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Pharmacogenetics

Approval gap of pharmacogenomic biomarkers and *in vitro* companion diagnostics between the United States and Japan

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SUMMARY

What is known and objectives: ***In vitro*** **companion diagnostic devices (CDx) provide information on pharmacogenomic biomarkers (PGBMs) to enable the safe and effective use of targeted agents for personalized therapy. These devices require specific regulations that strike a balance between scientific evidence and financial burden. The aims were to compare approval of PGBMs and CDx in the USA and Japan and to help inform current discussions on personalized medicine.**

Methods: **We analysed published documentation from the USA and Japan for CDx and PGBMs, listed by the US Food and Drug Administration (FDA). Aspects evaluated were aim, approval state and therapeutic area. Coverage by the National Health Insurance in Japan was also investigated.**

Results and discussion: **Thirty-eight PGBMs were listed in the FDA table as of March 2013. In the USA, the aim was efficacy in 55% (21/38). The largest therapeutic area was oncology (39%, 15/38). Fifty-three per cent (20/38) of the PGBMs had a corresponding CDx approved. Of the 38 PGBMs in the FDA table, six had no approved drug in Japan; in 16 of the remaining 32 PGBMs, the aim was efficacy. The largest therapeutic area was oncology (34%, 11/32). Of the 32 PGBMs, 15 were associated with an approved and/or covered CDx, with only 11 having an approved CDx. Four PGBMs had a covered CDx without prior approval in Japan.**

What is new and conclusion: **Our study confirms that there is still a substantial gap in the approval of PGBMs and CDx between Japan and the USA. Complementary coverage of unapproved CDx by the National Health Insurance, however, is raising access to a similar level in both countries. Because the number of expensive personalized medicines and CDx is increasing, patient access will continue to be an important challenge to healthcare systems in all countries.**

WHAT IS KNOWN AND OBJECTIVE

For many years, healthcare professionals have used diagnostic tests to select appropriate treatments for patients or to optimize dosing regimens. Pharmacogenomic biomarkers (PGBMs) can help inform therapeutic decisions in personalized medicine.[1–3] More than 100 drug labels are included in the table of PGBMs published by the US Food and Drug Administration (FDA).[4] *In vitro* companion diagnostics (CDx) provide information essential for the safe and effective use of targeted therapeutic products.[5] Ethical implementation of personalized medicine, however, requires balancing scientific evidence and financial burden.[6]

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities and pharmaceutical companies in the USA, Europe and Japan to discuss scientific and technical aspects of drug registration. Harmonization in the development and regulation of PGBMs and CDx, however, remains to be implemented. In July 2011, the FDA issued draft guidance on CDx,[5] whereas the European Medicines Agency (EMA) issued a draft reflection paper[7] focusing on the use of PGBMs in the clinical development of CDx and patient selection. In contrast, the Pharmaceuticals and Medical Devices Agency (PMDA), the Japanese counterpart of the FDA and EMA, has not yet issued any document on the development of CDx. Although the FDA and EMA desire co-development of drugs and diagnostics, most approved CDx were not developed concurrently with the drugs concerned.[8]

In addition to approval by a regulatory authority, general use of a CDx requires coverage and reimbursement by health insurers. Coverage decisions are critical factors in patient access to personalized medicine. Policy makers and payers have to make decisions about the financial sustainability of healthcare delivery, whereas regulatory authorities have to optimize access to safe and effective medications.[9] In the USA, FDA approval is not a guarantee of coverage.[8,10] Lack of evidence for the clinical use of many CDx has led payers to deny or restrict reimbursements.[6,11] For example, the CMS does not routinely cover genotyping for CYP 2C9 and VKORC1[12] in patients being prescribed warfarin. It requires evidence that such testing will deliver improved clinical outcomes.

Assessment of health outcome measures[13] has shown that Japan holds a favourable position in the development of personalized medicine through its industrial, regulatory and reimbursement processes. The National Health Insurance (NHI) in Japan[14] covers virtually all medications and diagnostics approved by the PMDA. Sometimes payers even reimburse for off-label medications and unapproved devices,[15] depending on clinical necessity. Surging healthcare costs, however, are challenging the system. For example, Japanese physicians are struggling with reimbursement for genetic testing.[16]

The objectives of this study were to investigate the differences in approval of PGBMs and CDx in the USA and Japan and to help

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inform current discussion on barriers to personalized medicine in both countries. We also evaluated coverage of CDx by the NHI in Japan.

