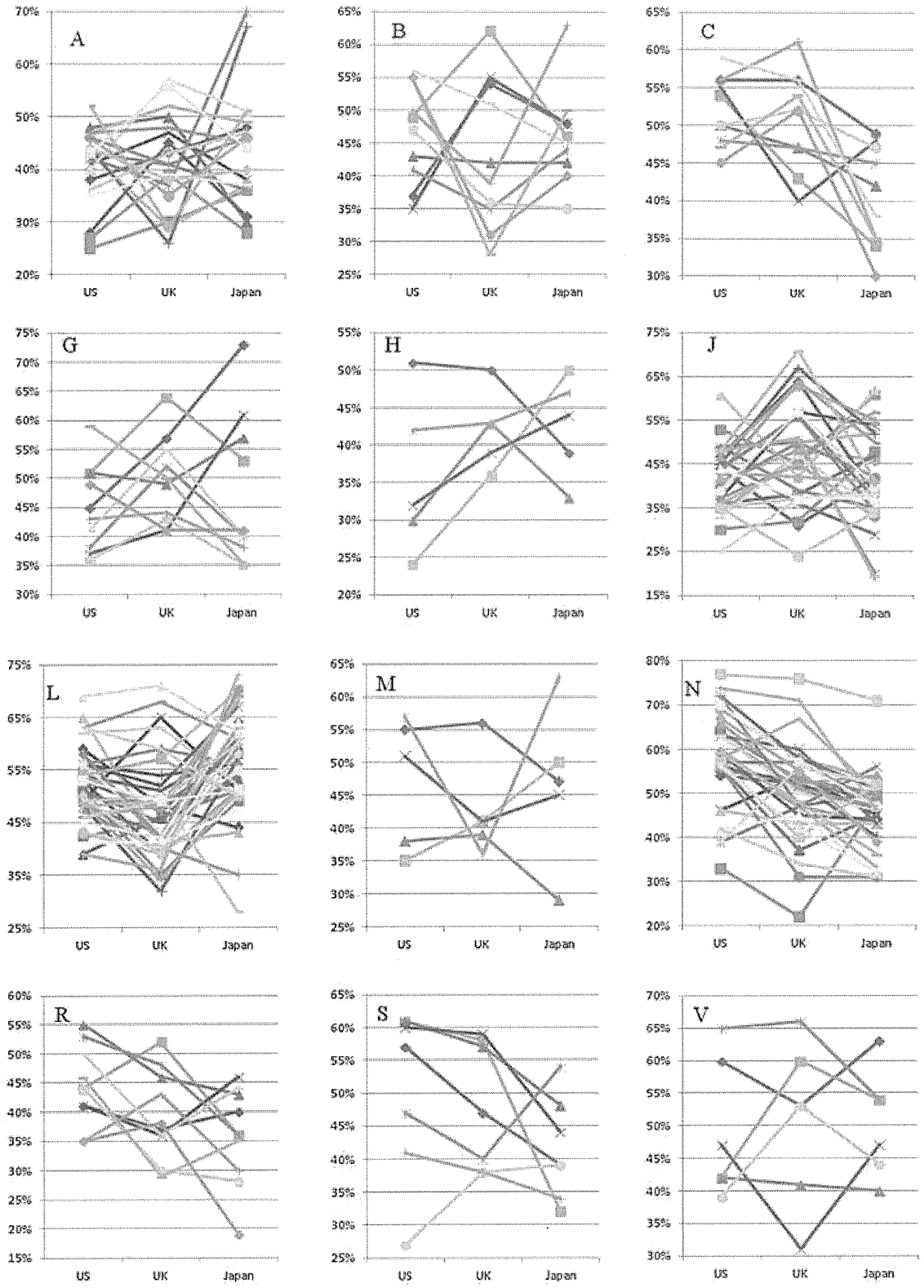

Figure 1. Direct comparison of the proportions of total safety information to all information on the label across the same drug in each therapeutic area among the three countries. Letters in each figure represent Anatomical Therapeutic Chemical system codes. A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; G, genitourinary system and sex hormones; H, systemic hormonal preparations, excluding sex hormones; J, general anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; R, respiratory system; S, sensory organs; V, various. Three drugs with code D (dermatologicals) and one drug with code P (antiparasitic products) were omitted because of their limited number

