ジーを明示すべきである。第四に，この通知の適応範囲を拡大し，より多くの未承認薬剤を早期に承認できる体制作りへと向けるべきである。最後に，「医学薬学上公知」の効能追加であることを鑑み，速やかな審査が望まれるところである。

4．55年通知問題

適応外使用の是正のために，いかにその薬剤の承認を得るかについての方法論をこれまで述べてきたが，より根本的な問題として，医師の裁量性についてもあえて触れておきたい。1980年（昭和55年）9月3日に社会保険診療報酬支払基金の理事長宛に出された，厚生省の保険局長通知[6]の中には，「診療報酬明細書の医薬品の審査にあたって，厚生大臣の承認した効能効果等を機械的に適用することによって都道府県の間においてアンバランスをきたすことのないようにすること」と明確に書き込まれている。すなわち，55年通知では保険適応がなくても学術的根拠があれば，支払基金の支払いを認めることができると言い換えることができる。その本質は，保険適応という行政による「印籠」に頼らずに，科学的根拠に基づいていかに診療現場と支払基金の間で話をつけるかという自律性をどこまで発揮できるかという根源的な問いかけがなされていると言える。しかしながら，この通知以後も，医師の裁量性に基づき，より適切で質の高い医療を提供するために行われた適応外使用が不必要に抑制される傾向が続いていることに対して，2002年の厚生労働委員会の中で，当時の保険局長はこの通知を再確認する答弁を行っている[15]。したがって，適応外処方の問題については，保険者が過剰介入することで，医師の裁量性をただ単に束縛するだけではなく，患者に対してより適切な治療を行おうとする医師の行為が阻まれてしまうという重大な問題が引き起こされることのないように[18]，支払基金体制の抜本的な見直しが必要と考えられる。その際には，国内外の臨床経験や研究結果が蓄積として共有化できるシステムの構築が前提になることは言うまでもない。

Ⅳ．ま と め

適応外使用の問題には，これまで述べてきたように様々な要素が包含されているが，その解決に向けての動きも少しずつ見られてきている。厚生労働省医薬食品局が2009年6月から8月までの間に行った「医療上の必要性が高い未承認薬・適応外医薬品に関する意見募集」では，376件の開発要望が寄せられた[4]。これを受けて，同局は関係企業に開発の意向を確認するための取り組みを開始するとともに，これまでの小児薬物療法検討会議や未承認薬使用問題検討会議を発展的に解消し，今後新たに立ち上げられる「未承認・適応外医薬品解消検討会議」において，要望のあった品目の中から，補正予算で行う開発支援の対象品目や，二課長通知に基づいて承認申請する「公知申請」の対象品目などを選定する見通しとなっている。一方，適応外使用薬の保険給付の容認は，支払基金の「審査情報提供検討委員会」で決定されている。2005年から年1回ペースで適応外使用薬の容認事例が追加されており，2009年に新たに33事例が追加されて，計142事例となった[3]。しかし，この委員会の内容は一切公開されておらず，そのペースも極めて遅いことは，今後の解決すべき大きな課題であろう。

以上のように，適応外使用解決のための課題は極めて多岐にわたるため，今後も多くの試行錯誤が予測される。しかし，何よりも重要なことは，より適切で質の高い医療を提供しようとする医師の意識，単に利益性を追求するだけにとどまらない製薬企業の倫理性と社会性，国民に安全で質の高い医療を提供するためには何が必要かという国の意識が一体化されて，この問題に取り組んでいくことではないかと考える。勿論，医師側の意見をとりまとめる関係学会の役割も重要である。そして，医師・製薬企業・国の三者がきちんとした情報提供をする中で，受療者，すなわち国民全体からの正しい認識・理解を得て，適切な薬剤開発が今後進んでいくことを期待したい。

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Medical Management of the Acute Radiation Syndrome

TO THE EDITOR: The nuclear accident at the Fukushima power station in Japan, which reminded us of the nightmare of Hiroshima and Nagasaki, raised serious international concerns about radiation exposure. Stable iodine (for example, potassium iodide) is indicated only as a thyroid-blocking agent to prevent the uptake of radioactive iodine; however, persons living within 1000 miles of Fukushima frantically tried to obtain potassium iodide (1) because they believed that it was a general radioprotective agent and a "magic bullet" in the event of a nuclear accident.

Current recommendations from guidelines on potassium iodide therapy derive almost exclusively from observational studies on the incidence of thyroid cancer in children after the accident at Chernobyl (2, 3). These data are the best evidence currently available, and the recommendations state that the risk for thyroid cancer in adults exposed to radioactive iodine is minimal. This conclusion seems appropriate, because many adult patients with hyperthyroidism have received radioactive iodine therapy to treat their condition. Persons older than 20 years who are exposed to radioactive iodine are at little risk for thyroid cancer, whereas persons older than 40 years are at virtually no risk (4).

Moreover, the use of potassium iodide for prophylaxis of thyroid cancer is a legitimate concern for children and pregnant and lactating women but not for other adults. After the Chernobyl disaster, 7 million adults in Poland took potassium iodide against the recommendations of the government (5). Because the window for prophylactic administration of potassium iodide is limited, health care officials should ensure that this agent is promptly available to persons who would most benefit from it during nuclear accidents and should avoid its overuse.

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importance. However, a system by which such prospective epidemiological studies could be done has not yet been established. Since the evacuees have started to scatter across the country, long-term follow-up of the victims should be started immediately. The government is expected to exercise leadership in running such a large-scale study, which would provide valuable information on the effect of drastic and diverse environmental changes on the health of vulnerable people, and help to prevent and control future public health threats.

We declare that we have no conflicts of interest.

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Reuters

Development of drugs against chemical, biological, radiological, or nuclear agents

The nuclear accident at Fukushima power station, Japan, which registered as level 7 on the International Nuclear and Radiological Event Scale, has raised serious global concern about exposure to radiation.[1]

On March 19, 2011, when the situation at the Fukushima Daiichi nuclear power plants remained very serious, we tried to import a potential but unapproved drug[2] against acute radiation syndrome,[3] at the proposal of a US company that had developed the drug. We had assumed the worst case-scenario—acute radiation syndrome—in some workers who had attempted to cool the reactor and had thus been directly exposed to ionising radiation. We found, however, that there were no regulations governing an emergency import and trial of unapproved drugs.

The Japanese regulatory scheme for drug development and approval is devoid of an emergency response in a crisis. First, it does not permit compassionate use[4]—ie, the administration of an investigational drug outside a clinical trial for the treatment of a patient with a serious disorder who has no other satisfactory alternative treatment options.

Second, the Japanese regulatory scheme does not have the Animal Rule[5] whereby new drugs or biological products can be approved after successful testing in animals when human efficacy studies with toxic chemical, biological, radiological, or nuclear (CBRN) agents are neither ethical nor feasible. The Animal Rule allows the US Food and Drug Administration to approve drugs that have been shown to be effective in animal models, even without clinical trials for validation of their efficacy.

