States were obtained from Drugs@FDA[12] and DailyMed,[13] whereas PIs from the UK (Summaries of Product Characteristics; SPCs) were obtained from the Electronic Medicines Compendium (eMC).[14] Japanese PIs were obtained from the PMDA website.[15] 'PI is not available' indicates that PIs were not available from the eMC in the UK or the PMDA in Japan, for yet-to-be approved or discontinued products.

Because the lists of pharmacogenomic biomarkers and PIs are updated from time to time at irregular intervals, results are subject to changes over time but were current on 1 October 2012. We chose to manually screen genomic biomarker information because it was scattered throughout different sections of PIs approved by the respective regulatory authorities.[16–19] Our screening was based on a set of selection criteria that identified descriptions of genomic biomarkers (genotype and/or phenotype) that affected drug efficacy, safety, pharmacokinetics, pharmacodynamics or dosage.

In the present study, a set of drugs and biomarkers was counted as one PI. For all PIs identified in this analysis, genomic biomarker information was extracted manually, according to the context in which the genomic biomarkers were included in the PIs. We divided PI sections in the three countries into five categories (Table 1). UK PI sections had no counterpart for the 'Warning' section. When genomic biomarker information was scattered throughout more than one section (e.g. 'Indications' and 'Dosage'), the upper-categorized section in Table 1 (e.g. 'Indications') was assigned priority.

In addition, we analysed associated factors, including type of biomarker, purpose of biomarker, therapeutic area and initial approval year of the drug in the United States. Biomarkers were categorized into three types (drug target, metabolizing enzyme and others), with two groups for 'purpose' (efficacy and safety). Therapeutic areas were designated according to the FDA table.[3]

RESULTS AND DISCUSSION

Characteristics of pharmacogenomic biomarkers in PIs

118 sets of drugs and genomic biomarkers in PIs (106 as drugs) were included on the FDA list as of 1 October 2012. The 39 individual genomic biomarkers on the list were tabulated by biomarker type and purpose (Table 2). Cytochrome P450 (CYP) 2D6 was the most frequent biomarker found in PIs (37 PIs, 31%). More than half of the biomarkers (69 PIs, 58%) were classified as metabolizing enzymes, and safety-related biomarkers constituted 69% (81 PIs). Numbers of PIs, stratified by therapeutic area and initial approval year in the United States, are shown in Table 3.

Table 1. Package insert section categories for analysis

	PI sections in the USA, the UK and Japan		
Section categories for analysis	USA	UK	Japan
Indications	Indications and usage	4·1 therapeutic indications	Indications Precautions for indications
Warning	Boxed warning	Not applicable	Warning
Dosage	Dosage and administration	4·2 posology and method of administration	Dosage and administration Precautions for dosage
Contraindications	Contraindications	4·3 contraindications	Contraindications
Precautions	Others	Others	Others

Table 2. Type and purpose of genomic biomarkers in the FDA list

Type (number of PIs)	Purpose	Biomarker (number of PIs)
Drug target (29)	Efficacy	ALK (1), BRAF (1), C-Kit (1), CCR5 (1), CD20 antigen (1), CD25 (1), CD30 (1), CFTR (1), EGFR (4), ER (2), ER &/PgR (2), FIP1L1-PDGFRα (1), Her2/neu (4), PDGFR (1), Ph chromosome (4), PML/RARα (2), VKORC1 (1)
Metabolizing enzyme (69)	Safety	CYP1A2 (1), CYP2C19 (14), CYP2C9 (3), CYP2D6 (37), DPD (2), G6PD (3), NAT1/NAT2 (2), TPMT (4), UGT1A1 (3)
Others (20)	Efficacy (8)	ApoE2 (1), chromosome 5q (1), IL28B (3), KRAS (2), LDLR (1)
	Safety (12)	AT III (1), factor V Leiden (2), HGPRT (1), HLA-B*1502 (2), HLA-B*5701 (1), prothrombin mutations (1), Rh genotype (1), UCD (3)

ALK, anaplastic lymphoma kinase; ApoE2, apolipoprotein E2; AT III, antithrombin III; BRAF, v-raf murine sarcoma viral oncogene homologue B1; C-Kit, v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homologue; CCR5, chemokine receptor type 5; CD, cluster of differentiation; CFTR, cystic fibrosis transmembrane conductance regulator; CYP, cytochrome P450; DPD, dihydropyrimidine dehydrogenase; EGFR, epidermal growth factor receptor; ER, oestrogen receptor; FDA, Food and Drug Administration; FIP1L1, FIP1 like 1; G6PD, glucose-6-phosphate dehydrogenase; Her2/neu, human epidermal growth factor receptor 2; HGPRT, hypoxanthine–guanine phosphoribosyltransferase; HLA, human leucocyte antigen; IL28B, interferon-lambda-3; KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue; LDLR, low-density lipoprotein receptor; NAT, N-acetyltransferase; PDGFR, platelet-derived growth factor receptor; PDGFRα, platelet-derived growth factor receptor, alpha polypeptide; Ph, Philadelphia; PgR, progesterone receptor; PML/RARα, promyelocytic leukaemia/retinoic acid receptor alpha; TPMT, thiopurine S-methyltransferase; UCD, urea cycle disorder; UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1; VKORC1, vitamin K epoxide reductase complex, subunit 1.

