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Expert Review of Molecular Diagnostics

ISSN: 1473-7159 (Print) 1744-8352 (Online) Journal homepage: informahealthcare.com/journals/iero20

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To cite this article: Rumiko Shimazawa & Masayuki Ikeda (2015) International differences in companion diagnostic approvals: how are we able to manage the differences?, Expert Review of Molecular Diagnostics, 15:2, 157-159, DOI: 10.1586/14737159.2015.969243

To link to this article: https://doi.org/10.1586/14737159.2015.969243

International differences in companion diagnostic approvals: how are we able to manage the differences?

Expert Rev. Mol. Diagn. 15(2), 157–159 (2015)

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One would expect regulations for drugs and diagnostics not to differ significantly between countries, given that regulatory authorities evaluate the same scientific data generated in an increasingly globally harmonized context. However, studies of our own and others have provided compelling evidence of differences in regulations for drugs and *in vitro* companion diagnostics in personalized medicine. Differing regulatory processes create hurdles for both pharmaceutical and companion diagnostics companies with different platforms that employ different technologies. The rising cost of healthcare caused by improvements in technology is another issue that faces all advanced countries. To address these issues and to facilitate access to personalized medicine, regulatory authorities, academia and the pharmaceutical industry should increase dialogue on the differences on an international platform.

Pharmacogenomic biomarkers (PGBMs) can help to inform therapeutic decisions in personalized medicine [1]. The success of personalized medicine depends on the identification of PGBMs and the development of *in vitro* companion diagnostics (CDx) that can provide information essential for safe and effective use of the corresponding drug. One would expect approvals for CDx not to differ significantly across countries, given that regulatory authorities evaluate the same scientific data. Differences in regulations of CDx arise [2,3], however, from biological and non-biological factors. Although the significance of regulatory factors in CDx approval is recognized, these factors have rarely been the focus of systematic research.

Differences in approvals for personalized medicine drugs

Approval for CDx is clearly affected by the approval for the corresponding drug, with the PGBM identified on the label. We found differences in the regulations of these drugs between the USA, the EU and Japan [4], although all three are members of the ICH. Of the 17 drugs approved by the US FDA, including 18 indications for which the biomarker was labeled as required, 13 drugs with 14 indications were approved in the EU, whereas 12 drugs with 12 indications were approved in Japan. The median delay from the time of submission in the USA was 0 months in the EU and 21 months in Japan. Both biological and non-biological factors affected regulatory decisions. For example, a much lower incidence of both cystic fibrosis and melanoma in Japan compared with the West could discourage the makers of ivacaftor and vemurafenib from filing applications in Japan. Denileukin diftitox and tositumomab which were approved for lymphoma by the FDA in 1999 and 2003, respectively, remain unavailable in both the EU and Japan, probably because better treatment modalities are available.

Differences in labels of personalized medicine drugs

Differences in labeling exist between regions because different laws and cultures

Keywords: biomarkers • diagnostic test approval • drug approval • individualized medicine • pharmacogenetics • US FDA

EXPERT REVIEWS

 10.1586/14737159.2015.969243 ISSN 1473-7159

can affect regulatory decisions [5]. A previous study revealed substantial differences in the pharmacogenomic information included on labels from the USA, the UK and Japan [3]. The UK was selected as a representative of the EU because all labels were not the same in all EU members and because drug/diagnostic co-development is complicated by the fact that medicines and diagnostics follow very different regulations across the EU.

Of the 118 labels included in the FDA table [6], PGBMs were described in 71 corresponding labels from the UK and in 44 from Japan. The differences varied according to label sections, the type and purpose of the PGBM and the strength of the evidence supporting the use of the PGBM. In the label section, the 'indications' section showed higher concordance between countries (UK/USA 65, Japan/USA 48 and Japan/UK 61%) than did the 'precaution' section (UK/USA 41, Japan/USA 17 and Japan/UK 37%) [3]. In regard to PGBM types, PGBMs appeared more consistently in the same section relative to the USA labels for drug targets (UK 55%, Japan 41%) than for metabolizing enzymes (UK 36%, Japan 14%) [3]. The differences likely arise because of the variations in the guidance issued by different drug regulators for inclusion of pharmacogenomic information on labels.