METHODS

Study design

This was a cross-sectional study of documents published on the FDA's and PMDA's websites as of March 2013. PGBMs approved only in Japan, for example HLA-A*3101[17] and CCR4,[18] were not included in this study because we used the FDA table[4] as the reference.

Data sources

PGBMs were listed in the Table of Pharmacogenomic Biomarkers in Drug Labels on the FDA's website.[4] We also obtained US CDx data from the FDA's database of 510(k) Premarket Notification[19] and Premarket Approval.[20] Japanese CDx data were obtained

Table 1. Approval in the USA and Japan of pharmacogenomic biomarkers and corresponding *in vitro* companion diagnostics

Biomarker	Aim	Therapeutic area	US CDx approval	JPN drug approval	JPN CDx approval	JPN CDx coverage
ALK	Efficacy	Oncology	A	A	A	C
Antithrombin III deficiency (SERPINC1)	Safety	Haematology	A	A	A	C
Apoprotein E2	Efficacy	Metabolic and endocrinology	U	A	U	NC
BRAF	Efficacy	Oncology	A	U	U	NC
C-Kit	Efficacy	Oncology	A	A	U	C
CCR5	Efficacy	Antivirals	U	A	U	NC
CD20 antigen	Efficacy	Oncology	A	U	A	C
CD25	Efficacy	Oncology	U	U	U	NC
CD30	Efficacy	Oncology	A	U	U	NC
CFTR (G551D)	Efficacy	Pulmonary	A	U	U	NC
Chromosome 5q	Efficacy	Haematology	U	A	U	C
CYP1A2	Monitoring	Gastroenterology	U	U	U	NC
CYP2C19	Monitoring	Two or more areas	A	A	A	NC
CYP2C9	Monitoring	Two or more areas	A	A	U	NC
CYP2D6	Monitoring	Two or more areas	A	A	A	NC
DPD	Safety	Two or more areas	U	A	U	NC
EGFR	Efficacy	Oncology	A	A	A	C
ERBB2 (HER2)	Efficacy	Oncology	A	A	A	C
Estrogen receptor	Efficacy	Oncology	A	A	A	C
Estrogen/progesterone receptor	Efficacy	Oncology	A	A	A	C
Factor V Leiden	Safety	Two or more areas	A	A	U	NC
FIP1L1-PDGFRα	Efficacy	Oncology	U	A	U	C
G6PD	Safety	Two or more areas	A	A	U	NC
HGPRT	Safety	Transplantation	U	A	U	NC
HLA-B*1502	Safety	Neurology	U	A	U	NC
HLA-B*5701	Safety	Antivirals	U	A	U	NC
IL28B	Efficacy	Antivirals	U	A	U	NC
KRAS	Efficacy	Oncology	A	A	A	C
LDL receptor	Efficacy	Metabolic and endocrinology	U	A	U	NC
NAT1; NAT2	Safety	Two or more areas	U	A	U	NC
PDGFR	Efficacy	Oncology	U	A	U	NC
Ph1/BCR-ABL	Efficacy	Oncology	U	A	A	C
PML/RARα translocation	Efficacy	Two or more areas	U	A	U	C
Prothrombin F2 mutation	Safety	Oncology	A	A	U	NC
TPMT	Safety	Two or more areas	U	A	U	NC
UCD	Safety	Two or more areas	U	A	U	NC
UGT1A1	Safety	Two or more areas	A	A	A	C
VKORC1	Monitoring	Haematology	A	A	U	NC

CDx, *in vitro* companion diagnostics; JPN, Japanese; ALK, anaplastic lymphoma kinase; A, approved; C, covered; SERPINC1, serpin peptidase inhibitor, clade C (antithrombin), member 1; U, unapproved; NC, not covered; BRAF, v-raf murine sarcoma viral oncogene homolog B1; C-Kit, v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homolog; 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; ERBB2 (Her2), v-erb-b2 avian erythroblastic leukaemia viral oncogene homolog 2 (human epidermal growth factor receptor 2); FIP1L1-PDGFRα, FIP1-like 1-platelet-derived growth factor receptor alpha fusion gene; G6PD, glucose-6-phosphate dehydrogenase; HGPRT, hypoxanthine-guanine phosphoribosyl transferase; HLA, human leucocyte antigen; IL, interleukin; KRAS, Kirsten rat sarcoma 2 viral oncogene homolog; LDL, low-density lipoprotein; NAT, N-acetyltransferase; PDGFR, platelet-derived growth factor receptor; Ph1/BCR-ABL, Philadelphia chromosome/breakpoint cluster region-Abelson tyrosine kinase; PML/RARα, promyelocytic leukaemia/retinoic acid receptor alpha; TPMP, thiopurine S-methyltransferase; UCD, urea cycle disorders; UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1; VKORC1, vitamin K epoxide reductase complex, subunit 1.