Table 3. Package inserts stratified by therapeutic area and initial approval year in the USA

	Number of PIs (%)
Therapeutic area	
Analgesics	3 (3)
Antiarrhythmic	1 (1)
Antifungals	2 (2)
Antiinfectives	2 (2)
Antivirals	5 (4)
Cardiovascular	8 (7)
Dermatology and dental	4 (3)
Gastroenterology	8 (7)
Haematology	5 (4)
Metabolic and endocrinology	2 (2)
Musculoskeletal	1 (1)
Neurology	6 (5)
Oncology	36 (31)
Psychiatry	27 (23)
Pulmonary	2 (2)
Reproductive	1 (1)
Reproductive and urologic	2 (2)
Rheumatology	2 (2)
Transplantation	1 (1)
US initial approval date	
1940s	1 (1)
1950s	9 (8)
1960s	11 (9)
1970s	9 (8)
1980s	7 (6)
1990s	26 (22)
2000s	44 (37)
2010s	11 (9)

The largest therapeutic area was oncology, followed by psychiatry. Sixty-nine per cent of the oncology group PIs (25/36 PIs) included drug target biomarkers, whereas 96% (26/27 PIs) of the psychiatry group PIs provided metabolizing enzyme polymorphisms, notably CYP isoenzymes. 75% (27/36 PIs) of the oncology drug PIs referred to biomarkers to highlight efficacy issues. In contrast, all 27 psychiatric drug PIs provided the information to comment on the drugs' safety. For initial US drug approvals, more than two-thirds (81 PIs, 69%) of the PIs with genomic biomarker information were approved from 1990 onwards. Of the 29 PIs with drug target biomarkers, the majority (26 PIs, 90%) were initially approved in 1990 or later, whereas 59% (41/69 PIs) of metabolizing enzyme biomarkers were approved after 1990.

The cross-sectional study design we used provides results specific to a time point. For example, the information on Rh genotype was deleted from the clomiphene PI from the United States on 22 October 2012. In addition, changes in the classification of the type and purpose of biomarkers may also vary over time. For example, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue (KRAS), not usually a direct target of drugs, may become so over time.[9]

Number of PIs containing pharmacogenomic biomarkers in the three countries

The numbers of PIs containing pharmacogenomic information from the United States, the UK and Japan by PI section, as categorized in Table 1, are shown in Fig. 1, along with types of biomarkers. With respect to the number of PIs that contained genomic information, those from the United States contained all 118 PIs, followed by the UK (71 PIs, 60%) and Japan (44 PIs, 37%). PIs classified as 'Precautions' were the most common PI sections cited in all three countries, followed by 'Indications' and 'Dosage'.

For the United States, information in the 'Indications' section typically comment on drug target biomarkers (25/31 PIs, 81%), whereas the 'Dosage' and 'Precautions' sections mainly included information on metabolizing enzyme biomarkers (14/15 PIs, 93% and 50/64 PIs, 78%, respectively). The genomic biomarker information in the 'Indications' section of the PIs was limited to seven therapeutic areas (antivirals, dermatology and dental, gastroenterology, haematology, metabolic and endocrinology, oncology, pulmonary), of which oncology predominated 77% (24/31 PIs). The 'Precautions' section of the PIs with genomic information included all 19 therapeutic areas, but 31% (20/64 PIs) of the PIs related to psychiatry.

For the UK and Japan, 21 (18%, 20 drugs) and 34 (29%, 32 drugs) of drugs with PIs that included genomic information in the United States were not approved or were discontinued. Of these, 18 PIs (15%, 17 drugs) were not available in either the UK or Japan. Relevant biomarkers were not described in 26 (22%) and 40 (34%) PIs from the UK and Japan, respectively, and 21 of these PIs (18%) did not mention relevant biomarkers in either the UK or Japan. As with the United States, the majority of the 'Indications' section PIs from the UK (18/23 PIs, 78%) and Japan (12/16 PIs, 75%) described drug targets. In contrast, no metabolizing enzyme biomarkers appeared in the 'Indications' section in any of the three countries. The 'Precautions' section mainly contained metabolizing enzyme information in the UK (27/38 PIs, 71%) and Japan (15/25 PIs, 60%); however, some PIs recommended or required a specific action according to the effect of the metabolizing enzyme in the 'Warning', 'Dosage' and 'Contraindication' sections. PIs from the UK had no counterpart to the 'Warning' section. The majority of the 'Indications' section PIs belonged to the area of oncology, both in the UK (19/23 PIs, 83%) and Japan (13/16 PIs, 81%), similar to those in the United States. On the other hand, only 18% (7/38 PIs) and 8% (2/25 PIs) of the 'Precautions' section PIs were in psychiatry in the UK and Japan, respectively. Most PIs of psychiatric drugs did not state relevant biomarkers or were not available in the UK (17/27 PIs, 63%) or in Japan (23/27 PIs, 85%).

Figure 1 shows that the United States was the country most likely to include pharmacogenomic information in PIs, followed by the UK and then Japan. The number of Japanese PIs that provided information on genomic biomarkers was small (44 PIs) compared with those of the United States (118 PIs) and the UK (71 PIs). The notorious 'drug lag' in Japan may have partly contributed to this.[20,21] Another reason for this discrepancy might be ethnic differences, such as differences in allele frequencies in the populations concerned. For example, factor V Leiden, which has an incidence of 5% among Caucasians in North America, is extremely rare in people of Asian descent.[22] The frequencies of CYP2D6 poor metabolizers (PMs), which was the most frequent biomarker found in PIs, are approximately 1% in Asians and approximately 5–10% in Caucasians. CYP2C19 PMs have prevalences of 15–30% in Asians and 3–6% in Caucasians.[23,24] Ethnic factors may therefore account for some of the differences seen in Japanese PIs relative to the other blocks.

