In addition, regarding NMEs that have been approved in the last five years, we investigated the presence/absence of approvals and the times in the US and the EU, based on review reports of Japan. If the precedent approvals in other countries were described, we included those situations. Furthermore, we sought confirmation for UK medicines at the website of electronic Medicines Compendium Updates (http://www.medicines.org.uk/mcupdates/). In the tables, ingredients are presented using International Non-proprietary Names (INN).

3. NMEs THAT WERE APPROVED IN 2006

The numbers of NMEs that were approved in 2006 in Japan, the US and the EU (EMEA) were 20, 24 and 25, respectively, showing no major differences (Table 1). Among them, there were no NMEs approved by all three regions in 2006; but entecavir was approved in both Japan and the EU, and 4 NMEs (sunitinib, varenicline, dasatinib and alglucosidase alfa) were approved in both the US and the EU.

4. ANALYSIS OF NMEs APPROVED IN MORE THAN ONE REGION AND PRECEDENT APPROVALS

Among the NMEs approved in Japan between 2002 and 2006 (including fixed combination drugs containing two NMEs), there were 70 ingredients that have been approved to date in the US or the EU; of which 69 were approved in the US, and 35 in the EU (Tables 2 and 3). On the other hand, there were 23 ingredients that were not approved in the EU but were approved in other countries including the UK. Of the 70 ingredients, only 3 received precedent approval in Japan: eletriptan, gefitinib and micafungin. The number of ingredients receiving precedent approval in the US was 57, and this included 42 ingredients that were approved before 2001. Inulin was approved in 1940 in the US and has been listed in the US Pharmacopeia, but is not sold in the US at present. Ten ingredients received precedent approval in the EU. Furthermore, there are 14 ingredients that were confirmed to have received precedent approval in countries other than the three regions: 6 ingredients in the UK, 2 each in France and Germany (among them, solifenacin was approved during the same period in both countries), and one each in Switzerland, New Zealand, Australia, the Netherlands, and Sweden.

On the other hand, there were 39 ingredients that were not approved in Japan but were approved in both the US and the EU between 2002 and 2006 (Tables 4 and 5). Of these 39 ingredients, those receiving precedent approvals numbered 28 in the US, and 11 in the EU.

Of the above 109 ingredients that were approved in two or three regions, those receiving precedent approval numbered 3 in Japan, 85 in the US, and 21 in the EU. If differences of 6 months or less in the timing of approval are regarded as simultaneous approvals, there were few simultaneously approved ingredients between Japan: 2 in 2003 in Japan and the US; and 1 in 2003, 2 in 2004, and 1 in 2006 in both Japan and the EU. On the other hand, for simultaneous approval in the US and the EU, the numbers were 6 before 2001, and then 2 in 2002, 5 in 2003, 6 in 2004, 1 in 2005, and 4 in 2006.

Table 2. NMEs approved in Japan and at least one other region (2002-2006)