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Table 2. Secular changes in proportion of total safety information to all information on the label classified by year of approval

Approval year	1994 and earlier	1995 and 1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
USA	51 [13] (16)	58 [14] (9†)	48 [8] (16)	50 [10] (18)	45 [11] (8)	41 [7] (5)	47 [10] (13)	53 [12] (15)	45 [8] (17)	46 [9] (15)	50 [10] (12)	48 [12] (13)	49 [9] (13)	50 [5] (6)	46 [6] (6)	44 [10] (5)	34 [10] (2)	48 [10] (189)
UK	58 [14] (5*)	49 [13] (9)	48 [10] (7)	48 [6] (13)	44 [6] (9)	47 [10] (14)	45 [13] (13)	49 [7] (16)	49 [11] (15)	46 [11] (19)	44 [9] (8)	44 [11] (16)	48 [10] (18)	48 [13] (11)	45 [6] (12)	45 [8] (2)	41 [3] (2)	47 [10] (189)
Japan							50 [11] (14)	41 [11] (13)	50 [8] (12)	42 [11] (9)	48 [12] (12)	44 [13] (18)	46 [7] (24)	45 [12] (26)	44 [12] (19)	49 [12] (20)	46 [10] (22)	46 [11] (189)

Values are means % [standard deviations] (number).
*Two or fewer drugs were approved per year in 1994 and earlier in the UK.
†In 1995, only two in the USA versus five in the UK were approved.

Table 3. Secular changes in the word or letter counts of total safety information and those of all information on the labels classified by year of approval

	Approval year	1994 and earlier	1995 and 1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
USA (words)	Safety	4337 [2573]	4806 [2932]	3595 [1711]	4336 [2186]	3360 [1616]	2917 [1715]	3862 [1683]	5070 [2972]	3529 [1859]	3404 [1786]	3385 [1672]	4153 [2339]	3095 [698]	3340 [891]	2908 [797]	3379 [1532]	2259 [846]	3813 [2030]
	Total	8487 [4231]	8411 [4684]	7279 [2506]	8679 [4236]	7255 [3043]	6973 [4072]	8480 [3651]	9303 [4120]	7807 [3901]	7302 [3442]	6609 [2660]	8852 [4550]	6330 [1283]	6592 [1590]	6386 [1603]	7975 [4036]	6542 [679]	7812 [3559]
	No.	16	9†	16	18	8	5	13	15	17	15	12	13	13	6	6	5	2	189
UK (words)	Safety	2191 [2097]	1936 [1095]	2426 [1272]	2246 [1199]	2582 [2013]	2055 [1154]	2071 [1539]	2804 [1514]	2407 [914]	2501 [1431]	2576 [1203]	2419 [1260]	2924 [1627]	2562 [1159]	2249 [936]	2650 [1501]	1873 [98]	2424 [1333]
	Total	3446 [2606]	3961 [1659]	4994 [2554]	4726 [2582]	5870 [4739]	4573 [2895]	4451 [2682]	5833 [3278]	5293 [2979]	5304 [2230]	5799 [2308]	5511 [2087]	5874 [2442]	5250 [1439]	4958 [1730]	5681 [2343]	4554 [123]	5162 [2581]
	No.	5*	9	7	13	9	14	13	16	15	19	8	16	18	11	12	2	2	189
Japan (letters)	Safety							6157 [2659]	4274 [2483]	6361 [2706]	4404 [1981]	5845 [2823]	4635 [2470]	4468 [1781]	4486 [2468]	4362 [2465]	4966 [1986]	4404 [1642]	4837 [2328]
	Total							11904 [3898]	9970 [4138]	12421 [3952]	10775 [4216]	11749 [3617]	9969 [3101]	9680 [3152]	9723 [4205]	9472 [3286]	9898 [3034]	9707 [3025]	10261 [3587]
	No.							14	13	12	9	12	18	24	26	19	20	22	189

Values are means [standard deviations] (number).
*Two or fewer drugs were approved per year in 1994 and earlier in the UK.
†In 1995, only two in the USA, whereas five in the UK, were approved.