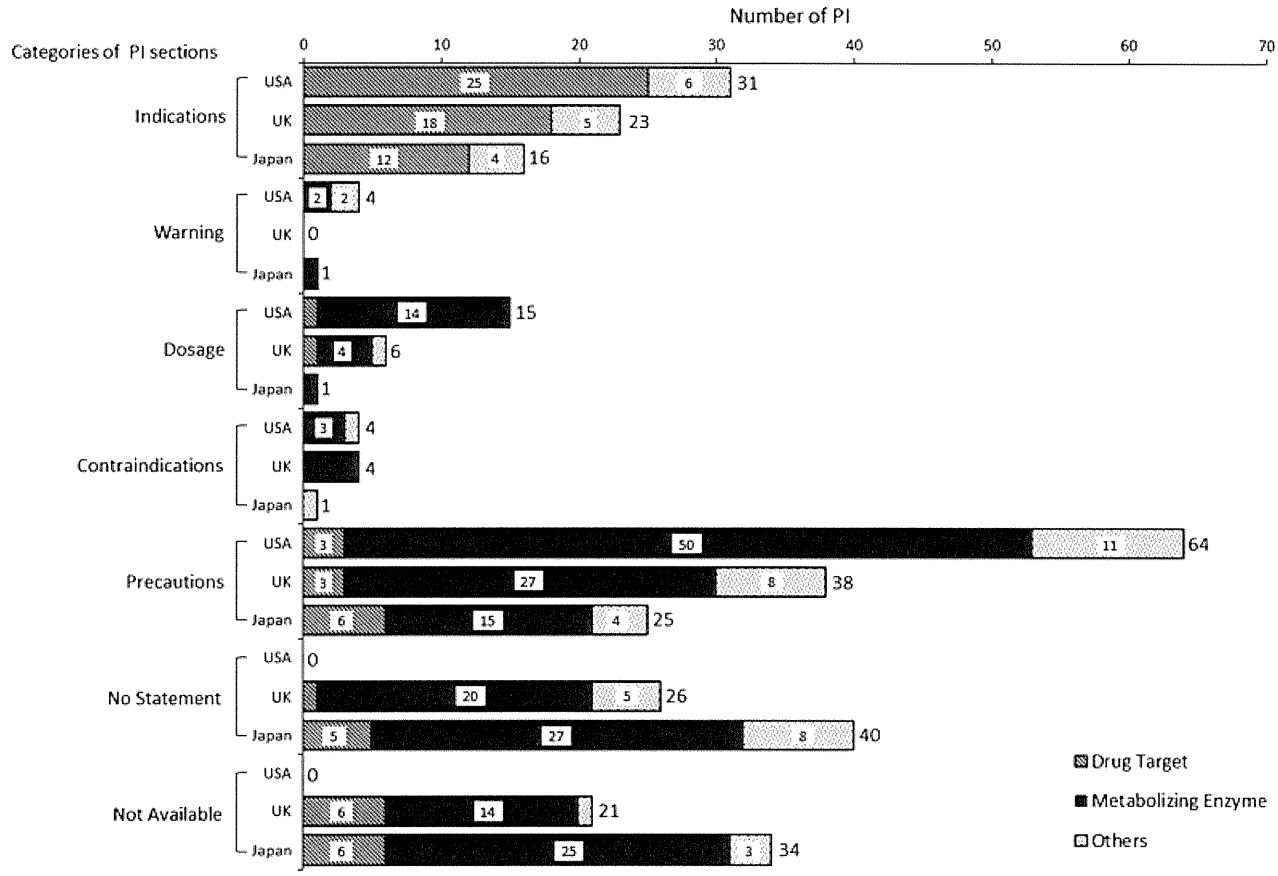

Fig. 1. Package insert sections for pharmacogenomic information in the USA, the UK and Japan.

Another reason for the difference is likely related to variations in the guidance issued by the different drug regulators for inclusion of pharmacogenomic information in PIs. The FDA and EMA provide instructions on how pharmacogenomic information should be incorporated into PIs,[17,19,25–27] whereas the Japanese regulatory guidelines have not been updated since 1997[18] and do not mention pharmacogenomics. In the United States, applicants have the option of creating a separate 'Pharmacogenomics' subsection in the Clinical Pharmacology section, if appropriate.[26] The establishment of guidelines and support from regulatory agencies would facilitate the translation of pharmacogenomic knowledge into routine clinical practice.

Comparisons of genomic biomarkers in PIs among the three countries

Details of the pharmacogenomic information in the 118 PIs from the United States, the UK and Japan are compared in Tables S1–S3 (online only), based on PI sections in the United States. Tables S1–S3 provide PI information on the 'Indications' section, 'Precautions' and sections other than 'Indications' and 'Precautions', respectively. Analyses of PI section differences between the United States and the UK, the United States and Japan, and the UK and Japan are shown in Tables 4–6, respectively. The 'not available' (NA) column was introduced to the tables between the United States and the UK or Japan (Tables 4 and 5) because 21 (18%) and 34 (29%) PIs were not available in the UK and Japan, respectively. The three tables show that there was significant disconcordance in the PI sections among the three countries, even though the regional authorities regulated the same product with considerable discussions on harmonization. We observed that the differences were stratified by PI section in the United States (Tables 4 and 5) or the UK (Table 6), type of biomarker, purpose of biomarker, therapeutic area and initial US approval period.