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from the PMDA label data of *in vitro* diagnostics.[21] We obtained US drug approval data of these drugs from Drugs@FDA[22] and Japanese drug approval data from the PMDA website's section on new drug approval.[23] We obtained Japanese coverage data of CDx from the NHI database.[24]

Evaluation and analysis

The aim of each PGBM was evaluated according to the FDA guidance[5] as follows. Efficacy is to identify patients who are most likely to benefit from a particular therapeutic product; safety is to identify patients likely to be at increased risk of serious adverse reactions as a result of treatment with a particular therapeutic product; monitoring is to monitor responses to treatment for the purpose of adjusting treatment (e.g. schedule, dose and discontinuation) to improve safety or effectiveness. We used Fisher's exact test to determine the relationship between the aim (efficacy/safety and monitoring) and therapeutic area (oncology/non-oncology) on the approval status of the CDx. A P value <0·05 was regarded as statistically significant.

RESULTS AND DISCUSSION

Characteristics of PGBMs

Detailed information on the PBGMs and corresponding CDx in Tables S1 (online only). Table 1 shows the 38 PGBMs listed in the FDA table as of March 2013.[4] The aims of the PGBMs included 21 (55%) for efficacy, 12 (32%) for safety and five (13%) for monitoring. Therapeutic areas with PGBMs included antivirals (3; 8%), gastroenterology (1; 3%), haematology (3; 8%), metabolic and endocrinology (2; 5%), neurology (1; 3%), oncology (15; 39%), pulmonary (1; 3%), transplantation (1; 3%) and two or more areas (11; 29%).

Of the 38 PGBMs in the FDA table, six did not have related approved drugs in Japan (Table 1). These included BRAF (vemurafenib), CD20 antigen (tositumomab), CD25 (denileukin diftitox), CD30 (brentuximab vedotin), CFTR (ivacaftor) and CYP1A2 (dexlansoprazole). Both biological and non-biological factors can affect regulatory decisions. For example, a much lower incidence of cystic fibrosis and melanoma in Japan compared with the West could discourage the makers of ivacaftor and vemurafenib to file an application to the PMDA.[3] Denileukin diftitox and tositumomab, which were approved for lymphoma by the FDA in 1999 and 2003, respectively, remain unavailable both in the EU and Japan probably because better treatment modalities are available now.

Of the remaining 32 PGBMs in Japan, the aims were efficacy in 50% (16/32), safety in 38% (12/32) and monitoring in 12% (4/32) (Table 2). The therapeutic areas were antivirals in 9% (3/32), haematology in 9% (3/32), metabolic and endocrinology in 6% (2/32), neurology in 3% (1/32), oncology in 34% (11/32), transplantation in 3% (1/32) and two or more areas in 34% (11/32) (Table 3).

Approval gap of CDx between the USA and Japan

Twenty of the PGBMs (53%) had a corresponding CDx approved in the USA. Of the 20 PGBMs with an approved CDx in the USA, only three [ALK, ERBB2 (HER2) and BRAF] showed successful drug diagnostic co-development.[25] In the other 17 PGBMs, the drug and its CDx were approved separately. Table 2 shows the aim of each PGBM and whether a CDx was approved. Approval was not associated with whether the aim of the PGBM was efficacy, safety or monitoring (P = 0·64). Table 3 shows the therapeutic area of each PGBM and whether a CDx was approved. The percentage of oncology PGBMs with an available CDx (73%, 11/15) was significantly higher than that of non-oncology PGBMs with an available CDx (39%, 9/23, P = 0·041).