NMEs	Japan	US	EU	Others*
Quinupristin/ Dalfopristin **	01/2002	09/1999	--	08/2002: UK
Infliximab	01/2002	08/1998	08/1999	--
Basiliximab	01/2002	05/1998	10/1998	--
Cladribine	01/2002	02/1993	04/2004	02/1995:UK
Risedronate	01/2002	03/1998	--	10/1999: UK
Palivizumab	01/2002	06/1998	08/1999	--
Gatifloxacin	04/2002	12/1999	--	--
Salmeterol	04/2002	02/1994	--	10/1996: UK
Eletriptan	04/2002	12/2002	--	02/2001:UK
Exemestane	07/2002	10/1999	--	12/1998: UK
Loratadine	07/2002	04/1993	--	09/2002: UK
Gefitinib	07/2002	05/2003	--	--
Esmolol	10/2002	12/1986	--	--
Ivermectin	10/2002	11/1996	--	--
Micafungin	10/2002	03/2005	--	--
Telmisartan	10/2002	11/1998	12/1998	--
Brinzolamide	10/2002	04/1998	03/2000	--
Sevelamer	01/2003	10/1998	01/2000	--
Leflunomide	04/2003	09/1998	--	07/1999: UK
Capecitabine	04/2003	04/1998	02/2001	--
Rizatriptan	07/2003	06/1998	--	06/1998: UK
Pramipexole	10/2003	07/1997	10/1997	--
Telithromycin	10/2003	04/2004	07/2001	--
Peginterferon Alfa-2a	10/2003	10/2002	6/2002	07/2001: Switzerland
Verteporfin	10/2003	04/2000	07/2000	--
Insulin glargine	10/2003	04/2000	06/2000	--
Atazanavir	12/2003	06/2003	03/2004	--
Dexmedetomidine	01/2004	12/1999	--	--
Raloxifene	01/2004	12/1997	--	07/2003: UK
Olmesartan	01/2004	04/2002	--	08/2002: Germany
Agalsidase Beta	01/2004	04/2003	--	--
Tenofovir	03/2004	10/2001	02/2002	--
Vardenafil	04/2004	08/2003	03/2003	--
Zoledronic Acid	10/2004	08/2001	04/2005	03/2003:UK
Tiotropium	10/2004	01/2004	--	05/2002:UK
Adefovir	10/2004	09/2002	03/2003	--
Peginterferon Alfa-2b	10/2004	01/2001	03/2000	--
Valganciclovir	11/2004	03/2001	--	04/2002: UK
Fosamprenavir	12/2004	10/2003	07/2004	--
Etanercept	01/2005	11/1998	02/2000	--
Rosuvastatin	01/2005	08/2003	--	03/2003:UK

NMEs	Japan	US	EU	Others*
Oxaliplatin	03/2005	08/2002	--	04/1998: France
Emtricitabine	03/2005	07/2003	10/2003	--
Bosentan	04/2005	11/2001	05/2002	--
Voriconazole	04/2005	05/2002	03/2002	--
Follitropin beta	04/2005	09/1997	05/1996	1995: New Zealand
Fludeoxyglucose(18F)	07/2005	1994	--	2002:UK
Gemtuzumab	07/2005	05/2000	--	--
Inulin	10/2005	1940	--	--
Finasteride	10/2005	06/1992	--	04/1992: Australia
Miglitol	10/2005	12/1996	--	07/1996: Netherland
Moxifloxacin	10/2005	12/1999	--	06/1999: Germany
Aripiprazole	01/2006	11/2002	06/2004	
Letrozole	01/2006	07/1997	--	11/1996:UK
Clopidogrel	01/2006	11/1997	07/1998	
Follitropin alpha	01/2006	09/1997	10/1995	
Cetrorelix	04/2006	08/2000	04/1999	
Tolterodine	04/2006	05/1998	--	09/1997: Sweden
Sertraline	04/2006	12/1991	--	
Solifenacin	04/2006	12/2004	--	12/2003: Germany, France
Gabapentin	07/2006	12/1993	--	11/2005: UK
Temozolomide	07/2006	08/1999	01/1999	
Interferon bera-1a	07/2006	05/1996	03/1997	
Entecavir	07/2006	03/2005	06/2006	
Bortezomib	10/2006	05/2003	04/2004	
Ropinirole	10/2006	09/1997	--	07/1996:UK
Remifentanil	10/2006	07/1996	--	10/1996:UK
Agalsidase alfa	10/2006	--	08/2001	
Laronidase	10/2006	04/2003	06/2003	

* Except for the drugs approved through EMEA centralized procedures.
** Combination drug.

Table 3. Number of approval and preceding drugs in Japan and other regions*

	Number of approval	Number of preceding drugs
Japan	70	3
US	69	57
EU	35	10

* Number of preceding drugs and NMEs approved in Japan and at least one other region in 2002 to 2006.