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Table 4. Proportion of contraindications to all information on the label classified according to ATC code

ATC code	A ($n=20$)	B ($n=10$)	C ($n=10$)	D ($n=3$)	G ($n=10$)	H ($n=5$)	J ($n=30$)	L ($n=40$)	M ($n=5$)	N ($n=32$)	P ($n=1$)	R ($n=10$)	S ($n=7$)	V ($n=6$)	All ($n=189$)
USA	0.3 [0.2]	0.6 [0.6]	1.8 [1.5]	1.3 [1.2]	1.3 [0.8]	0.7 [0.5]	0.8 [0.9]	0.5 [0.5]	0.4 [0.2]	0.8 [0.9]	1.4	0.5 [0.4]	1.0 [0.4]	0.6 [0.7]	0.7‡ [0.9]
UK	0.4 [0.3]	0.8 [0.8]	1.5 [0.9]	1.1 [1.4]	2.8 [1.3]	1.4 [1.0]	1.0 [0.9]	0.6 [0.5]	0.9 [1.1]	1.7 [1.7]	3.9	0.8 [0.7]	0.8 [0.4]	1.2 [1.0]	1.1 [1.1]
Japan	0.8* [0.5]	1.4 [1.2]	1.9 [1.1]	0.9 [0.4]	3.9* [2.2]	1.6 [1.6]	1.2 [1.2]	0.9* [0.6]	1.8 [1.4]	1.6 [1.8]	3.0	0.7 [0.6]	1.0 [0.6]	1.0 [0.5]	1.3 [1.4]
p-value	<.001	0.104	0.713	0.870	0.004	0.450	0.211	0.014	0.146	0.038†		0.461	0.774	0.46	<.001

Abbreviation: ATC, Anatomical Therapeutic Chemical; A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; D, dermatologicals; G, genitourinary system and sex hormones; H, systemic hormonal preparations, excluding sex hormones; J, general anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; P, antiparasitic products; R, respiratory system; S, sensory organs; V, various. Values are means % [standard deviations].

*Larger than the USA and the UK.

†Analysis of variance indicates *p*-value = 0.04, but a Scheffe's post hoc test does not show significant differences between the means.

‡Smaller than the UK and Japan.

it was similar between biologics and nonbiologics both on the US and the Japanese labels. PCI was larger in nonbiologics (0.80 [0.88]) than in biologics (0.38 [0.63]) on the US labels, whereas it was similar between biologics and nonbiologics both on the UK and the Japanese labels. Table 9 shows the effects of the nature of the drug substance on PwB. PwB was larger in biologics than in nonbiologics both in the USA and in Japan. PwB showed a good concordance between the USA and Japan both for biologics (76%) and nonbiologics (70%).

DISCUSSION

Among the three countries, we noted differences in the amount of safety information on drug labels, even though the regional regulatory authorities reviewed the same product. We also observed many similarities among countries. The large gap in time frames for NME approvals between Japan and the USA or between Japan and the UK resulted from launch delay in Japan.[30] This delay, however, is unlikely to affect the results in the present study because we based our analysis on the updated labels.

Proportion of total safety information

Mean PSI on all the labels was similar among the countries. This is not surprising given that the regulatory decisions depended mainly on common scientific data. Nevertheless, there were substantial differences in some therapeutic areas.

The lower incidence of cardiovascular diseases in Japan than in the West may contribute to the smaller PSI on the Japanese labels for the cardiovascular system, although this awaits further quantitative and qualitative investigations.