Stratification by PI section

The 'Indications' section showed higher concordance rates between countries (UK/USA 65%, Japan/USA 48% and Japan/UK 61%) than those of the 'Precaution' section (UK/USA 41%, Japan/USA 17% and Japan/UK 37%). As Fig. 1 demonstrates, PI section was linked to type of biomarkers, and the majority of the 'Indications' section PIs described drug targets in all three countries.

Stratification by type and purpose of biomarker

In the PIs from both the UK and Japan, the genomic information appeared more consistently in the same section relative to the US PIs for drug targets (UK 55%, Japan 41%) than that for metabolizing enzyme (UK 36%, Japan 14%). In this study, pharmacogenomic information in the PIs was classified roughly as describing the drug's pharmacological target (mainly efficacy oriented) or the drug's

Table 4. Analysis of differences in information in package inserts between the USA and the UK

Stratified factor (number of PIs)	Number of PIs: Differences between the USA and the UK: Concordant (51)	Different (46)	NA in UK[a] (21)
PI section in the USA			
Indications (31)	20	4	7
Precautions (64)	26	26	12
Others (23)	5	16	2
Type of biomarker			
Drug target (29)	16	7	6
Metabolizing enzyme (69)	25	30	14
Others (20)	10	9	1
Purpose of biomarker			
Efficacy (37)	20	11	6
Safety (81)	31	35	15
Therapeutic area			
Oncology (36)	18	13	5
Psychiatry (27)	7	13	7
Others (55)	26	20	9
Initial US approval period			
Before 1979 (30)	6	18	6
1980–1999 (33)	20	11	2
After 2000 (55)	25	17	13

[a]PI was not available in the UK.

Table 5. Analysis of differences in information in package inserts between the USA and Japan

Stratified factor (number of PIs)	Number of PIs: Differences between the USA and Japan: Concordant (29)	Different (55)	NA in Japan[a] (34)
PI section in the USA			
Indications (31)	15	8	8
Precautions (64)	11	32	21
Others (23)	3	15	5
Type of biomarker			
Drug target (29)	12	11	6
Metabolizing enzyme (69)	10	34	25
Others (20)	7	10	3
Purpose of biomarker			
Efficacy (37)	16	14	7
Safety (81)	13	41	27
Therapeutic area			
Oncology (36)	14	16	6
Psychiatry (27)	4	11	12
Others (55)	11	28	16
Initial US approval period			
Before 1979 (30)	2	20	8
1980–1999 (33)	7	18	8
After 2000 (55)	20	17	18

[a]PI was not available in Japan.

metabolizing enzymes (mainly safety oriented). A drug target can be used to stratify a disease into two or more distinct illnesses or syndromes based on their biological characteristics, and clinical trials are increasing designed with the use of genomic biomarkers for inclusion eligibility. The majority of genomic biomarkers in the 'Indications' section consisted of drug targets in all three countries examined. The four biomarkers that were not drug targets, included in the 'Indications' section, were chromosome 5q (USA, Japan), KRAS (all), low-density lipoprotein receptor (LDLR, all) and urea cycle disorder (UCD, USA and UK). Chromosome 5q, KRAS and LDLR are not direct targets of drugs but are markers of efficacy. UCD is a safety biomarker for valproic acid but an efficacy biomarker for sodium phenylbutyrate. Differences in drug target descriptions in the PIs among the three countries were mainly related to whether the relevant indication was approved.

Compared with drug target biomarkers, polymorphisms of metabolic enzymes affect drug pharmacokinetics and usually have more modest impacts on drug response. The present study shows that inclusion of information on a metabolic enzyme's genomics is more inconsistent across the three countries when with drug target information. Interindividual variability in drug pharmacokinetics is caused by several factors, including sex, age, weight, renal and hepatic function and genetics. Therefore, pharmacokinetic variability does not necessarily influence drug safety and/or efficacy significantly. The inclusion of information on genomic biomarkers in the PIs for clopidogrel, tamoxifen and warfarin illustrates this issue well. The FDA updated the clopidogrel PI to include, in the 'Warning' section, information stating that the patient's genotype for CYP2C19 could affect the antiplatelet activity of the drug.[28] The warning recommends alternative medications for CYP2C19 PMs. On the other hand, the UK and Japanese PIs provide information on CYP2C19 PM in the 'Precautions' sections (Table S3). The American College of Cardiology Foundation and the American Heart Association published a Clinical Alert that emphasized that information regarding the predictive value of genetic testing is still very limited and that current evidence is insufficient to recommend routine genetic function testing at the present time.[29] Current evidence also does not support personalized treatment with clopidogrel tailored to the CYP2C19 genotype.[30]

In contrast, although several studies of tamoxifen have addressed the association between CYP2D6 genotype and clinical outcome,[31–38] only the UK PI includes information about CYP2D6 pharmacogenomics in the 'Precautions' section. A possible reason for this discrepancy could be differences in the results of relatively small and mostly retrospective studies.[39–41]

The information on genomic biomarkers for tamoxifen was more consistent as there was no information described in only one country.