Table 4. NMEs approved solely in US and EU (2002-2006)

NMEs	US	EU
Nitisinone	01/2002	02/2005
Fulvestrant	04/2002	03/2004
Oxybate	07/2002	10/2005
Pegvisomant	03/2003	11/2002
Enfuvirtide	03/2003	05/2003
Aprepitant	03/2003	11/2003
Miglustat	07/2003	11/2002
Palonosetron	07/2003	03/2005
Daptomycin	09/2003	01/2006
Memantine	10/2003	05/2002
Tadalafil	11/2003	11/2002
Bevacizumab	02/2004	01/2005
Cetuximab	02/2004	06/2004
Pemetrexed	02/2004	09/2004
Cinacalcet	03/2004	10/2004
Insulin glulisine	04/2004	09/2004
Duloxetine	08/2004	12/2004
Erlotinib	11/2004	09/2005
Natalizumab	11/2004	06/2006
Iloprost	12/2004	09/2003
Pregabalin	12/2004	07/2004
Darifenacine	12/2004	10/2004
Ziconotide	12/2004	02/2005
Palifermin	12/2004	10/2005
Pegaptanib	12/2004	01/2006
Clofarabine	12/2004	05/2006
Exenatide	04/2005	11/2006
Galsulfase	05/2005	01/2006
Insulin Detemir	06/2005	06/2004
Tripranavir	06/2005	10/2005
Tigecycline	06/2005	04/2006
Deferasirox	11/2005	08/2006
Sorafenib	12/2005	07/2006
Sunitinib	01/2006	07/2006
Alglucosidase alpha	04/2006	03/2006
Rasagiline	05/2006	02/2005
Varenicline	05/2006	09/2006
Dasatinib	06/2006	11/2006
Posaconazole	09/2006	10/2005

Table 5. Number of approval and preceding drugs in US and EU*

Year of approval	Number of approval in US	US preceding	EU preceding
2002	3	3	0
2003	8	4	4
2004	15	12	3
2005	7	6	1
2006	6	3	3
Total	39	28	11

* Number of preceding drugs and NMEs approved solely in US and EU (2002-2006).

CONCLUSION

For the year 2006, there were no major differences in the number of approvals among the three regions. On the other hand, the analysis of NMEs approved in the three regions between 2002 and 2006 showed that the number judged to have been simultaneously approved in both Japan and the US or the EU was only 6, in contrast to 18 ingredients approved in both the US and the EU. In this study, the evaluation for the EU included only those ingredients approved by the Centralized Approval Process by the EMEA, and hence did not include individual ingredients approved by each country's government or by the Mutual Recognition Procedure in the EU region. As a consequence, the number of approved ingredients may have been reduced; though new ingredients that have already been used in the EU region but approved for the first time by the EMEA for brand new indications such as orphans may have been counted in the annual number of approvals. In the investigation performed previously to review the period between 2000 and August 2004 [1], it was shown that among 105 ingredients approved in the US, the average review periods for 21 ingredients approved in both Japan and the US were 18.2 months and 19.0 months, respectively, not significantly different, despite 82 ingredients were not approved in Japan at that time. This result may suggest that there are many cases in which a drug marketed in Western countries is introduced to Japan after effectiveness, safety have been confirmed. In the US, as the review system has been strengthened by the Prescription Drug User Fee Act, new drugs have received precedent approval, thereby allowing the public to benefit from the newest medical advances [2]. However, it has been pointed out that people are initially exposed to risks, and this analysis also confirmed that observation. In Japan, there is increasing concern about promptly providing necessary drugs to clinical practitioners in terms of enhancing both medical care and economy. Japan established the Pharmaceuticals and Medical Devices Agency in 2004 to strength the review system. Furthermore, numerous proposals have been made regarding strengthening of the review system and expediting the review process in the "New Health Frontier Strategy (Eminent Persons Meeting on New Health Frontier Strategy, April 18, 2007)," the "5-Year Strategy for Innovative Pharmaceuticals and Medical Devices Creation (Ministry of Education, Culture, Sports, Science and Technology; Ministry of Health, Labour and Welfare; and Ministry of Economy, Trade and Industry, April 26, 2007)", Innovation 25 (promulgated at a Cabinet meeting, June 01, 2007), the Basic Policies for Economic and Fiscal Reform 2007 (Council on Economic and Fiscal Policy, June 19, 2007),

The Report of the Study Group on promptly providing safe and effective drugs (Ministry of Health, Labor and Welfare, July 27, 2007) , etc. However, we must consider not only the review time, but also the necessity of striving for promotion of development stages leading up to the approval application that involves improving the environments of clinical studies designed to promote participation and competition in simultaneous global developments.

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