

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 the 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 access them. Further, it may even delay the progress of clinical research in Japan.

We analysed Japanese and UK data regarding the approval of new neurological drugs. The Japanese data were obtained from the website of the Japan Pharmaceutical Information Center (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 harmonised 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). 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 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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- 3 Hirai Y, Kinoshita H, Kusama M, Yasuda K, Sugiyama Y, Ono S. Delays in new drug applications in Japan and industrial R&D strategies. Clin Pharmacol Ther 2010; 87: 212-218.
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Table Japanese and UK data regarding the approval neurological drugs

Generic name (proprietary)	Indication	Approval Application	Approval Date		Lag	Review Time
		Japan	Japan	UK	(Months)	Japan
Donepezil	Alzheimer disease	Jul 98	Oct 99	Feb 97	32	14
Galantamine	Alzheimer disease			Sep 00		
Memantine	Alzheimer disease			May 02		
Rivastigmine	Alzheimer disease			Dec 98		
Clobazam	Epilepsy	Mar 97	Mar 00	Jan 02	-22	36
Fosphenytoin	Epilepsy			Jul 04		
Gabapentin	Epilepsy	Apr 04	Jul 06	Jun 05	14	27
Lamotrigine	Epilepsy	Dec 05	Oct 08	Aug 97	134	34
Levetiracetam	Epilepsy			Sep 00		
Oxcarbazepine	Epilepsy			Nov 01		
Rufinamide	Epilepsy			Jan 07		
Topiramate	Epilepsy	Jul 04	Jul 07	Jul 95	145	36
Vigabatrin	Epilepsy			Jan 01		
Clopidogrel	Ischaemic stroke	Feb 04	Jan 06	Jul 98	90	23
Almotriptan	Migraine			Oct 00		
Eletriptan	Migraine	Jun 00	Apr 02	Feb 01	14	21
Frovatriptan	Migraine			Oct 02		
Naratriptan	Migraine	Apr 06	Jan 08	Apr 02	69	21
Rizatriptan	Migraine	Nov 01	Jul 03	Jun 98	61	20

Sumatriptan	Migraine	May 01	Apr 03	May 96	83	23
Sumatriptan succinate	Migraine	Aug 00	Jun 01	Feb 03	-20	11
Zolmitriptan	Migraine	Mar 00	Jun 01	Jun 00	12	15
Glatiramer acetate	Multiple sclerosis			Apr 03		
Interferon beta-1a (Avonex)	Multiple sclerosis	Jun 03	Jul 06	Mar 97	113	37
Interferon beta-1a (Rebif)	Multiple sclerosis			May 98		
Interferon beta-1b	Multiple sclerosis	Sep 99	Sep 00	Nov 95	58	12
Natalizumab	Multiple sclerosis			Jun 06		
Piracetam	Myoclonus	NA	Sep 99	Dec 92	81	NA
Pregabalin	Neuropathic Pain	NA	Apr 10	Jul 04	69	NA
Cabergoline	Parkinson disease	NA	Jun 99	Feb 96	40	NA
Entacapone	Parkinson disease	Apr 05	Jan 07	Sep 98	100	21
Pramipexole	Parkinson disease	Dec 01	Oct 03	Feb 98	68	22
Rasagiline	Parkinson disease			Feb 05		
Ropinirole	Parkinson disease	Dec 02	Oct 06	Jan 02	57	46
Rotigotine	Parkinson disease			Feb 06		
Alglucosidase alfa	Pompe disease	Apr 05	Apr 07	Mar 06	13	24
Ziconotide	Severe chronic pain			Feb 05		
Zinc acetate	Wilson disease	May 06	Jan 08	Oct 04	39	21

NA: Not available