The warfarin's PI included genomic information on both drug target (VKORC1; vitamin K epoxide reductase complex, subunit 1) and metabolizing enzyme (CYP2C9). A number of retrospective studies have reported a strong association between the presence of VKORC1 and CYP2C9 variants and warfarin dosing, and polymorphisms in VKORC1 have been shown to be more important than those in CYP2C9.[42–44] However, prospective evidence for any clinically relevant benefit of VKORC1 and/or CYP2C9 testing is limited or of uncertain clinical relevance.[45–49] The US warfarin PI provided dosing schedules according to a combination of

Table 6. Analysis of differences in information in package inserts between the UK and Japan

	Number of PIs	
	Differences between the UK and Japan	
Stratified factor (number of PIs)	Concordant (68)	Different (50)
PI section in the UK		
Indications (23)	14	9
Precautions (38)	14	24
Others (10)	1	9
No statement (26)	21	5
Not available (21)	18	3
Type of biomarker		
Drug target (29)	19	10
Metabolizing enzyme (69)	38	31
Others (20)	11	9
Purpose of biomarker		
Efficacy (37)	25	12
Safety (81)	43	38
Therapeutic area		
Oncology (36)	23	13
Psychiatry (27)	16	11
Others (55)	29	26
Initial US approval period		
Before 1979 (30)	14	16
1980–1999 (33)	18	15
After 2000 (55)	36	19

VKORC1 and CYP2C9 genotypes, whereas the PI from the UK gave information only on genetic variability of VKORC1 and CYP2C9. The Japanese PI only presented information on the existence of CYP2C9 polymorphism (Table S3).

The way in which genomic information was described in the PIs depended on the strength of the available data and on the efficacy and expected safety consequences. When the biomarker is a drug target, there is preliminary evidence that the genomic biomarker was associated with drug response prior to initiating the clinical trials. Confirmatory trials were then undertaken for prospective validation of the biomarker. Differences in PIs occurred when there was a lack of strong evidence to provide clear information and recommendations to the prescriber and when the safety or efficacy consequences differed according to subpopulations considered.

Some of the differences may result from differences in health insurance provisions between the three countries. For example, the national health services of the UK and Japan do not reimburse CYP genotyping tests. In the United States, some payers have championed personalized approaches, even if reimbursement is limited.[50] This might lead to some US PIs (e.g. iloperidone, pimozide, tetrabenazine) strongly recommending CYP2D6 genotyping to individualize dosing, whereas there were no recommendations in the PIs from the UK and Japan (Table S3).

Stratification by therapeutic area

The present study showed contrasting results between oncology and psychiatry. The majority of the PIs with genomic information in the 'Indications' section were of the oncology area for all three countries (USA 77%, UK 83%, Japan 81%). In cancer treatment, diagnostic tests are available and pharmacogenomic approaches are already implemented in clinical practice in all three countries. On the other hand, molecular personalized medicine is still not common in psychiatry. Pharmacogenomic studies with concrete results in psychiatry have largely been on genes encoding metabolic enzymes because most psychiatric drugs are metabolized by CYP isoenzymes.

Stratification by initial approval year in the United States

The PIs from the UK and Japan were more likely to differ from PIs from the United States for drugs approved prior to 1980 (Tables 4 and 5). PIs with drug target biomarkers tended to be approved in the United States later than PIs with biomarkers for metabolizing enzymes.

WHAT IS NEW AND CONCLUSION

The United States was the country most likely to introduce genomic information into PIs, followed by the UK and Japan. Pharmacogenomic information in PIs differed among the three countries depending on type of biomarkers and therapeutic area. These differences appeared to vary according to the strength of the evidence supporting use of the genomic biomarkers and on the practicability of translating pharmacogenomic knowledge into PIs. Guidance by drug regulators on appropriate presentation of pharmacogenomic data in PIs should help facilitate the wider use of such information.

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CONFLICT OF INTEREST

The authors report no conflict of interests in this work.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Pharmacogenomic information in the 'Indications' section of the package inserts (PI) of products marketed in the US, UK and Japan.

Table S2 Pharmacogenomic information in the 'Precautions' section of the package inserts (PI) of products marketed in the US, UK and Japan.

Table S3 Pharmacogenetic information in sections, other than 'Indications' and 'Precautions' sections of the package inserts (PI) of products marketed in the US, UK and Japan.

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ORIGINAL ARTICLE
Cardiovascular Intervention

Global Cardiovascular Device Innovation: Japan-USA Synergies

– Harmonization by Doing (HBD) Program, a Consortium of Regulatory Agencies, Medical Device Industry, and Academic Institutions –

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on behalf of the Harmonization by Doing Program Working Group

Background: Global medical devices have become more popular, but investment money for medical device development is not easily available in the market. Worldwide health-care budget constraints mean that efficient medical device development has become essential. To achieve efficient development, globalization is a key to success. Spending large amounts of money in different regions for medical device development is no longer feasible.

Methods and Results: In order to streamline processes of global medical device development, an academic, governmental, and industrial consortium, called the Harmonization by Doing program, has been set up. The program has been operating between Japan and the USA since 2003. The program has 4 working groups: (1) Global Cardiovascular Device Trials; (2) Study on Post-Market Registry; (3) Clinical Trials; and (4) Infrastructure and Methodology Regulatory Convergence and Communication. Each working group has as its goals the achievement of speedy and efficient medical device development in Japan and the USA. The program has held multiple international meetings to deal with obstacles against efficient medical device development.