The larger PSI on the Japanese labels for antineoplastic and immunomodulating agents could result from the history of these agents in Japan. In 1989, HIV-infected hemophiliacs in Japan filed lawsuits demanding compensation from the Ministry of Health, Labour and Welfare and five pharmaceutical companies.[31] In 1993, the antiviral sorivudine combined with 5-fluorouracil caused 18 deaths in patients with cancer.[32] These incidents deeply affected both regulators and pharmaceutical companies regarding drug safety, and they became extremely cautious in developing and approving new drugs, particularly biologics and antineoplastic drugs. These concerns grew stronger during the 2000s when the high incidence of interstitial lung disease was identified in Japanese patients who were administered leflunomide[16] or gefitinib.[33]

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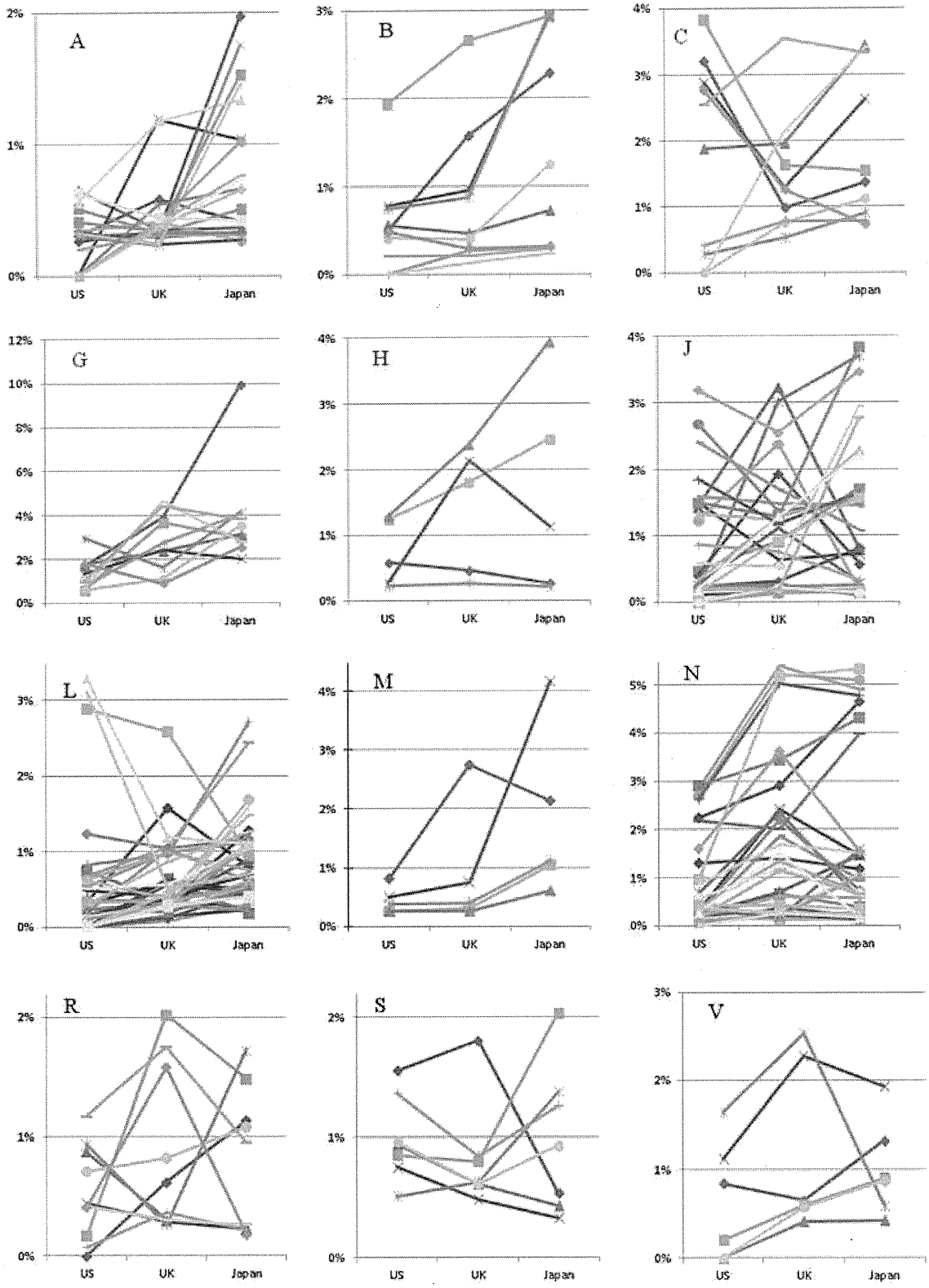