Third, we have no guidelines for collecting human data for establishing the safety and efficacy of a drug in an emergency caused by a CBRN agent. Unexpected exposure to a CBRN agent would provide an opportunity to collect human data on the safety and efficacy of a potential drug against a CBRN agent in the real world, when a strictly controlled clinical trial is unfeasible. Furthermore, good clinical practice in such an emergency setting has not been considered in any country or region.

Since CBRN emergencies can cross any border, the international harmonisation of comprehensive regulations, including compassionate use of investigational drugs, the Animal Rule, and good clinical practice in an emergency setting, is indispensable for the efficient development of drugs against CBRN agents.

We declare that we have no conflicts of interest.

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Gore FM, Bloem PJN, Patton GC, et al. Global burden of disease in young people aged 10–24 years: a systematic analysis. Lancet *2011;* **377:** *2093–102*—In this Article (June 18), in table 2 on page 2097 the headings for "Total DALYs" should be "100 000s", and on page 2099 the figure legend should have been "Figure 6: DALYs attributable to the most important risk factors by region and sex in 2004". These corrections have been made to the online version as of Aug 5, 2011.

INTERNAL MEDICINE

ORIGINAL ARTICLE

Delays in Neurological Drug Development in Japan

Rumiko Shimazawa and Masayuki Ikeda

Abstract

Objective The lag in the approval and development of neurological drugs between Japan and other countries has been a major issue for patients with neurological diseases. The objective of this study was to analyze the factors contributing to the delay in the launching of neurological drugs in Japan.

Methods We analyzed data from Japan and the US for the approval of 36 standard neurological drugs and examined the potential factors that may cause the delay of their launch.

Results Of the 36 standard neurological drugs, all of which were approved in the US, only 21 were introduced in Japan from June 1999 to April 2010, whereas the other 15, whose indications were Alzheimer disease, epilepsy, migraine, multiple sclerosis, and Parkinson disease, remained unapproved. The US led Japan in the number of introductions (20 versus 1), with introductions in Japan occurring at a median of 87 months after introductions in the US. Japan's review time of new drug applications (23 months) could not explain this lag. In 15 of the 21 approved drugs, the application data package included overseas data. The mean review time of these 15 drugs was significantly shorter than that of the other 6 drugs without overseas data. The maximum daily doses of 7 of the drugs were higher in the US than in Japan.

Conclusion These results show that there is still a large gap between Japan and the US with regard to access to standard neurological drugs, despite several important reforms in the Japanese drug approval system.

Key words: drug approval, clinical trials, food and drug administration, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

(Intern Med 50: 1565-1568, 2011)
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Introduction

There is still a large gap between Japan and other developed countries with regard to access to new drugs, despite several important reforms in the Japanese drug approval system (1, 2), including implementation of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) good clinical practice (GCP), establishment of the new regulatory authority in 1997, and implementation of Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH E5) guidelines in 1998. A study of the top 100 drugs by sales in 2004 shows a 2.5-year gap between the launch dates in Japan and those in the US (3). "Drug lag" (4, 5) is the term coined to describe this situation. Of the 398 new chemical entities that were approved in either the US, European Union (EU), or Japan between 1999 and 2007, 325 (82%) and 314 (79%) were approved in the US and EU, respectively, whereas only 220 (55%) were approved in Japan (5). The longest delays in approval were for drugs of the central nervous system (CNS) (4, 5). Japan lags behind the UK in neurological drug approvals with a median delay of 65 months (6).

Because of this lag, Japanese patients with neurological diseases cannot gain access to these drugs as early as patients in other developed nations. Drug lag may not only prevent Japanese patients from receiving certain treatments available in other regions but also delay the progress of clinical research in Japan. The purpose of this study was to analyze the factors contributing to the drug lag of neurological drugs in Japan by comparing Japanese approval data with those of the US.

Materials and Methods

We analyzed Japanese and US data for the approval of

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Table 1. Japanese and US Data Regarding the Approval of Neurological Drugs

Generic name (proprietary)	Indication	Application Date	Approval Date		Review Time	Lag	Overseas Data	Maximum Dose/day (*1)	
		Japan	Japan	US	(Months)	(Months)		Japan	US
Donepezil	Alzheimer disease	Jul-98	Oct-99	Nov-96	14	34	Yes	10	10
Galantamine	Alzheimer disease			Feb-01					
Memantine	Alzheimer disease			Oct-03					
Rivastigmine	Alzheimer disease			Apr-00					
Clobazam	Epilepsy	Mar-97	Mar-00	Feb-79	36	253	No	40	60
Fosphenytoin	Epilepsy			Aug-96					
Gabapentin	Epilepsy	Apr-04	Jul-06	Dec-93	27	151	No	2400	4800
Lamotrigine	Epilepsy	Dec-05	Oct-08	Dec-94	34	166	Yes	400	500
Levetiracetam	Epilepsy			Nov-99					
Oxcarbazepine	Epilepsy			Jan-00					
Rufinamide	Epilepsy			Nov-08					
Topiramate	Epilepsy	Jul-04	Jul-07	Dec-96	36	127	No	600 (*2)	*3
Vigabatrin	Epilepsy			Aug-09					
Clopidogrel	Ischemic stroke	Feb-04	Jan-06	Nov-97	23	98	No	75	75
Almotriptan	Migraine			May-01					
Eletriptan	Migraine	Jun-00	Apr-02	Dec-02	21	-9	Yes	40	80
Frovatriptan	Migraine			Nov-01					
Naratriptan	Migraine	Apr-06	Jan-08	Feb-98	21	120	Yes	5	5
Rizatriptan	Migraine	Nov-01	Jul-03	Jun-98	20	61	Yes	20	20
Sumatriptan	Migraine	May-01	Apr-03	Aug-97	23	68	Yes	40	40
Sumatriptan succinate	Migraine	Aug-00	Jun-01	Jun-95	11	73	Yes	200	300
Zolmitriptan	Migraine	Mar-00	Jun-01	Nov-97	15	43	Yes	10	10
Glatiramer acetate	Multiple sclerosis			Dec-87					
Interferon beta-1a (Avonex)	Multiple sclerosis	Jun-03	Jul-06	May-96	37	122	Yes	30μg (*4)	30μg (*4)
Interferon beta-1a (Rebif)	Multiple sclerosis			Mar-02					
Interferon beta-1b	Multiple sclerosis	Sep-99	Sep-00	Jul-93	12	86	Yes	250μg (*5)	250μg (*5)
Natalizumab	Multiple sclerosis			Nov-04					
Pregabalin	Neuropathic Pain	May-08	Apr-10	Dec-04	23	64	Yes	3	3
Cabergoline	Parkinson disease	NA	Jun-99	Dec-96		30	No	4.5	4.5
Entacapone	Parkinson disease	Apr-05	Jan-07	Oct-99	21	87	Yes	1600	2000
Pramipexole	Parkinson disease	Dec-01	Oct-03	Jul-97	22	76	Yes	15	15
Rasagiline	Parkinson disease			May-06					
Ropinirole	Parkinson disease	Dec-02	Oct-06	Sep-97	46	109	No	15	24
Rotigotine	Parkinson disease			May-07					
Alglucosidase alfa	Pompe disease	Apr-05	Apr-07	Apr-06	24	12	Yes	20mg/kg (*6)	20mg/kg (*6)
Zinc acetate	Wilson disease	May-06	Jan-08	Jan-97	21	132	Yes	250	250

*1 Doses are in mg except if otherwise specified.

