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Letter to the Editors

Japan lags behind the UK in neurological drug approvals

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Many drugs that are available in the overseas market have not yet been approved by the Ministry of Health, Labour and Welfare (MHLW) in Japan. A study of the top 100 drugs by sales in 2004 shows a 2.5-year gap between the launch dates in the UK/US and Japan [1]. Of a total of 398 new chemical entities that were approved in either the US, EU or Japan between 1999 and 2007, 325 (82%) were approved in the US, 314 (79%) in the EU, but only 220 (55%) were approved in Japan [2]. This gap, or so-called drug lag, differs among drugs with different therapeutic indications. Drugs against infectious diseases have short lags, whereas those for the treatment of central nervous system diseases have much longer lags [2, 3]. The lag prevents Japanese patients with neurological diseases from accessing these drugs at the same time as patients in other developed nations. Further, it may even delay the progress of clinical research in Japan.

We analyzed Japanese and UK data regarding the approval of new neurological drugs. The Japanese data were obtained from the website of the Japan Pharmaceutical Information Centre (JAPIC), from the section on new drug approval (http://www.shinsahoukokusho.jp/), which included a review report of all new molecular entities and new biologics approved in Japan between June 1999 and April 2010. The UK data were obtained from the Electronic Medicines Compendium (http://www.medicines.org.uk/emc/). We selected the UK because according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines [4], the regulation of drugs is harmonized between Japan and the UK; in addition, the UK, like Japan, provides a national health service that covers the neurological drugs discussed in the present study.

We defined approval lag as the difference between the date of approval in Japan and the date of first authorization in the UK. Japan's review time was defined as the time between the date of application for approval and the date of approval.

During the 11 years from June 1999 and April 2010, 22 new neurological drugs were introduced in Japan (Table 1). Of these, 20 were already available in the UK when they were approved in Japan, with a median lag of 65 months. The median review time (from application for approval to approval) of these 20 drugs was 22 months. Only clobazam and sumatriptan succinate were first approved in Japan and then in the UK, with lag times of 22 months and 20 months, respectively. Sixteen neurological drugs were available in the UK but not in Japan.

Few studies have quantified Japan's drug lag in terms of therapeutic indications. Hirai *et al*. [3] studied a data set of all new molecular entities and new biologics approved between January 2000 and December 2006 in Japan, the US and the EU and showed that Japan's median delay in development time was 35.5 months. Among drugs from different therapeutic areas, those for central nervous system diseases showed the longest delay of 53.5 months [3]. Our analysis, focusing on the introduction of new neurological drugs, showed that Japan lags behind the UK by 65 months.

Drug lag consists of the delay in development time (i.e. up to application for approval) as well as review time. The median review time of 22 months observed in our study was longer than the European Medicines Agency (EMA) review time of 13.5 months [5]. However, this 9 month difference cannot explain the overall lag of 65 months. Although we could not precisely identify the development time, the above data show that most of the lag is presumably due to delays in development, not review. In contrast to these 22 drugs already approved in Japan, 16 (42%) of 38 drugs are approved in the UK but not in Japan, showing the so-called absolute drug lag [2].

The data presented in this study confirm that Japan's drug lag in the case of neurological drugs is quite substantial and keeps Japanese patients from the benefits of new treatments. The general public in Japan hopes that the simultaneous development of drugs on a global scale and improvements of the regulatory system would effectively reduce the delay, but the following problems make this goal seem difficult to achieve. First, the difference in the prevalence of some neurological disorders, e.g. multiple

Table 1

Japanese and UK data regarding the approval of neurological drugs

Generic name (proprietary)	Indication	Approval application Japan	Approval date Japan	UK	Lag (months)	Review time Japan
Donepezil	Alzheimer's disease	July 1998	October 1999	February 1997	32	14
Galantamine	Alzheimer's disease			September 2000		
Memantine	Alzheimer's disease			May 2002		
Rivastigmine	Alzheimer's disease			December 1998		
Clobazam	Epilepsy	March 1997	March 2000	January 2002	–22	36
Fosphenytoin	Epilepsy			July 2004		
Gabapentin	Epilepsy	April 2004	July 2006	June 2005	14	27
Lamotrigine	Epilepsy	December 2005	October 2008	August 1997	134	34
Levetiracetam	Epilepsy			September 2000		
Oxcarbazepine	Epilepsy			November 2001		
Rufinamide	Epilepsy			January 2007		
Topiramate	Epilepsy	July 04	July 2007	July 1995	145	36
Vigabatrin	Epilepsy			January 2001		
Clopidogrel	Ischemic stroke	February 2004	January 2006	July 1998	90	23
Almotriptan	Migraine			October 2000		
Eletriptan	Migraine	June 2000	April 2002	February 2001	14	21
Frovatriptan	Migraine			October 2002		
Naratriptan	Migraine	April 2006	January 2008	April 2002	69	21
Rizatriptan	Migraine	November 2001	July 2003	June 1998	61	20
Sumatriptan	Migraine	May 2001	April 2003	May 1996	83	23
Sumatriptan succinate	Migraine	August 2000	June 2001	February 2003	–20	11
Zolmitriptan	Migraine	March 2000	June 2001	June 2000	12	15
Glatiramer acetate	Multiple sclerosis			April 2003		
Interferon beta-1a (Avonex)	Multiple sclerosis	June 2003	July 2006	March 1997	113	37
Interferon beta-1a (Rebif)	Multiple sclerosis			May 1998		
Interferon beta-1b	Multiple sclerosis	September 1999	September 2000	November 1995	58	12
Natalizumab	Multiple sclerosis			June 2006		
Piracetam	Myoclonus	NA	September 1999	December 1992	81	NA
Pregabalin	Neuropathic pain	NA	April 2010	July 2004	69	NA
Cabergoline	Parkinson's disease	NA	June 1999	February 1996	40	NA
Entacapone	Parkinson's disease	April 2005	January 2007	September 1998	100	21
Pramipexole	Parkinson's disease	December 2001	October 2003	February 1998	68	22
Rasagiline	Parkinson's disease			February 2005		
Ropinirole	Parkinson's disease	December 2002	October 2006	January 2002	57	46
Rotigotine	Parkinson's disease			February 2006		
Alglucosidase alfa	Pompe disease	April 2005	April 2007	March 2006	13	24
Ziconotide	Severe chronic pain			February 2005		
Zinc acetate	Wilson's disease	May 2006	January 2008	October 2004	39	21

NA, Not available.

sclerosis, between Japan and the UK makes it difficult to recruit sufficient numbers of patients for clinical trials in Japan. Second, language problems among Japanese participants in multinational trials delay the development of new drugs in Japan. Third, the high cost and underperformance of clinical trials in Japan [2, 3] may have a significant effect on drug lag.

Our results underscore the necessity for further analysis into the causes of the lag, with close attention not only to the role played by the Japanese regulatory authority but also to that played by the pharmaceutical companies and citizens.

Competing interests

There are no competing interests to declare.

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