Figure 2. Direct comparison of the proportions of contraindications to all information on the label across the same drug in each therapeutic area among the three countries. Letters in each figure represent Anatomical Therapeutic Chemical system codes. A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; G, genitourinary system and sex hormones; H, systemic hormonal preparations, excluding sex hormones; J, general anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; R, respiratory system; S, sensory organs; V, various. Three drugs with code D (dermatologicals) and one drug with code P (antiparasitic products) were omitted because of their limited number

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Table 5. Secular changes in proportion of contraindications to all information on the label classified by year of approval

Approval year	1994 and earlier	1995 and 1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
USA	0.6 [0.5] (16)	1.0 [1.1] (9‡)	0.9 [0.9] (16)	1.0 [1.1] (18)	0.7 [0.6] (8)	0.7 [0.5] (5)	0.7 [0.9] (13)	1.0 [1.0] (15)	0.8 [0.9] (17)	0.4 [0.4] (15)	0.6 [0.9] (12)	0.6 [0.9] (13)	0.6 [1.3] (13)	0.8 [1.3] (6)	0.6 [1.1] (6)	0.4 [0.4] (5)	0.4 [0.02] (2)
UK	2.9* [1.6] (5†)	1.4 [1.6] (9)	0.9 [0.7] (7)	0.9 [0.8] (13)	1.3 [1.0] (9)	1.0 [0.9] (14)	1.4 [1.1] (13)	1.6 [1.5] (16)	1.6 [1.7] (15)	0.9 [1.0] (19)	0.7 [0.7] (8)	0.5 [0.6] (16)	0.7 [0.6] (18)	1.0 [1.1] (11)	0.9 [1.0] (12)	0.8 [1.0] (2)	0.3 [0.02] (2)
Japan							1.5 [1.5] (14)	1.4 [1.4] (13)	1.8 [1.5] (12)	1.7 [1.4] (9)	1.5 [1.1] (12)	1.6 [1.4] (18)	1.0 [1.0] (24)	1.0 [1.0] (26)	1.5 [1.3] (19)	1.4 [2.1] (20)	1.1 [1.0] (22)

Values are means % [standard deviations] (number).
*Larger than the means in the years 2004–2007.
†Two or fewer drugs were approved per year in 1994 and earlier in the UK.
‡In 1995, only two in the USA versus five in the UK were approved.

Table 6. Proportion of the number of labels with a boxed warning to that of all labels classified according to ATC code

ATC code	A ($n=20$)	B ($n=10$)	C ($n=10$)	D ($n=3$)	G ($n=10$)	H ($n=5$)	J ($n=30$)	L ($n=40$)	M ($n=5$)	N ($n=32$)	P ($n=1$)	R ($n=10$)	S ($n=7$)	V ($n=6$)	All ($n=189$)
USA	20 (4)	70 (7)	50 (5)	0	20 (2)	20 (1)	33 (10)	58 (23)	20 (1)	41 (13)	0	30 (3)	0	50 (3)	38 (72)
Japan	25 (5)	40 (4)	20 (2)	0	40 (4)	0	33 (10)	95 (38)	60 (3)	25 (8)	100 (1)	0	14 (1)	50 (3)	42 (79)
USA$^+$/Japan$^+$	15 (3)	30 (3)	20 (2)	0	0	0	27 (8)	58 (23)	20 (1)	16 (5)	0	0	0	50 (3)	25 (48)
USA$^+$/Japan$^-$	5 (1)	40 (4)	30 (3)	0	20 (2)	20 (1)	7 (2)	0	0	25 (8)	0	30 (3)	0	0	13 (24)
USA$^-$/Japan$^+$	10 (2)	10 (1)	0	0	40 (4)	0	7 (2)	38 (15)	40 (2)	9 (3)	100 (1)	0	14 (1)	0	16 (31)
USA$^-$/Japan$^-$	70 (14)	20 (2)	50 (5)	100 (3)	40 (4)	80 (4)	60 (18)	5 (2)	40 (2)	50 (16)	0	70 (7)	86 (6)	50 (3)	46 (86)
Concordance*	85 (17)	50 (5)	70 (7)	100 (3)	40 (4)	80 (4)	87 (26)	63 (25)	60 (3)	66 (21)	0	70 (7)	86 (6)	100 (6)	71 (134)