Conclusions: This kind of program is very important to deliver novel medical devices. Involvement of physicians in this type of activity is also very helpful to achieve these goals. (*Circ J* 2013; **77:** 1714–1718)

Key Words: Cardiovascular devices; Harmonization by Doing; Medical device innovation

Innovation and Safety Issues in Cardiovascular Devices

Cardiovascular devices continue to revolutionize and transform practice with unique solutions to unmet clinical needs. Coronary stents continue to become smaller, more flexible, and yet more durable. Percutaneous heart valves now deliver life-saving therapies that once required surgical implantation. Improved and smaller designs of defibrillators, pacemakers, and ventricular assist devices now allow treatment of a broader group of patients and/or disease states. As they advance, however, the design and manufacturing of these novel devices become progressively complex. Animal and bench models are limited in their ability to characterize device performance in humans, especially for novel devices, and thus, careful, well-designed and ethical clinical trials in patients continue to be the gold standard to provide data to establish a reasonable assurance of safety and effectiveness to support approval by regulatory authorities. Even after approval, widespread post-market use of breakthrough medical device technologies may produce unexpected safety concerns,[1] such as reports of very late stent thrombosis in patients treated with drug-eluting stents (DES).[2]

In addition, investment money is not easily available for medical device development in the market. The worldwide health-care budget constraint has been putting pressure on the medical device industry. Krucoff et al address such points well in the July issue of *JACC Cardiovascular Interventions*.[3] Dr Maisel also addressed regulatory challenges and opportunities in medical device development from the US Food and Drug Administration (FDA)'s standpoint in the same issue.[4]

Increasingly, development and evaluation of novel medical devices require a global approach. Although regulatory standards and processes differ across countries and regions, regulatory authorities in the USA and Japan have undertaken an

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Table. Harmonization by Doing Working Groups

Working group	Current mission
1. Global Cardiovascular Device Trials	Improve the interactions and exchange of ideas between Japan MHLW/PMDA, US FDA, academia, and industry, and to provide a forum to identify, discuss, and develop solutions to barriers to single-protocol clinical trials to be conducted in both the USA and Japan, in order to facilitate the timely and more cost-effective global introduction of new, safe, and effective device technologies.
2. Study on Post-market Registry	Facilitate multilevel discussion and collaboration between Japanese and US institutions regarding post-market global monitoring of MCSDs, including the incorporation of Japanese data with that of the USA in the INTERMACS registry and to use these data to guide future use of this technology. While the current WG2 mission is currently concentrated on MCSDs, WG2 activities should be expanded to include global post-market data collection for other cardiovascular devices, and the application of this information to guide the continued use of these device technologies, as well as to guide the evaluation of future devices.
3. Clinical Trial Infrastructure and Methodology	Facilitate the development of a robust and effective clinical trial infrastructure in the USA and Japan to support the conduct of global clinical trials to allow the timely introduction of new safe and effective medical devices into the USA and Japan.
4. Regulatory Convergence and Communication	Facilitate the timely global introduction of new medical technologies by identifying and addressing specific regulatory barriers through proof-of-concept projects, specifically, to improve administrative practices within the context of existing regulations with the goal of convergence between Japanese and US practices and improved communication between stakeholders.

FDA, Food and Drug Administration; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MCSD, mechanical circulatory support device; MHLW, Ministry of Health, Labor and Welfare; PMDA, Pharmaceuticals and Medical Devices Agency.

initiative to demonstrate how cardiovascular device development and evaluation can be efficiently conducted using such a global approach, to the benefit of patients in both countries.

Device Lag in Japan and the USA Compared to Europe

Historically, new medical devices have been launched onto the market in Europe, because the regulatory standard in the European Union (EU) is the demonstration of safety and performance, which typically has been accomplished through a small or medium-sized clinical study. Additional preclinical evaluation and larger pivotal clinical trials are then performed to support marketing of these devices in the USA, and sometimes further trials in Japan lead to marketing approval and release in Japan. Despite the fact that the USA and Japan constitute the 2 most lucrative medical device markets in the world, this approach has meant that doctors and patients in Japan and the USA have had, at times, significant delays in access to new medical devices, and certain devices are never marketed in these countries at all. In Japan, this delay has been called "device lag" and the Japanese regulatory authority the Pharmaceuticals and Medical Devices Agency (PMDA), recognizes this phenomenon as an important issue. PMDA has made tremendous efforts to solve this problem since the first Mid-term Plan started in April 2004.[5,6] The current approach followed by industry, to obtain marketing approval in Europe first, and only then in the USA and Japan, not only results in time delays to access, but also to redundancy and added cost in research and development as clinical trials are independently performed in each country. Most importantly, such fragmented efforts can ultimately lead to poorer quality data overall, particularly for information related to rare but catastrophic safety problems.

Global Regulatory Collaboration

The recognition that the biology and epidemiology of cardiovascular disease is largely driven by common risk factors independent of ethnic, scientific, clinical and economic factors, has encouraged growing interest in efforts to study new devices through more efficient, high-quality global collaborations. Such efforts respect the independence of individual governmental jurisdictions of national regulatory authorities, while concomitantly encouraging the convergence of basic principles of medical device safety and performance evaluation through the best ethics, science, and methods of human clinical research. The Global Harmonization Task Force (GHTF), through its founding member nations, Japan, Canada, Australia, the EU, and the USA, has focused manufacturers and regulators on the development of consensus guidelines for such principles for more than a decade.[7] Moreover, a new consortium, the International Medical Device Regulators Forum (IMDRF) was set up in February 2011 as a forum to discuss future directions in medical device regulatory harmonization. The IMDRF is a voluntary group of medical device regulators from Australia, Brazil, Canada, China, the EU, Japan and the USA, as well as the World Health Organization, who have come together to build on the strong foundational work of the GHTF, and to accelerate international medical device regulatory harmonization and convergence.[7] Furthermore, a more pragmatic program that includes academic clinicians along with other stakeholders, the Japan-USA Harmonization by Doing (HBD) program,[8] was initiated in 2003.