*2 Only adjunctive therapies for epilepsy are approved in Japan.

*3 The US label states, "The usual daily dose is 200-400 mg in two divided doses." without description of the maximum dose.

*4 Administered by intramuscular injection once a week

*5 Administered subcutaneously every other day

*6 Administered once every 2 weeks as an intravenous infusion

standard neurological drugs recommended in the guidelines (http://www.guideline.gov/). 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 data set of all new molecular entities and biologics approved in Japan between June 1999 and April 2010. US data were obtained from Drugs@FDA (http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/index.cfm).

Approval delay was defined as the difference between the date of approval in Japan and that in the US. Japan's review time was defined as the time between the date of application for approval and the actual date of approval. We used the Mann-Whitney *U* test to compare the data between the two groups. A p value less than 0.05 was regarded as statistically significant.

Results

Table 1 shows the results of our analysis. Of the 36 standard neurological drugs, only 21 were introduced in Japan from June 1999 to April 2010. The therapeutic indications of the 15 unapproved drugs were Alzheimer disease, epilepsy, migraine, multiple sclerosis, and Parkinson disease. To investigate the effect of the time of development in the US on the approval date in Japan, we compared the date of approval in the US between the approved 21and unapproved 15 drugs in Japan; however, we found no significant differ-

Table 2. Effects of Overseas Data on the Lag and Review Time of Approved Neurological Drugs

	Overseas Data		p value
	Yes (n = 15)	No (n = 6)	
Review Time	21 (7)	34 (9)	<0.02
Lag	76 (46)	128 (75)	NS

Data represent mean (SD).
Statistical analysis was performed by means of the Mann-Whitney *U* test.

Table 3. Effects of Maximum Doses on the Lag and Review Time of Approved Neurological Drugs

	Maximum Dose		p value
	Same (n = 14)	Lower (n = 7)	
Review Time	22 (7)	28 (12)	NS
Lag	77 (39)	119 (82)	NS

Data represent mean (SD).
Statistical analysis was performed by means of the Mann-Whitney *U* test.

ence (p >0.05).

The median review time (from approval application to final approval) of the 21 drugs approved in Japan was 23 months. Twenty drugs were approved in Japan after their approval in the US, except for eletriptan, which was approved in Japan 9 months before its approval in the US. The delay of approval in Japan after approval in the US was 87 months (median time).

Fifteen of the 21 drugs included overseas data in their application package. Between these 15 drugs and the other 6 drugs without overseas data, a significant difference was noted in the review time (p <0.02; Table 2). The mean delay in approval in Japan after approval in the US was longer in the 15 drugs with overseas data than in those without, but the difference was not statistically significant.

Of the 21 drugs approved in Japan, the maximum daily doses of 7 drugs (clobazam, gabapentin, lamotrigine, eletriptan, sumatriptan succinate, entacapone, and ropinirole) were higher in the US than in Japan. Between these 7 drugs and the other 14 drugs with the same maximum daily dose as that in the US, no significant difference was noted in either the review time or delay in the approval in Japan after approval in the US (Table 3).

The 21 drugs approved in Japan fell into four categories with the two variables (overseas data and maximum dose); drugs with overseas data and with the same maximum dose (n=11), those with overseas data but with lower maximum doses (n=4), those without overseas data and with the same maximum dose (n=3), and those without overseas data but with lower maximum doses (n = 3). Table 4 shows the lag and Table 5 shows the review time in these four categories. No significant difference was noted in either the lag or review time.

Table 4. Effects of Maximum Doses and Overseas Data on the Lag of Approved Neurological Drugs

		Maximum Dose		p value
		Same	Lower	
Overseas Data	Yes	65 (35)	79 (72)	NS
	No	85 (50)	171 (74)	NS
p value		NS	NS	

Data represent mean (SD).
Statistical analysis was performed by means of Mann-Whitney *U* test.

Table 5. Effects of Maximum Doses and Overseas Data on the Review Time of Approved Neurological Drugs

		Maximum Dose		p value
		Same	Lower	
Overseas Data	Yes	21 (7)	22 (9)	NS
	No	30 (9)	36 (10)	NS
p value		NS	NS	

Data represent mean (SD).
Statistical analysis was performed by means of Mann-Whitney *U* test.

Discussion

Our analysis, which focused on the introduction of neurological drugs in Japan, showed that only 21 of the 36 standard drugs were approved, with delays of 87 months after their approval in the US. The launch delay includes the delay in development (i.e., up to approval application) as well as the delay in review. The median review time of 23 months as determined in our study is longer than that of 10 months in the Food and Drug Administration (7). The 13-month difference in review time, however, cannot explain the overall 87 month delay in Japan after approval in the US. Although we could not precisely identify the development time, the above-mentioned data show that most of the delay is presumably due to delays in development and not review. The median clinical development time, defined as the time from initial clinical trial plan notification to submission of new drug application, was 61.2 and 58.7 months in the US and Japan, respectively, for drugs approved between 1998 and 2007 in Japan (7). Thus, a substantial part of the submission delay is assumed to be caused by the delay in initiation of clinical development in Japan and not clinical development itself.

A development strategy (8, 9) based on the ICH-E5 guidelines exists to minimize the duplication of clinical data. After the implementation of the guidelines, many new drug applications that utilized overseas data were approved in Japan. The shorter review time and lag in the cases with overseas data in the present study, although the latter was not statistically significant, suggest that the simultaneous development of drugs on a global scale effectively reduces the delay. Because of the following problems, however, this goal seems difficult to achieve. The difference in the preva-

lence of some neurological disorders, e.g., multiple sclerosis, between Japan and the US hinders the recruitment sufficient numbers of patients for clinical trials in Japan. Social barriers, e.g., language problems among Japanese participants in multinational trials and the high cost and low performance of clinical trials in Japan (5), may have a significant effect on drug development in Japan.

The lower maximum daily doses in Japan than those in the US, as observed in the present and other studies (10, 11), is another hindrance to the development of neurological drugs in Japan. Although we found no statistically significant effect of the maximum doses on the lag and review time in the present study, differences in doses between the two regions often result in difficulties in extrapolating data from one region to the other. Although the difference in doses (10, 11) could affect clinical development time in Japan, no study provides direct evidence for such effect. First, we could not precisely identify the development time, since the starting date of clinical development is confidential. Second, even if we knew the date, some strategies, e.g. the bridging study (8, 9), to minimize the duplication of clinical data, may have reduced the effect of the difference in doses on clinical development time in Japan.