Differences in CDx approvals

A previous study has confirmed a substantial gap in the approval of CDx between Japan and the USA [2]. Of the 38 PGBMs listed in the FDA table [6], 20 PGBMs had a corresponding CDx approved in the USA. In Japan, six PGBMs had no approved drug. Of the remaining 32 PGBMs, 11 were associated with an approved CDx, and four were associated with a covered CDx. These results confirm that there is still a substantial gap in the approval of CDx between Japan and the USA. However, complementary coverage of unapproved CDx by Japan's National Health Insurance is increasing access to the four PGBMs with a covered CDx.

The development and regulation of a CDx is more complex than that of a drug [7]. First, the two partners in CDx development, a diagnostic company and a pharmaceutical company, have different platforms that employ different technologies. Second, differing regulatory processes between the CDx and the corresponding drug create hurdles for both partners. Third, the review and approval process varies because of different guidance from different jurisdictions. For example, the FDA considers investigations with a CDx to be clinical studies of a medical device regulated under the Investigational Device Exemption regulation in Title 21 Code of Federal Regulations Part 812 (21 CFR 812) [8]. The EMA, in contrast, considers a CDx to be a device for performance evaluation as specified in the European *In Vitro* Diagnostic Medical Devices Directive (98/79/EC) [9]. In Japan, CDx are regulated as high-risk class III devices by the Pharmaceuticals and Medical Devices Agency and require approval based on clinical trials that prove the quality, safety and efficacy.

The KRAS (Kirsten rat sarcoma 2 viral oncogene homolog) scenario illustrates several critical issues facing CDx development and approvals. In February 2004, Erbitux (cetuximab) was approved for the treatment of epidermal growth factor receptor-expressing metastatic colorectal cancer. In April 2006, retrospective analysis showed that *KRAS* mutation status was found to be predictive of non-response to cetuximab therapy in colorectal cancer [10], and subsequent analyses on Erbitux [11,12] supported the results of the initial study. The FDA found these retrospective data insufficient to change the labeling, but, in May 2008, the EMA revised the indications of Erbitux to exclude patients with tumors with *KRAS* mutations. In November 2008, The National Comprehensive Cancer Network revised its protocol to recommend that metastatic colorectal cancer be analyzed for *KRAS* status, and that Erbitux be used only in patients with wild-type *KRAS* tumors. In July 2009, more than a year after its European counterpart's action, the FDA applied a new label for Erbitux stating that its use is not recommended for the treatment of colorectal cancer with *KRAS* mutations.

Differences in CDx reimbursement

In addition to approval by a regulatory authority, reimbursement decisions are critical factors in patient access to personalized medicine. A growing number of developed countries use health technology assessment, which challenges personalized medicine [13]. Clinical cost–effectiveness is considered in reimbursement decisions on CDx even in countries without a health technology assessment approach, such as the USA [14] and Japan [15]. Approved CDx are generally covered by the National Health Insurance in Japan [2], but FDA approval is not a guarantee of coverage for CDx in the USA [14]. Lack of evidence for the clinical use of many CDx has led payers to deny or restrict coverage [16]. For example, the Centers for Medicare and Medicaid Services do not routinely cover genotype-informed risk adjustment for dosing in patients who are prescribed warfarin. Centers for Medicare and Medicaid Services require evidence that such testing will deliver improved clinical outcomes [17].

The complexity of the USA health insurance system challenges detailed analyses of CDx coverage in the USA. There are few easily accessible data about payer decision-making processes regarding reimbursement for personalized medicine and CDx [14]. In Europe, the environment surrounding market access to diagnostics is even more complicated, because the EU is a heterogeneous region in terms of regulatory and reimbursement approaches, with every country having its own unique characteristics [18]. Whereas the number of drugs available varies across the EU [19], coverage for a CDx varies much more than coverage for the corresponding drug [20].

Why do the differences exist and how are we able to manage the differences?