Abbreviation: ATC, Anatomical Therapeutic Chemical; A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; D, dermatologicals; G, genitourinary system and sex hormones; H, systemic hormonal preparations, excluding sex hormones; J, general anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; P, antiparasitic products; R, respiratory system; S, sensory organs; V, various. Values are % (number).
$^+$Represents labels with a boxed warning.
$^-$Represents labels without a boxed warning.
*Concordance represents the sum of labels with a boxed warning both in the USA and in Japan and those without a boxed warning either in the USA or in Japan.

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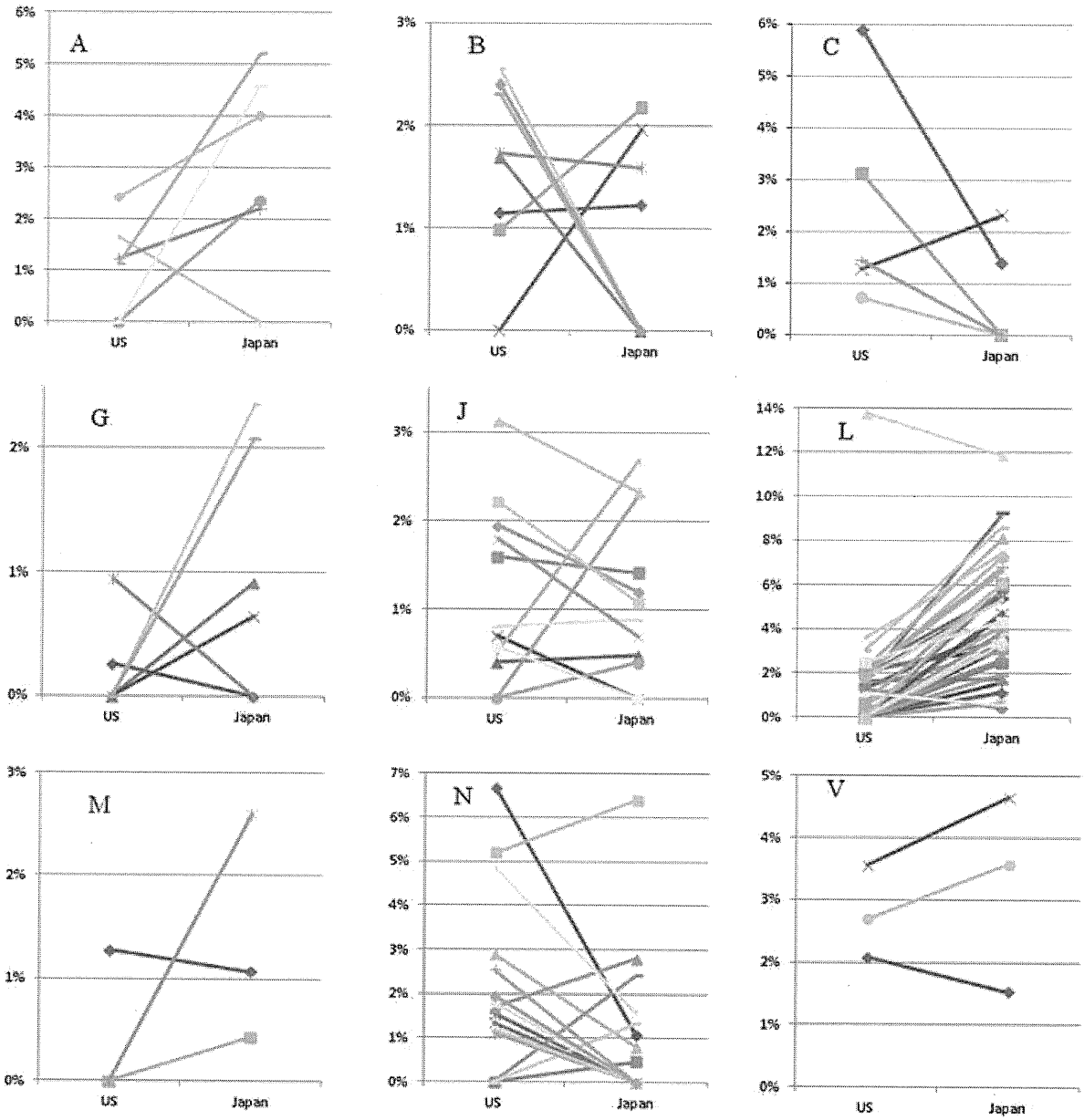

