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Letter to the Editors

Are there any differences in the regulations of personalized medicine among the USA, EU and Japan?

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In their cautious review, Shah and Shah [1] emphasized differences in regulations of personalized medicine (PM) among the three major authorities, the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. Specific points regarding the differences, however, were not raised for the drugs they selected for discussion in their review. Given that the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities and pharmaceutical industries of the USA, Europe and Japan, scientific and technical aspects of drug registration should be harmonized. To identify differences, if any, in regulations of PM, we investigated approvals of PM drugs in the three regions.

As a typical example of PM, we focused on PM [2] drugs whose pharmacogenomic biomaker is required on the label. We also studied ivacaftor and pertuzumab, which were omitted in the list [2] simply because they were approved after publication of the list. The US, European and Japanese approval data on these drugs were obtained from Drugs@FDA (http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/), European public assessment reports (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125) and the PMDA website (http://www.info.pmda.go.jp/approvalSrch/PharmacySrchInit?), respectively. We defined submission/approval delay as the difference between the date of submission/approval in the USA and that in the EU or in Japan.

Of 17 FDA-approved drugs and 18 indications whose biomarker is labelled as required, 13 drugs and 14 indications were approved in the EU, whereas 12 drugs and 12 indications were approved in Japan (Table 1). The median submission delay from the submission in the USA was 0 months in the EU and 21 months in Japan. The median approval delay from the approval in the USA was 6 months in the EU and 28 months in Japan.

One would expect that labels would not differ significantly among countries, given that regulatory authorities evaluate the same scientific data. Both biological and non-biological factors, however, can affect regulatory decisions. For example, a much lower incidence of cystic fibrosis [3] and melanoma [4] in Japan compared with the West could discourage the makers of ivacaftor and vemurafenib to file an application to the PMDA. 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 now.

The approval delay in Japan was observed in other therapeutic areas [5]. The present study shows that three-quarters of the approval delay consisted of delays in submission. The approval delay without submission delay in the EU indicates that the reviews took longer for the EMA than for the FDA. The cross-sectional design of our study makes causal inference of these delays difficult.

Our results show some similarities and differences in the approvals of PM drugs among the three regions of the ICH. Further studies are needed to investigate differences in postmarketing regulations of PM drugs, because such regulations are important for risk–benefit assessment of PM and are greatly affected by local factors, such as health polices, culture and financial settings.

Competing Interests

There are no competing interests to declare.

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Table 1

US, EU and Japanese data on the approval of personalized medicine drugs whose pharmacogenomic biomarker is required on the label

Generic name	US trade name	Indication	Biomarker	Submission date			Approval date			Submission delay (months)		Approval delay (months)	
				USA	EU	Japan	USA	EU	Japan	USA–EU	USA–Japan	USA–EU	USA–Japan
Arsenic trioxide	Trisenox	APL	PML/RARα	March 2000	December 2000	June 2003	September 2000	March2002	October2004	8	38	17	49
Cetuximab	Erbitux	Colon cancer	EGFR, KRAS	August 2003	July 2003	January 2007	February 2004	June 2004	July 2008	–1	42	5	53
Crizotinib	Xalkori	Lung cancer	ALK	March 2011	NA	March 2011	August 2011	Unapproved	March 2012	—	0	—	7
Dasatinib	Sprycel	CML/Ph1+ ALL	Ph1/BCR-ABL	December 2005	January 2006	August 2007	June 2006	November 2006	January 2009	0	20	5	31
Denileukin diftitox	Ontak	Lymphoma	CD25	December 1997	NA	NA	February 1999	Unapproved	Unapproved	—	—	—	—
Imatinib (1)	Gleevec	CML	Ph1/BCR-ABL	February 2001	March 2001	April 2001	May 2001	November 2001	November 2001	0	2	6	6
Imatinib (2)	Gleevec	MDS/MPD	PDGFR	December 2005	NA	NA	October 2006	November 2006	Unapproved	—	—	1	—
Ivacaftor	Kalydeco	Cystic fibrosis	CFTR (G551D)	October 2011	October 2011	NA	January 2012	July 2012	Unapproved	0	—	6	—
Lapatinib	Tykerb	Breast cancer	Her2/neu	September 2006	October 2006	March 2007	March 2007	June 2008	April 2009	1	7	15	25
Lenalidomide	Revlimnid	Multiple myeloma	Chromosome 5q	April 2005	February 2006	June 2009	December 2005	June 2007	August 2010	11	51	18	56
Maraviroc	Selzentry	HIV	CCR5	December 2006	December 2006	October 2008	August 2007	September 2007	December 2008	0	22	1	17
Nilotinib	Tasigna	CML/Ph1+ ALL	Ph1/BCR-ABL	September 2006	October 2006	June 2007	October 2007	November 2007	January 2009	0	9	1	15
Panitumumab	Vectibix	Colon cancer	EGFR, KRAS	December 2005	April 2006	June 2008	September 2006	December 2007	April 2010	4	30	14	43
Pertuzumab	Perjeta	Breast cancer	Her2/neu	December 2011	NA	NA	June 2012	Unapproved	Unapproved	—	—	—	—
Tositumomab	Bexxar	Lymphoma	CD20 antigen	June 1999	NA	NA	June 2003	Unapproved	Unapproved	—	—	—	—
Trastuzumab	Herceptin	Breast cancer	Her2/neu	May 1998	February 1999	January 2000	September 1998	August 2000	April 2001	9	21	23	30
Tretinoin	Vesanoid	APL	PML/RARα	NA	NA	NA	November 1995	December 1996	January 1995	—	—	13	–10
Vemurafenib	Zelboraf	Melanoma	BRAF	April 2011	May 2011	NA	August 2011	February 2012	Unapproved	0	—	6	—

Abbreviations are as follows: ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukaemia; APL, acute promyelocytic leukaemia; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CCR5, chemokine receptor type 5; CD, cluster of differentiation; CEL, chronic eosinophilic leukaemia; CFTR, cystic fibrosis transmembrane conductance regulator; CML, chronic myelogenous leukaemia; EGFR, epidermal growth factor receptor; GIST, malignant gastrointestinal stromal tumours; Her2/neu, human epidermal growth factor receptor 2; HES, hypereosinophilic syndrome; KRAS, Kirsten rat sarcoma 2 viral oncogene homolog; MDS/MPD, myelodysplastic syndrome/myeloproliferative diseases; NA, not available; PDGFR, platelet-derived growth factor receptor; Ph1/BCR-ABL, Philadelphia chromosome/breakpoint cluster region-Abelson tyrosine kinase; PML/RARα, promyelocytic leukemia/retinoic acid receptor alpha.

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