HBD Program

The HBD program provides a forum for collaboration between Japanese and US regulators, industry, and academic clinicians, where all stakeholders can engage in open discussions toward the identification and resolution of obstacles to conducting global clinical trials and harmonization of regulatory processes. The objective of HBD is to eliminate redundancies, added costs, and time delays inherent in sequential clinical trials. The intent of HBD is not simply to create guidance and discuss policy but to develop common protocols for investigational clinical studies that would allow safe and effective breakthrough cardiovascular technologies to benefit patients worldwide. HBD is uniquely different from other global harmonization initiatives in that the program aims to fulfill its mission through practical experience – that is, by doing – and sharing lessons learned from these experiences. This is achieved through proof-of-concept projects, in which specific challenges are identified and potential solutions are tested. The current membership of HBD includes members of the FDA, Japan's Ministry of Health,

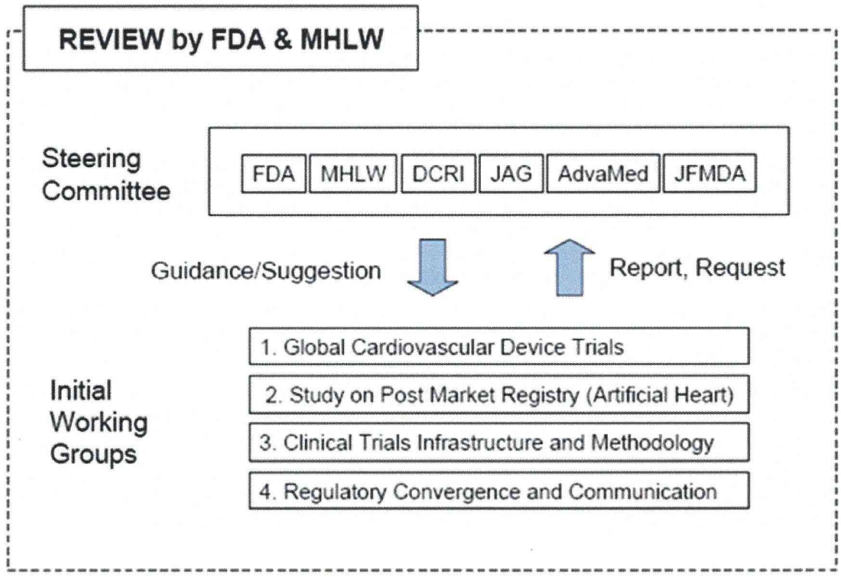

Figure. Structure of Harmonization by Doing. The Steering Committee is composed of representatives from the industry, academia, and government agencies in both the USA and Japan. AdvaMed, Advanced Medical Technology Association; DCRI, Duke Clinical Research Institute; FDA, US Food and Drug Administration; JAG, Japanese Academic Group; JFMDA, Japan Federation of Medical Devices Associations; MHLW, Ministry of Health, Labor and Welfare.

Labour and Welfare (MHLW)/PMDA, US industry (represented by the Advanced Medical Technology Association [AdvaMed] and other cardiovascular device manufacturers who are not members of AdvaMed), Japanese industry (represented by the Japan Federation of Medical Devices Associations [JFMDA]), US cardiovascular academia (represented by Duke Clinical Research Institute [DCRI]), and the Japanese academic community from cardiovascular fields. The HBD program is overseen by a steering committee, which includes members from each stakeholder group, and includes 4 working groups (WGs). **Table** outlines the 4 WGs and their current mission.

Through the activities of each of the WG, as well as the HBD steering committee, the complex array of challenges faced when designing and executing global clinical trials can be overcome in a more manageable stepwise manner. Furthermore, potential harmonization of regulatory practices and communication between US and Japanese regulatory authorities can shorten the device approval time lag through the streamlining of processes and the gaining of a common understanding of the scientific challenges, without adversely affecting current review practices or time lines. HBD's premise is that if all stakeholders share a portion of their experiences on different aspects of global trials, as well as lessons learned through the regulatory review processes required to conduct such global trials and achieve market approval for new devices where possible, all parties involved would benefit through a reduction in duplicative efforts by solving common problems. This sharing of information, however, must be carried out in a manner that protects the confidential and trade secret information of industry sponsors that are involved, and with the agreement of all stakeholders involved.

HBD History

From December 2003 to March 2004, joint meetings between FDA, MHLW-PMDA, DCRI and industry were held at FDA in Rockville, Maryland, USA to talk about the HBD concept and the HBD collaboration process. This was followed by other similar meetings at MHLW in Tokyo, Japan, and the first public announcement in a program at the annual scientific meeting of the Japan Circulation Society in March of 2004. The first in-depth HBD East Think-Tank Meeting took place in Tokyo in December 2005. Three main outcome goals were agreed on at the 2005 Think Tank meeting: (1) build a more robust clinical research infrastructure; (2) compare medical device good clinical practice (GCP) to determine if any significant differences exist that could be obstacles to the HBD process; and (3) define and clarify the rules for increased and better cooperation among all parties involved. The second HBD Think-Tank Meeting was successfully held in January 2007 in Durham, North Carolina, USA as HBD West 2007. Representatives from more than 25 academic institutions, industry organizations and companies as well as government regulators from the USA and Japan attended and engaged in discussion during this 2-day meeting. During the HBD West 2007 meeting, the HBD structure (**Figure**) and the initial 4 HBD WG missions were introduced. The third HBD Think-Tank Meeting, HBD East 2008, was convened in July of 2008 in Tokyo, Japan. This meeting provided a forum for discussion on convergence of regulatory requirements and practices through concrete experience "by doing" in the USA and Japan. To continue the discussions and review the past HBD activities, the HBD West 2009 Think-Tank Meeting was held in Silver Spring, Maryland, USA in July of 2009. Unfortunately, the HBD East 2011 Thank-Tank Meeting planned on 16 and 17 March in Tokyo was cancelled due to the earthquake in East Japan that occurred on 11 March 2011. There were several HBD sessions, however, held by each WG to share progress and accomplishment during the AdvaMed Medtech Conferences 2011 on 26 September in Washington, DC, USA, as well as the Transcatheter Cardiovascular Therapeutics (TCT) 2011 meeting on 4–7 November 2011 in San Francisco, California, USA Another global educational program titled "Japan-USA Synergies in Global Medical Device Innovation: Harmonization by Doing" was held at the TCT 2012 meeting.[9] Most recently, an HBD-related open-to-the-public meeting was held during the Kamakura Live 2012 in Kamakura, Japan.