Figure 3. Direct comparison of the proportions of content in a boxed warning to all information on the label across the same drug in each therapeutic area between the USA and Japan. Letters in each figure represent Anatomical Therapeutic Chemical system codes. A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; G, genitourinary system and sex hormones; J, general anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; V, various. Drugs with code D (dermatologicals), H (systemic hormonal preparations, excluding sex hormones), P (antiparasitic products), R (respiratory system), and S (sensory organs) were omitted because of their limited number

On the labels for the nervous system, we found significantly larger PSI on the US labels compared with the UK and the Japanese labels. This finding is compatible with the high volume of adverse drug events on the US labels for neuropsychiatric drugs.[4] Warnings on the US labels of those drugs are up to 10 times longer than those on Australian labels.[14]

One might expect that the volume of safety information on drug labels is growing because the number of new drugs that carry specific risks is growing and because newer drugs might face more rigorous clinical trials and postmarketing surveillance compared with older ones. Both PSI and the absolute number of words (in the USA and the UK) or letters (in Japan) over the years, however, showed no obvious trend in any of the three countries.

Proportion of contraindications

Whereas PSI constitutes all the safety information on the label, PCI should be an indicator for more critical

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Table 7. Secular changes in the proportion of the number of labels with a boxed warning to that of all labels

	1994 and earlier	1995 and 1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
USA	44 (7/16)	11 (1/9*)	19 (3/16)	56 (10/18)	25 (2/8)	0 (0/5)	38 (5/13)	73 (11/15)	18 (3/17)	33 (5/15)	42 (5/12)	54 (7/13)	46 (6/13)	17 (1/6)	33 (2/6)	60 (3/5)	50 (1/2)	38 (72/189)
Japan							50 (7/14)	31 (4/13)	58 (7/12)	56 (5/9)	67 (8/12)	50 (9/18)	46 (24/11)	42 (11/26)	26 (5/19)	35 (7/20)	23 (5/22)	42 (79/189)

Values are % (number).
*In 1995, only two in the USA were approved.

Table 8. Proportion of total safety information and of contraindications to all information on the label of biologics and nonbiologics

	USPSI	UKPSI	JPNPSI	USPCI	UKPCI	JPNPCI
Biologics ($n=34$)	46 [8]	41[9]	48 [11]	0.38 [0.63]	0.64 [0.53]	1.16 [0.83]
Nonbiologics ($n=155$)	49 [11]	48 [8]	46 [11]	0.80 [0.88]	1.20 [1.21]	1.38 [1.44]
p	NS	<0.001	NS	<0.001	NS	NS

PSI, proportion of total safety information to all information on the label; PCI, proportion of contraindications to all information on the label; JPN, Japan; NS, nonsignificant.
Values are means % [standard deviation].

Table 9. Proportion of the number of labels with a boxed warning in the USA or in Japan to that of all labels classified according to the nature of the product

Biologics/nonbiologics	Biologics ($n=34$)	Nonbiologics ($n=155$)	All ($n=189$)
USA	62 (21)	33 (51)	38 (72)
Japan	68 (23)	36 (56)	42 (79)
$USA^{+}/Japan^{+}$	53 (18)	19 (30)	25 (48)
$USA^{+}/Japan^{-}$	9 (3)	14 (21)	13 (24)
$USA^{-}/Japan^{+}$	15 (5)	17 (26)	16 (31)
$USA^{-}/Japan^{-}$	24 (8)	50 (78)	46 (86)
USA/Japan Concordance*	76 (26)	70 (108)	71 (134)

Values are % (number).
*Concordance represents the sum of labels with a boxed warning both in the two countries and those without a boxed warning in either of the two countries.
$^{+}$Represents labels with a boxed warning.
$^{-}$Represents labels without a boxed warning.

issues related to the drug. Omission of hypersensitivity and infusion reactions from the CONTRAINDICATION section on the 38 US labels could have contributed to the smallest PCI on all the labels.