In contrast to these 21 drugs already approved in Japan, 15 (42%) of 36 drugs are approved in the US but not in Japan. This figure, the so-called absolute drug lag, is similar to that reported by Tsuji and Tsutani (5). They showed that 27 (47%) of 58 drugs approved in either the US or UK for neurological or psychiatric diseases were not available in Japan in 2007. In conclusion, the data presented in this study confirm that Japan's drug lag in the case of neurological drugs is quite substantial and underscore the necessity for viable approaches to enhance access to novel treatments for patients with neurological diseases.

The authors state that they have no Conflict of Interest (COI).

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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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Global Cardiovascular Device Innovation: Japan-USA Synergies

– Harmonization by Doing (HBD) Program, a Consortium of Regulatory Agencies, Medical Device Industry, and Academic Institutions –

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on behalf of the Harmonization by Doing Program Working Group

Background: Global medical devices have become more popular, but investment money for medical device development is not easily available in the market. Worldwide health-care budget constraints mean that efficient medical device development has become essential. To achieve efficient development, globalization is a key to success. Spending large amounts of money in different regions for medical device development is no longer feasible.

Methods and Results: In order to streamline processes of global medical device development, an academic, governmental, and industrial consortium, called the Harmonization by Doing program, has been set up. The program has been operating between Japan and the USA since 2003. The program has 4 working groups: (1) Global Cardiovascular Device Trials; (2) Study on Post-Market Registry; (3) Clinical Trials; and (4) Infrastructure and Methodology Regulatory Convergence and Communication. Each working group has as its goals the achievement of speedy and efficient medical device development in Japan and the USA. The program has held multiple international meetings to deal with obstacles against efficient medical device development.

Conclusions: This kind of program is very important to deliver novel medical devices. Involvement of physicians in this type of activity is also very helpful to achieve these goals.

Key Words: Cardiovascular devices; Harmonization by Doing; Medical device innovation

Innovation and Safety Issues in Cardiovascular Devices

Cardiovascular devices continue to revolutionize and transform practice with unique solutions to unmet clinical needs. Coronary stents continue to become smaller, more flexible, and yet more durable. Percutaneous heart valves now deliver life-saving therapies that once required surgical implantation. Improved and smaller designs of defibrillators, pacemakers, and ventricular assist devices now allow treatment of a broader group of patients and/or disease states. As they advance, however, the design and manufacturing of these novel devices become progressively complex. Animal and bench models are limited in their ability to characterize device performance in humans, especially for novel devices, and thus, careful, well-designed and ethical clinical trials in patients continue to be the gold standard to provide data to establish a reasonable assurance of safety and effectiveness to support approval by regulatory authorities. Even after approval, widespread post-market use of breakthrough medical device technologies may produce unexpected safety concerns,[1] such as reports of very late stent thrombosis in patients treated with drug-eluting stents (DES).[2]

In addition, investment money is not easily available for medical device development in the market. The worldwide health-care budget constraint has been putting pressure on the medical device industry. Krucoff et al address such points well in the July issue of *JACC Cardiovascular Interventions*.[3] Dr Maisel also addressed regulatory challenges and opportunities in medical device development from the US Food and Drug Administration (FDA)'s standpoint in the same issue.[4]

Increasingly, development and evaluation of novel medical devices require a global approach. Although regulatory standards and processes differ across countries and regions, regulatory authorities in the USA and Japan have undertaken an

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Table. Harmonization by Doing Working Groups

Working group	Current mission
1. Global Cardiovascular Device Trials	Improve the interactions and exchange of ideas between Japan MHLW/PMDA, US FDA, academia, and industry, and to provide a forum to identify, discuss, and develop solutions to barriers to single-protocol clinical trials to be conducted in both the USA and Japan, in order to facilitate the timely and more cost-effective global introduction of new, safe, and effective device technologies.
2. Study on Post-market Registry	Facilitate multilevel discussion and collaboration between Japanese and US institutions regarding post-market global monitoring of MCSDs, including the incorporation of Japanese data with that of the USA in the INTERMACS registry and to use these data to guide future use of this technology. While the current WG2 mission is currently concentrated on MCSDs, WG2 activities should be expanded to include global post-market data collection for other cardiovascular devices, and the application of this information to guide the continued use of these device technologies, as well as to guide the evaluation of future devices.
3. Clinical Trial Infrastructure and Methodology	Facilitate the development of a robust and effective clinical trial infrastructure in the USA and Japan to support the conduct of global clinical trials to allow the timely introduction of new safe and effective medical devices into the USA and Japan.
4. Regulatory Convergence and Communication	Facilitate the timely global introduction of new medical technologies by identifying and addressing specific regulatory barriers through proof-of-concept projects, specifically, to improve administrative practices within the context of existing regulations with the goal of convergence between Japanese and US practices and improved communication between stakeholders.

FDA, Food and Drug Administration; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MCSD, mechanical circulatory support device; MHLW, Ministry of Health, Labor and Welfare; PMDA, Pharmaceuticals and Medical Devices Agency.

initiative to demonstrate how cardiovascular device development and evaluation can be efficiently conducted using such a global approach, to the benefit of patients in both countries.

Device Lag in Japan and the USA Compared to Europe

Historically, new medical devices have been launched onto the market in Europe, because the regulatory standard in the European Union (EU) is the demonstration of safety and performance, which typically has been accomplished through a small or medium-sized clinical study. Additional preclinical evaluation and larger pivotal clinical trials are then performed to support marketing of these devices in the USA, and sometimes further trials in Japan lead to marketing approval and release in Japan. Despite the fact that the USA and Japan constitute the 2 most lucrative medical device markets in the world, this approach has meant that doctors and patients in Japan and the USA have had, at times, significant delays in access to new medical devices, and certain devices are never marketed in these countries at all. In Japan, this delay has been called "device lag" and the Japanese regulatory authority the Pharmaceuticals and Medical Devices Agency (PMDA), recognizes this phenomenon as an important issue. PMDA has made tremendous efforts to solve this problem since the first Mid-term Plan started in April 2004.[5,6] The current approach followed by industry, to obtain marketing approval in Europe first, and only then in the USA and Japan, not only results in time delays to access, but also to redundancy and added cost in research and development as clinical trials are independently performed in each country. Most importantly, such fragmented efforts can ultimately lead to poorer quality data overall, particularly for information related to rare but catastrophic safety problems.