WG Key Activities

WG1: HBD-Related Clinical Studies – Endeavor Japan and SPIRIT Japan Trials

As described here, the ultimate goal of the HBD initiatives is to lead to more expeditious development and marketing in both countries for those new therapies that have been demonstrated to be reasonably safe and effective. One important step toward accomplishing this objective is the carrying out of global clinical trials enrolling patients worldwide using harmonized study protocols. In line with this HBD concept, the Endeavor Japan trial was initiated in the spring of 2005 for Medtronic's Endeavor® Zotarolimus-Eluting Coronary Stent. This Japanese study for a new DES utilized the identical study protocol that was used in the global Endeavor-II trial,[10] which was an important supporting study for US marketing approval. Following the Endeavor Japan study, a second study, the SPIRIT Japan study, to evaluate the Abbott Vascular XIENCE V Everolimus-Eluting Coronary Stent, was conducted in the USA and Japan simultaneously under a global DES development strategy.

There were several discussion points in executing these clinical trials. One was whether these trials should be separated from a larger global trial of each. It was a dilemma. Future clinical trials might not happen if these trials failed, but if the trials were separated, Japan might lose opportunities to catch up with the advanced countries. Finally, as a learning step, the separated study design with an identical study was chosen.

Experience from these studies then demonstrated that the Japanese cardiology community was in fact ready to participate fully in global DES trials. Ten Japanese sites joined a global DES trial, the PLATINUM trial, and contributed very effectively.[11]

WG2: INTERMACS and J-MACS

Referring to the INTERMACS program,[12] the J-MACS program[13] was launched in 2010 for post-marketing follow-up for the 2 left ventricular assist devices approved in Japan in 2010, EVAHEART[14] and DuraHeart.[15] HBD WG2 fully supports this program.

WG3: Infrastructure for Clinical Studies in Japan

Through the clinical studies described here (the WGs 1- and 2-related studies), infrastructure for clinical studies in Japan was further developed. This might lead to more clinical studies from Japan such as the 2 post-market studies in cardiology, the TAXUS Japan Postmarket surveillance study[16] and, the MIRACLE-ICD outcome measured in Japanese indication (MOMIJI) study.[17]

WG4: Collaborative Consultation and Review of Pre-Marketing Applications Pilot Program and Research Papers

Led by WG4, a direct consequence of HBD is the Medical Device Collaborative Consultation and Review of Pre-marketing Applications pilot program.[18,19] This unique program involves the active engagement of the industry sponsor with both US FDA and MHLW/PMDA. A goal of the pilot program is to advance both the speed and quality of clinical/statistical consultations and the regulatory review process for potential earlier market access and improved public health benefit.

WG4 compared GCP between Japan and the USA. The outcome was published as a key accomplishment of WG4.[20] The research concluded that there were several administrative differences but no essential differences between the 2 sets of GCP.

HBD Future and Conclusions

The next HBD East Think-Tank Meeting, HBD East 2013 is currently planned for 9 and 10 July in Tokyo, Japan. As a dynamic program, HBD has recognized that it must be able to adapt as necessary to address new therapies and new scientific challenges. In addition to innovations in DES technology, such as the use of biodegradable materials, this meeting will address transcatheter aortic and mitral valve interventions. Moreover, it is envisioned that, over time and with appropriate support from its participating stakeholders, HBD could expand to include other medical devices such as orthopedic products. Finally, as the HBD program matures, other regulatory bodies in other countries could be involved.

Development of innovative medical devices is often a driver for evolution in medicine. Physicians, industry, and regulators all have an important role to play in ensuring that new medical devices provide safe and effective therapy. Physicians are primary contributors to medical device development through their participation in clinical trials. In clinical research activities for medical device development, collaboration among clinicians, the device industry, and regulators is an essential to making innovative therapy available to patients. Unlike GHTF, HBD provides physicians with an open platform on which to collaborate with industry and regulators. Contributions from each stakeholder group will be needed to ensure the future success of HBD, but with a focus on clinical and scientific challenges and new product innovation, HBD will continue to streamline the advance of new medical devices.

Disclaimer

This article represents the personal views of the authors and does not represent official FDA correspondence or guidance or official MHLW/PMDA correspondence or guidance. The HBD program is focused on collaborative efforts and demonstration projects that promote harmonization of clinical trial practices and medical device regulatory approval processes between the USA and Japan.

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Disclosures

Conflict of Interest: Gary Thompson is a full-time employee of Abbott Vascular. He receives travel expenses and salary, which are unrelated to research and exceed an annual total of 50,000 yen from the company.

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