Labels with a boxed warning

When we studied PwB according to the ATC classification system, we found results similar to those of PSI. This is not surprising given that the presence of a BW is an indicator of critical safety issues. The low concordance on the labels for blood and blood-forming organs is because of four labels with BWs on the US labels but not on the Japanese labels and one label with a BW on the Japanese labels but not on the US labels. The four labels are for clopidogrel, eltrombopag olamine, darbepoetin alfa, and epoetin beta. The one label is for dabigatran. The low concordance on the labels for the genitourinary system is because of two labels with BWs on the US labels but not on the Japanese labels and four labels with BWs on the Japanese labels but not on the US labels. The former two labels are for the combination of ethinylestradiol/drospirenone and raloxifene. The latter four labels are for follitropin alfa, follitropin beta, tadalafil, and vardenafil.

To take account of the fact that the number of new drugs and biologics with specific risks is growing, the smaller PwB on the Japanese labels approved in 2009 and later compared with that on labels approved earlier is unexpected. The cause is unknown. In the case of the FDA, drug-review deadlines are associated with safety problems,[34] but further analysis is necessary to link any feature of the pressure to shorten "drug lag"[30,35] on the PMDA and the reduction of BWs on the Japanese labels.

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Differences in proportion of total safety information, contraindications, and boxed warnings between biologics and nonbiologics

When specific risks of biologics[3] are taken into account, the smaller PSI on the UK biologics labels and the smaller PCI on the US biologics labels compared with the nonbiologics labels were unexpected. The regulatory authorities might give priority to established risks of nonbiologics on labels instead of potential risks of biologics. Otherwise, they focus on BWs, not on other sections, to publish safety concerns related to biologics.

LIMITATIONS

Our study has several limitations. The outcome measures generated by counting words/characters, PSI, PCI, and PBW are crude measurements that do not always imply critical safety issues. A higher PSI, PCI, or PBW neither imply that a label more sufficiently conveys all potential adverse effects nor imply that they evaluate the success of a label in highlighting clinically relevant adverse events that might affect the decision to initiate treatment. There are also differences in the amount of information conveyed by a kana versus kanji character in Japanese. This phenomenon does not exist in English, further weakening the comparison based on word/character counts alone. Because the data set was based on publicly available data, subtle issues might not have been captured. The cross-sectional design makes causal inference difficult and might provide differing results if another time frame had been chosen. We decided to only include NMEs approved in Japan from April 2001 onward because of availability of the information, including reviews and approval history. As a result, the relatively small sample size makes interpretation of statistically nonsignificant findings challenging. Focus on the UK precluded study of divergence within Europe. Further study is necessary to understand behavioral consequences resulting from drug labeling either to healthcare providers or to the general public.[36]

CONCLUSION

Drug safety regulations involve the challenge of finding harmonization among regulatory authorities. The differences demonstrated in our study confirm that drug labels can be adapted to local healthcare circumstances. Whereas there has been major progress in the collection, analysis, and reporting of efficacy data, efforts to assess and improve the quality of analysis and reporting of safety data lag behind. This defect needs to be corrected if we wish to use quantitative objective evidence of the safety of specific treatments to optimize therapeutic decisions. A systematic approach to the diversity of regulations and their effects would enable us to work out what risks should be included on labels and how the information should be presented for each regional healthcare setting.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- Substantial differences in the amount of safety information exist depending upon therapeutic area among the USA, the UK, and the Japanese drug labels.
- These differences likely arise mainly because of regional factors (e.g., healthcare systems) because the regulatory authorities evaluate the same scientific data.
- A systematic approach to the diversity of regulations and their effects would enable working out what risks should be included on labels and how the information should be presented for each regional healthcare setting.

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