Global Regulatory Collaboration

The recognition that the biology and epidemiology of cardiovascular disease is largely driven by common risk factors independent of ethnic, scientific, clinical and economic factors, has encouraged growing interest in efforts to study new devices through more efficient, high-quality global collaborations. Such efforts respect the independence of individual governmental jurisdictions of national regulatory authorities, while concomitantly encouraging the convergence of basic principles of medical device safety and performance evaluation through the best ethics, science, and methods of human clinical research. The Global Harmonization Task Force (GHTF), through its founding member nations, Japan, Canada, Australia, the EU, and the USA, has focused manufacturers and regulators on the development of consensus guidelines for such principles for more than a decade.[7] Moreover, a new consortium, the International Medical Device Regulators Forum (IMDRF) was set up in February 2011 as a forum to discuss future directions in medical device regulatory harmonization. The IMDRF is a voluntary group of medical device regulators from Australia, Brazil, Canada, China, the EU, Japan and the USA, as well as the World Health Organization, who have come together to build on the strong foundational work of the GHTF, and to accelerate international medical device regulatory harmonization and convergence.[7] Furthermore, a more pragmatic program that includes academic clinicians along with other stakeholders, the Japan-USA Harmonization by Doing (HBD) program,[8] was initiated in 2003.

HBD Program

The HBD program provides a forum for collaboration between Japanese and US regulators, industry, and academic clinicians, where all stakeholders can engage in open discussions toward the identification and resolution of obstacles to conducting global clinical trials and harmonization of regulatory processes. The objective of HBD is to eliminate redundancies, added costs, and time delays inherent in sequential clinical trials. The intent of HBD is not simply to create guidance and discuss policy but to develop common protocols for investigational clinical studies that would allow safe and effective breakthrough cardiovascular technologies to benefit patients worldwide. HBD is uniquely different from other global harmonization initiatives in that the program aims to fulfill its mission through practical experience – that is, by doing – and sharing lessons learned from these experiences. This is achieved through proof-of-concept projects, in which specific challenges are identified and potential solutions are tested. The current membership of HBD includes members of the FDA, Japan's Ministry of Health,

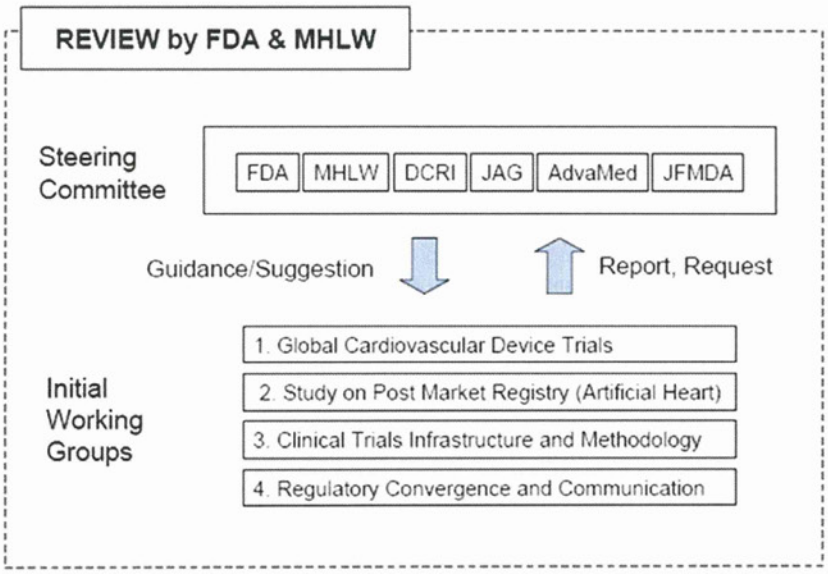

Figure. Structure of Harmonization by Doing. The Steering Committee is composed of representatives from the industry, academia, and government agencies in both the USA and Japan. AdvaMed, Advanced Medical Technology Association; DCRI, Duke Clinical Research Institute; FDA, US Food and Drug Administration; JAG, Japanese Academic Group; JFMDA, Japan Federation of Medical Devices Associations; MHLW, Ministry of Health, Labor and Welfare.

Labour and Welfare (MHLW)/PMDA, US industry (represented by the Advanced Medical Technology Association [AdvaMed] and other cardiovascular device manufacturers who are not members of AdvaMed), Japanese industry (represented by the Japan Federation of Medical Devices Associations [JFMDA]), US cardiovascular academia (represented by Duke Clinical Research Institute [DCRI]), and the Japanese academic community from cardiovascular fields. The HBD program is overseen by a steering committee, which includes members from each stakeholder group, and includes 4 working groups (WGs). **Table** outlines the 4 WGs and their current mission.

Through the activities of each of the WG, as well as the HBD steering committee, the complex array of challenges faced when designing and executing global clinical trials can be overcome in a more manageable stepwise manner. Furthermore, potential harmonization of regulatory practices and communication between US and Japanese regulatory authorities can shorten the device approval time lag through the streamlining of processes and the gaining of a common understanding of the scientific challenges, without adversely affecting current review practices or time lines. HBD's premise is that if all stakeholders share a portion of their experiences on different aspects of global trials, as well as lessons learned through the regulatory review processes required to conduct such global trials and achieve market approval for new devices where possible, all parties involved would benefit through a reduction in duplicative efforts by solving common problems. This sharing of information, however, must be carried out in a manner that protects the confidential and trade secret information of industry sponsors that are involved, and with the agreement of all stakeholders involved.

HBD History

From December 2003 to March 2004, joint meetings between FDA, MHLW-PMDA, DCRI and industry were held at FDA in Rockville, Maryland, USA to talk about the HBD concept and the HBD collaboration process. This was followed by other similar meetings at MHLW in Tokyo, Japan, and the first public announcement in a program at the annual scientific meeting of the Japan Circulation Society in March of 2004. The first in-depth HBD East Think-Tank Meeting took place in Tokyo in December 2005. Three main outcome goals were agreed on at the 2005 Think Tank meeting: (1) build a more robust clinical research infrastructure; (2) compare medical device good clinical practice (GCP) to determine if any significant differences exist that could be obstacles to the HBD process; and (3) define and clarify the rules for increased and better cooperation among all parties involved. The second HBD Think-Tank Meeting was successfully held in January 2007 in Durham, North Carolina, USA as HBD West 2007. Representatives from more than 25 academic institutions, industry organizations and companies as well as government regulators from the USA and Japan attended and engaged in discussion during this 2-day meeting. During the HBD West 2007 meeting, the HBD structure (**Figure**) and the initial 4 HBD WG missions were introduced. The third HBD Think-Tank Meeting, HBD East 2008, was convened in July of 2008 in Tokyo, Japan. This meeting provided a forum for discussion on convergence of regulatory requirements and practices through concrete experience "by doing" in the USA and Japan. To continue the discussions and review the past HBD activities, the HBD West 2009 Think-Tank Meeting was held in Silver Spring, Maryland, USA in July of 2009. Unfortunately, the HBD East 2011 Thank-Tank Meeting planned on 16 and 17 March in Tokyo was cancelled due to the earthquake in East Japan that occurred on 11 March 2011. There were several HBD sessions, however, held by each WG to share progress and accomplishment during the AdvaMed Medtech Conferences 2011 on 26 September in Washington, DC, USA, as well as the Transcatheter Cardiovascular Therapeutics (TCT) 2011 meeting on 4–7 November 2011 in San Francisco, California, USA Another global educational program titled "Japan-USA Synergies in Global Medical Device Innovation: Harmonization by Doing" was held at the TCT 2012 meeting.[9] Most recently, an HBD-related open-to-the-public meeting was held during the Kamakura Live 2012 in Kamakura, Japan.