One would expect that regulations for drugs and diagnostics would not differ significantly among countries, given that regulatory authorities evaluate the same scientific data. As noted above, however, previous studies have provided compelling

evidence for differences in regulation for personalized medicine drugs and CDx among different regulatory authorities. These differences should arise from biological and non-biological factors. Although the significance of various non-biological factors in drug regulations is widely recognized, these factors have rarely been the focus of systematic research. Regulatory requirements, evaluation processes, healthcare systems and the general public's perception are non-biological factors that might differentially impact the information on labels depending upon regulatory region.

The important issue is why the differences exist and how to manage these differences. To optimize product development and avoid unnecessary replication of clinical trials, regulatory authorities, academia and the pharmaceutical industry should increase dialogue on the differences on an international platform, such as the ICH, with the aim of setting common standards for data requirements. Sharing information on challenging cases, in which drug-diagnostic co-development could not be achieved, would provide useful insight into more efficient development. We can move much further toward a system that supports better gathering and sharing of high-quality evidence for personalized medicine. All stakeholders can play a role in this process.

Financial & competing interests disclosure

This study was supported by a Grant-in-Aid for Scientific Research (C) (24590619, 26460604) from the Japan Society for the Promotion of Science. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1. Ong FS, Das K, Wang J, et al. Personalized medicine and pharmacogenetic biomarkers: progress in molecular oncology testing. Expert Rev Mol Diagn 2012;12:593-602
2. Shimazawa R, Ikeda M. Approval gap of pharmacogenomic biomarkers and in vitro companion diagnostics between the United States and Japan. J Clin Pharm Ther 2014;39:210-14
3. Shimazawa R, Ikeda M. Differences in pharmacogenomic biomarker information in package inserts from the United States, the United Kingdom and Japan. J Clin Pharm Ther 2013;38:468-75
4. Shimazawa R, Ikeda M. Are there any differences in the regulations of personalized medicine among the USA, EU and Japan? Br J Clin Pharmacol 2013;75:1365-7
5. Shimazawa R, Ikeda M. Safety information in drug labeling: a comparison of the USA, the UK, and Japan. Pharmacoepidemiol Drug Saf 2013;22:306-18
6. U.S. Food and Drug Administration. Table of pharmacogenomic biomarkers in drug labels. Available from: www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
7. Jorgensen JT. A challenging drug development process in the era of personalized medicine. Drug Discov Today 2011;16:891-7
8. USFDA. Code of Federal Regulations Title 21. Available from: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812
9. European Commission. Proposal for a regulation of the European Parliament and of the Council on in vitro diagnostic medical devices. Available from: http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_541_en.pdf
10. Lievre A, Bachet JB, Le Corre D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res 2006;66:3992-5
11. Moroni M, Veronese S, Benvenuti S, et al. Gene copy number for epidermal growth factor receptor (EGFR) and clinical response to antiEGFR treatment in colorectal cancer: a cohort study. Lancet Oncol 2005;6:279-86
12. Benvenuti S, Sartore-Bianchi A, Di Nicolantonio F, et al. Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. Cancer Res 2007;67:2643-8
13. Chalkidou K, Rawlins M. Pharmacogenetics and cost-effectiveness analysis: a two-way street. Drug Discov Today 2011;16:873-7
14. Cohen J, Wilson A, Manzolillo K. Clinical and economic challenges facing pharmacogenomics. Pharmacogenomics J 2013;13:378-88
15. Fujiwara Y. Genomics, health care, and society. N Engl J Med 2011;365:2339
16. Meckley LM, Neumann PJ. Personalized medicine: factors influencing reimbursement. Health Policy 2010;94:91-100
17. The Centers for Medicare and Medicaid Services. Decision memo for pharmacogenomic testing for warfarin response (CAG-00400N). Available from: www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=224&fromdb=true
18. Miller I, Ashton-Chess J, Spolders H, et al. Market access challenges in the EU for high medical value diagnostic tests Pers Med. 2011;8:137-48
19. Folino-Gallo P, Walley T, Frolich JC, et al. Availability of medicines in the European Union: results from the EURO-Medicines project. Eur J Clin Pharmacol 2001;57:441-6
20. Garfield S. Advancing access to personalized medicine: a comparative assessment of European reimbursement systems. Available from: www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/pmc_europe_reimbursement.pdf