Of the 32 PGBMs approved in Japan, 15 (47%) were associated with an approved and/or covered CDx, with only 11 having an approved CDx. The four PGBMs with an unapproved but covered CDx in Japan are c-kit, chromosome 5q, FIP1L1-PDGFRα and PML/RARα translocation. The four PGBMs for which a CDx is covered in Japan, but not approved in the USA, were chromosome 5q, FIP1L1-PDGFRα, Ph1/BCR-ABL and PML/RARα transloca-

Table 2. Aims of pharmacogenomic biomarkers with or without an *in vitro* companion diagnostic device available in the USA and Japan

	USA		Japan	
	CDx		CDx	
Pharmacogenomic biomarker aim	Available	Unavailable	Available	Unavailable
Efficacy	11	10	11	5
Safety	5	7	2	10
Monitoring	4	1	2	2
Total	20	18	15	17

CDx, *in vitro* companion diagnostics.
Availability in the USA signifies approval, whereas availability in Japan signifies approval and/or coverage.

Table 3. Therapeutic areas of pharmacogenomic biomarkers with or without an *in vitro* companion diagnostic device available in the USA and Japan

	USA		Japan	
	CDx		CDx	
Therapeutic area	Available	Unavailable	Available	Unavailable
Antivirals	0	3	0	3
Gastroenterology	0	1	0	0
Haematology	2	1	2	1
Metabolic and endocrinology	0	2	0	2
Neurology	0	1	0	1
Oncology	11	4	9	2
Pulmonary	1	0	0	0
Transplantation	0	1	0	1
Two or more	6	5	4	7
Total	20	18	15	17

CDx, *in vitro* companion diagnostics.
Availability in the USA signifies approval, whereas availability in Japan signifies approval and/or coverage.

tion. CDx for CYP2C19 and CYP2D6 are approved, but not covered in Japan. A CDx for CD20 antigen is approved and covered, although the corresponding drug, tositumomab, has not been introduced in Japan, probably because rituximab, indicated for the treatment of patients with CD20-positive B-cell non-Hodgkin lymphoma, is already approved in Japan.

Table 2 shows the aim of the 32 PGBMs according to the availability of the CDx (i.e. whether it is approved and/or covered). The percentage of PGBMs aiming at efficacy and with an available CDx (69%, 11/16) was significantly higher than that of PGBMs aiming at safety or monitoring (25%, 4/16, $P = 0{\cdot}016$). Table 3 shows the therapeutic area of the 32 PGBMs according to the availability of a CDx. The percentage of oncology PGBMs with an available CDx (82%, 9/11) was significantly higher than that of non-oncology PGBMs with an available CDx (29%, 6/21, $P = 0{\cdot}006$).

Our study confirmed that there is still a substantial approval gap for PGBMs and CDx between Japan and the USA. Approval gaps between the two countries were also observed for neurological[26] and psychiatric drugs.[27] When we focused on oncology, however, there was no approval gap for CDx. The percentage of oncology PGBMs that had an approved CDx was 73% (11/15) in the USA and 82% (9/11) in Japan. This is probably because the drug lag has been markedly reduced in oncology[28] where PGBMs play an important role.

Complementary coverage by the National Health Insurance to close the approval gap

Although the percentage of PGBMs with an approved CDx was lower in Japan (34%, 11/32) than in the USA (50%, 19/38), availability (i.e. the percentage of CDx approved or covered) was similar in Japan (47%, 15/32). This is because although four PGBMs, chromosome 5q, c-kit, FIP1L1-PDGFRα and PML/RARα translocation, were associated with unapproved CDx, they were covered and reimbursed by the NHI. The reason for this is unclear although testing for these four PGBMs is specified as required in the Japanese labels of the corresponding drugs[23] and in the relevant guidelines.[29] We could not provide data on coverage or reimbursement of CDx in the USA because the healthcare reimbursement and payment system in the USA is much more complex[10,12] than that of the NHI in Japan. Coverage and reimbursement for a CDx are separate from and more multifaceted than for the corresponding drug in the USA.[6,30]

WHAT IS NEW AND CONCLUSION

Our study confirms that there is still a substantial gap in the approval of PGBMs and CDx between Japan and the USA. However, complementary coverage of an unapproved CDx by the NHI has increased availability to Japanese patients to a level similar to that of US patients. Caution should be exercised, however, because of the marked differences in the two healthcare systems. Because the number of expensive and targeted personalized medicine drugs and CDx is increasing, patient access will continue to be an important challenge to healthcare systems of all countries.

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CONFLICT OF INTEREST

The authors report no conflict of interest in this work.

SUPPORTING INFORMATION

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

Table S1 Information on the pharmacogenomic biomarkers and corresponding *in vitro* companion diagnostics. It includes the type of biomarker, approved assay method, disease or molecule in focus, CDx target, and corresponding drugs.

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