WG Key Activities

WG1: HBD-Related Clinical Studies – Endeavor Japan and SPIRIT Japan Trials

As described here, the ultimate goal of the HBD initiatives is to lead to more expeditious development and marketing in both countries for those new therapies that have been demonstrated to be reasonably safe and effective. One important step toward accomplishing this objective is the carrying out of global clinical trials enrolling patients worldwide using harmonized study protocols. In line with this HBD concept, the Endeavor Japan trial was initiated in the spring of 2005 for Medtronic's Endeavor® Zotarolimus-Eluting Coronary Stent. This Japanese study for a new DES utilized the identical study protocol that was used in the global Endeavor-II trial,[10] which was an important supporting study for US marketing approval. Following the Endeavor Japan study, a second study, the SPIRIT Japan study, to evaluate the Abbott Vascular XIENCE V Everolimus-Eluting Coronary Stent, was conducted in the USA and Japan simultaneously under a global DES development strategy.

There were several discussion points in executing these clinical trials. One was whether these trials should be separated from a larger global trial of each. It was a dilemma. Future clinical trials might not happen if these trials failed, but if the trials were separated, Japan might lose opportunities to catch up with the advanced countries. Finally, as a learning step, the separated study design with an identical study was chosen.

Experience from these studies then demonstrated that the Japanese cardiology community was in fact ready to participate fully in global DES trials. Ten Japanese sites joined a global DES trial, the PLATINUM trial, and contributed very effectively.[11]

WG2: INTERMACS and J-MACS

Referring to the INTERMACS program,[12] the J-MACS program[13] was launched in 2010 for post-marketing follow-up for the 2 left ventricular assist devices approved in Japan in 2010, EVAHEART[14] and DuraHeart.[15] HBD WG2 fully supports this program.

WG3: Infrastructure for Clinical Studies in Japan

Through the clinical studies described here (the WGs 1- and 2-related studies), infrastructure for clinical studies in Japan was further developed. This might lead to more clinical studies from Japan such as the 2 post-market studies in cardiology, the TAXUS Japan Postmarket surveillance study[16] and, the MIRACLE-ICD outcome measured in Japanese indication (MOMIJI) study.[17]

WG4: Collaborative Consultation and Review of Pre-Marketing Applications Pilot Program and Research Papers

Led by WG4, a direct consequence of HBD is the Medical Device Collaborative Consultation and Review of Pre-marketing Applications pilot program.[18,19] This unique program involves the active engagement of the industry sponsor with both US FDA and MHLW/PMDA. A goal of the pilot program is to advance both the speed and quality of clinical/statistical consultations and the regulatory review process for potential earlier market access and improved public health benefit.

WG4 compared GCP between Japan and the USA. The outcome was published as a key accomplishment of WG4.[20] The research concluded that there were several administrative differences but no essential differences between the 2 sets of GCP.

HBD Future and Conclusions

The next HBD East Think-Tank Meeting, HBD East 2013 is currently planned for 9 and 10 July in Tokyo, Japan. As a dynamic program, HBD has recognized that it must be able to adapt as necessary to address new therapies and new scientific challenges. In addition to innovations in DES technology, such as the use of biodegradable materials, this meeting will address transcatheter aortic and mitral valve interventions. Moreover, it is envisioned that, over time and with appropriate support from its participating stakeholders, HBD could expand to include other medical devices such as orthopedic products. Finally, as the HBD program matures, other regulatory bodies in other countries could be involved.

Development of innovative medical devices is often a driver for evolution in medicine. Physicians, industry, and regulators all have an important role to play in ensuring that new medical devices provide safe and effective therapy. Physicians are primary contributors to medical device development through their participation in clinical trials. In clinical research activities for medical device development, collaboration among clinicians, the device industry, and regulators is an essential to making innovative therapy available to patients. Unlike GHTF, HBD provides physicians with an open platform on which to collaborate with industry and regulators. Contributions from each stakeholder group will be needed to ensure the future success of HBD, but with a focus on clinical and scientific challenges and new product innovation, HBD will continue to streamline the advance of new medical devices.

Disclaimer

This article represents the personal views of the authors and does not represent official FDA correspondence or guidance or official MHLW/PMDA correspondence or guidance. The HBD program is focused on collaborative efforts and demonstration projects that promote harmonization of clinical trial practices and medical device regulatory approval processes between the USA and Japan.

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Disclosures

Conflict of Interest: Gary Thompson is a full-time employee of Abbott Vascular. He receives travel expenses and salary, which are unrelated to research and exceed an annual total of 50,000 yen from the company.

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The vaccine gap between Japan and the UK

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ABSTRACT

Objective: To study and compare the Japanese vaccine policy with the policy in the UK and to discuss factors that may explain the gap in vaccine availability between the two countries.
Methods: We analysed approval and immunisation programme data from Japan and the UK for 20 common vaccines, all of which were approved and available from the UK National Health Service.
Results: Of these 20 common vaccines, only four were introduced in Japan. Of the 16 unapproved vaccines, 11 were combination vaccines. Indications for the other five unapproved vaccines were the prevention of infection with meningococcus (3 vaccines) and pneumococcus (2 vaccines). Coverage of diphtheria, tetanus, pertussis, and poliomyelitis vaccines was similar between the two countries whereas that of measles and rubella was higher in Japan.
Conclusions: These results show that there is still a large gap between Japan and the UK regarding access to 20 common vaccines and immunisation programmes. The keys to closing this gap include: (1) revision of vaccine regulations, (2) amendment of vaccine-related laws to secure funding and cooperation between professionals and public health authorities, and (3) improvement in the perception of vaccines among the general public and mass media.

1. Introduction

Although many health-related indicators, such as life expectancy and the infant mortality rate show that the health situation in Japan is among the best in the world [1], there is a large gap between Japan and other developed countries in the use of vaccines to prevent serious infections [2]. For example, the 7-valent pneumococcal conjugate vaccine (PCV) was only recently approved in Japan (October 2009), more than 8 years after its approval in the UK. Many common vaccines, including those for measles, mumps, and rubella (MMR), the inactivated poliovirus vaccine, and combination vaccines, are not yet available in Japan. This vaccine gap has major implications for public health both in Japan and in other countries. From the perspective of global public health, Japan is cited as an exporter of infectious diseases to countries that have those diseases under better control through vaccination [3]. Global interconnectedness allows infectious diseases to spread greater distances than ever before.

In the case of meningococcal vaccines, the epidemiology of meningococcal meningitis, which has an incidence of around 1000 cases per year in England and Wales [4], but only around 10–20 cases per year in Japan [5], can explain the vaccine availability gap. In other cases, however, the characteristics and causes of the vaccine gap are multifactorial. A large gap between Japan and other developed countries still exists regarding access to new drugs [6,7], despite several important reforms in the Japanese drug approval system. These included the implementation of the International Conference on Harmonisation of

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Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) good clinical practice, the establishment of a new regulatory authority in 1997, and the implementation of Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH E5) guidelines in 1998 [8,9]. Apart from vaccine development and regulation, one possible cause for the gap relates to the organisation and funding of the immunisation programme [10]. In Japan, the immunisation programme is outside the national health insurance system, whereas in the UK, the immunisation programme is an important part of the NHS. Funding of the immunisation programme in Japan [11,12] has historically been determined by local governments, with the effect of subsidies being sometimes questionable [13]. The effect of public perception on vaccine use is another common problem in developed countries. This is exemplified by the low MMR vaccine coverage in the UK following negative publicity about possible links between the vaccine and autism [14]. The outbreak of pertussis in several US states was probably caused by perception-related vaccine refusal [15].

The purpose of this study was to identify factors contributing to the vaccine gap between Japan and the UK and to advocate solutions for overcoming the problem. We compared data from the vaccine approval and immunisation programmes of the two countries. We selected the UK as a comparator because Japan and the UK have the following background features in common. First, the UK, like Japan, provides a National Health Service. Second, both the UK and Japan offer a non-compulsory immunisation programme. Third, according to ICH guidelines [16], the regulation of vaccines is harmonised between Japan and the EU, of which the UK is a member state. Fourth, both the UK [14] and Japan [17] suffered the effects of negative public perception and widespread concern regarding the MMR vaccine. These similarities highlight the vaccine gap and allow us to analyse its causes.

2. Methods

2.1. Study design

Cross-sectional study of documents published on regulatory agencies' websites.

2.2. Data sources

To compare the approval status of vaccines in Japan with that in the UK, we analysed data on 20 common vaccines routinely offered to children or available from the NHS to adults in certain 'at risk' groups. The 20 common vaccines are all approved in the UK and listed in the electronic Medicines Compendium (eMC) [18] and European public assessment reports (EPAR) [19]. European legislation aims to ensure that the terms by which vaccines are authorised are harmonised across the EU. The European Medicines Agency takes responsibility for the authorisation of vaccines, working with national medicines regulatory authorities, such as the Medicines and Healthcare products Regulatory Agency in the UK.

Japanese approval data were obtained from the Pharmaceuticals and Medical Devices Agency (PMDA) website in the new drug approval section [20], which included a review of all new molecular entities and biologics approved in Japan between June 1999 and March 2012. The UK approval (market authorisation) data were obtained from the eMC [18]. A more detailed description of the regulatory review of the vaccines is given in EPAR [19]. The Japanese immunisation data were obtained from the Infectious Disease Surveillance Center [21]. The UK immunisation data were obtained from the NHS Information Centre website [22].

2.3. Evaluation and analysis

Documents were examined for administrative information and the dates and types of regulatory approval were recorded. Approval delay was defined as the difference between the date of approval in Japan and that of first authorisation in the UK. Review time was defined as the time between the date of application for approval and the actual date of approval. Because of the limited number of vaccines analysed, results are presented in a descriptive manner without statistical interpretation.

3. Results

Table 1 shows approval status data for 20 common vaccines. Four vaccines, i.e., *Haemophilus influenzae* type b (Hib), bivalent and quadrivalent human papillomavirus (HPV), and 7-valent PCV, were introduced in Japan 173, 25, 57, and 104 months later, respectively, than in the UK, whereas the review times for bivalent and quadrivalent HPV, and 7-valent PCV were longer by only 7, 2, and 9 months, respectively, than those in the UK. Although the review time for the Haemophilus b conjugate vaccine was 46 months, this is still much shorter than the launch delay which was 173 months. Of the 16 unapproved vaccines in Japan, 11 were combination vaccines. Indications of the five other unapproved vaccines were for the prevention of infection with meningococcus (3 vaccines) and pneumococcus (2 vaccines).

Table 2 shows the recommendations for and coverage of the vaccines. Hib, PCV, mumps, and HPV vaccines, which are recommended in the UK, are all voluntary in Japan. Meningococcal vaccines are not available in Japan. The coverage of diphtheria, tetanus and pertussis (DTP), and poliomyelitis vaccines was similar between Japan and the UK. That of measles and rubella was higher in Japan. No official coverage data were available for voluntary immunisation in Japan, i.e., for Hib, PCV, and mumps.

4. Discussion

Our study confirmed and characterised the vaccine gap between Japan and the UK. Two of the 4 vaccines that were approved by both countries were approved in Japan 173 and 104 months after their approval in the UK, with a review time of 46 and 25 months, respectively. Although we could not precisely identify the development time, the review time cannot explain the launch delay of these vaccines. Most of the delay is presumably due to delays in

Table 1
Approval data on 20 common vaccines in Japan and the UK.[a]

Generic name	Proprietary name	Approval application (Japan)	Date of approval		Approval delay[b,c]	Review time[b,d]	
			Japan	UK		Japan	UK
Diphtheria, tetanus and poliomyelitis	Revaxis	NA	UA	Jun-03			
Diphtheria, tetanus, pertussis and poliomyelitis	Repevax	NA	UA	Nov-01			
Diphtheria, tetanus, pertussis and poliomyelitis	Infanrix-IPV	NA	UA	Aug-06			
Diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b	Infanrix-IPV + Hib	NA	UA	Jan-05			
Diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b	Pediacel	NA	UA	Oct-02			
Haemophilus influenzae typeb	ActHIB	Mar-03	Jan-07	Aug-92	173	46	
Haemophilus influenzae type b and Meningococcal group C conjugate	Menitorix	NA	UA	Dec-05			
Hepatitis A and Hepatitis B	Ambirix	NA	UA	Aug-02			15
Hepatitis A and Hepatitis B	Twinrix Adult	NA	UA	Sep-96			14
Hepatitis A and Hepatitis B	Twinrix Paediatric	NA	UA	Feb-97			10
Human papillomavirus bivalent	Cervarix	Sep-07	Oct-09	Sep-07	25	25	18
Human papillomavirus quadrivalent	Gardasil	Jul-10	Jul-11	Sep-06	57	11	9
Measles, mumps and rubella (live)	MMRvaxpro	NA	UA	May-06			23
Measles, mumps and rubella (live)	Priorix	NA	UA	Dec-97			
Meningococcal group C conjugate	Meningitec	NA	UA	Sep-07			
Meningococcal group C conjugate	Menjugate	NA	UA	Mar-10			
Meningococcal group A, C, W135 and Y conjugate	Menveo	NA	UA	Mar-10			16
Pneumococcal 7-valent conjugate	Prevenar	Sep-07	Oct-09	Feb-01	104	25	16
Pneumococcal 10-valent conjugate	Synflorix	NA	UA	Mar-09			14
Pneumococcal 13-valent conjugate	Prevenar13	NA	UA	Dec-09			12

NA: not available; UA: unapproved.
[a] As of March 2012.
[b] Represented in months.
[c] Approval delay was defined as the difference between the date of approval in Japan and that of first authorisation in the UK.
[d] Review time was defined as the time between the date of application for approval and the actual date of approval.

application and/or development. The 16 vaccines unapproved in Japan provide stronger evidence for the gap.

The term 'drug lag' [6,7] describes the launch delay of new drugs. Of the 398 new drugs approved either in the US, the EU, or Japan between 1997 and 2007, 220 (55.3%) were approved in Japan [7]; however, the percentage of approval depended on the therapeutic indication. The vaccine gap, with an approval rate only 20% (4/20) in the present study, is outstanding when compared with the much higher anti-infectives approval rate (71.4%) [7].

With the exception of meningococcal meningitis, which has an incidence of only around 10–20 cases per year in Japan [5,23], the vaccine gap results from a complex of regulatory and social problems. We identify three here. First, vaccine regulations in Japan remain to be reformed. There are many stakeholders and governmental organisations for immunisation programmes and policies, including the Ministry of Health, Labour and Welfare (MHLW) Health Service Bureau, the Pharmaceutical and Food Safety Bureau, the PMDA, and the National Institute of Infectious Diseases. Nonetheless, there is no organisation or committee that can gather vaccine data from different areas, assess and evaluate the collected information, and present a recommendation to the government. A body that can lead

Table 2
Comparison of immunisation programme between Japan and the UK.

	Japan		UK	
	Recommendation	Coverage (%)	Recommendation	Coverage (%)
Diphtheria, tetanus, and pertussis[a]	Recommended	98	Recommended	93
Poliomyelitis[a]	Recommended[c]	99	Recommended[d]	93
Haemophilus influenzae type b[a]	Voluntary	ND	Recommended	93
Pneumococcal[a]	Voluntary	ND	Recommended	91
Meningococcal[a]	NA	NA	Recommended	91
Measles[b]	Recommended[e]	94	Recommended[f]	85
Rubella[b]	Recommended[e]	94	Recommended[f]	85
Mumps[b]	Voluntary	ND	Recommended[f]	85
Human papillomavirus	Voluntary	ND	Recommended[g]	87

NA: not available; ND: no official data.
[a] Coverage among 1-year-olds (%) in 2008–2009.
[b] Coverage among 2-year-olds (%) in 2008–2009.
[c] Live attenuated oral vaccine.
[d] Inactivated vaccine given as a combined vaccine with diphtheria, tetanus, and pertussis.
[e] Measles and rubella, but not mumps, given as a combined vaccine.
[f] Measles, rubella, and mumps given as a combined vaccine.
[g] Girls of 12–13 years of age. The number represents the percentage of eligible girls receiving the first dose.

multiple organisations and propose immunisation policies [24] should therefore be established to close the gap. No regulatory guidelines existed for the clinical development and approval of vaccines in Japan before May 2010 [25]. The EU [26] and the European Federation of Pharmaceutical Industries and Associations (EFPIA) [2] have urged the Japanese government to harmonise clinical, regulatory, and technical standards for vaccines with the EU, the US, and the World Health Organization so that foreign vaccines can be imported and Japanese-produced products can be exported. An exemplary case is the polio vaccine. Japan still uses a live vaccine instead of an inactivated one, which has not been approved despite the fact that the live vaccine causes several cases of paralysis per year. On December 15, 2010, an association of polio victims submitted a petition to the MHLW, calling for approval of the importing of an inactivated vaccine. A panel of experts within the ministry also called for such an importation. The ministry's policy, however, is to wait for the four domestic makers to develop an inactivated vaccine. This obvious inaction only deepens the notion that the ministry may try to protect domestic manufacturers' vested interests [11]. Instead, the ministry should delegate vaccine-related decisions to a transparent advisory board [24].

Second, vaccine availability does not provide a single solution for overcoming the gap. The National Health Service in Japan only covers the treatment of diseases, not their prevention. In the case of vaccines covered by the Immunization Law [27], DTP, poliomyelitis, measles, and rubella vaccines are supported by governmental funds and generally provided free throughout Japan, but this does not apply to Hib, HPV, PCV, or mumps vaccines. Some local governments provide subsidies for these vaccines, but the financing policies and recipients' charges differ among these governments [12]. The inevitable consequences are regional disparities [28]. The Immunization Law should be revised to cover Hib, HPV, PCV, and mumps vaccines.

Third is the issue of public perception [29]. In Japan, as in other developed countries, fear of vaccine-preventable diseases has waned and the awareness of potential vaccine-related risks has increased [30]. The history of the MMR vaccine in Japan provides a case study showing that negative public perception threatens vaccine acceptance.

In Japan, a high incidence of aseptic meningitis [17] followed the introduction of the MMR vaccine in 1989, which was then mandatory. The UK NHS replaced the Urabe mumps strain, which was associated with aseptic meningitis, with the Jeryl Lynn strain and avoided the problem, but the MHLW did not. A huge public outcry ensued, with a number of lawsuits against the Japanese government leading to the withdrawal of the MMR vaccine in 1993. This incident made regulators extremely wary of being sued for vaccine-related adverse events. In 1994, the MHLW revised the Immunization Law, which covered vaccines for measles and rubella but not for mumps. Today, instead of the MMR vaccine, a combined MR (measles and rubella) vaccine is provided, with the mumps vaccine being optional. The withdrawal of the MMR vaccine led to a decrease in coverage, resulting in the exportation of measles [3]. This discrimination has also led to a high incidence of mumps-associated complications in Japan [31]. Despite the availability of the MMR vaccine, the lower coverage rate of measles and rubella in the UK compared with Japan provides further evidence of the negative effect of public perception and widespread concern about the association between the MMR vaccine and autism [14].

Our study has some limitations. First, the cross-sectional observational design limits the establishment of the cause of the gap. Second, the study was based on publicly available data, which do not include subtle issues that were not captured in the deliberation process. Third, there are only a limited number of vaccines approved in Japan or in the UK. This limitation made comparisons between the two countries less conclusive. Fourth, given the heterogeneity in the vaccines considered, formal statistical analysis of the reasons for the gap was not possible.

In Japan, the vaccine programme has been planned and implemented, not on the basis of scientific evidence, but in part as a reaction to lawsuits against the government and media coverage, which has sensationalised the adverse