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Research paper

Approval of new biopharmaceuticals 1999–2006: Comparison of the US, EU and Japan situations

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Abstract

Biopharmaceuticals, defined as either proteins derived from recombinant DNA technology (rDNAs) or therapeutic monoclonal antibodies (mAbs), have become the therapeutics of significance in the 21st century. This article identifies the new biopharmaceuticals approved in the three major pharmaceutical markets (US, EU and Japan) and analyzes the so-called ''drug lag'' in said regions. Between 1999 and 2006, a total of 65 new biopharmaceuticals were approved. Of this total, 59 (90.8%) were approved in the US, 52 (80.0%) in EU and 22 (33.8%) in Japan. The mean approval lag was 3.7 months in the US, 7.5 months in EU and 52.6 months in Japan. The US was ahead of the two other regional markets in approvals of biopharmaceuticals, while there was a significant drug lag in Japan. The authors also found that US companies were the licensors of 42 out of 65 new biopharmaceuticals, followed by European companies with 21 licensors and Japanese companies with only 2 licensors. These figures suggest that Japanese companies are still weak in biopharmaceuticals innovation and licensing, and this weakness appears to be a major contributing factor to the drug lag in the country.

Keywords: Drug lag; Three regions (US, EU, Japan); Drug approval; Biopharmaceuticals

1. Introduction

For many years now, ''drug lag'' has been of great interest and a much debated issue among health policymakers around the world. The term ''drug lag'' was first coined and described by Wardell in the 1970s [1,2]. While Andersson, in his review of ''drug lag'' studies during the 1970s–1980s, described the term to imply two meanings – ''absolute drug lag'' which denotes a measurement of availability, i.e., a tally of the number and proportion of new drugs introduced in a country, and ''relative drug lag'' which denotes a measurement of how fast new drugs get to a country) [3]. Wardell showed in his studies during the 1970s that new drugs were introduced later and in fewer numbers in the US than in the UK. His findings sparked a heated discussion in the US on the issue. The debate on drug lag, which started in the US, expanded to the international arena during the1980s. Several studies revealed that drug lag exists not only between the US and UK but also among European countries and other drug markets such as Japan. In 1989, Parker ranked the 12 industrialized countries from the perspective of relative drug lag [4,5], and Japan was ranked lowest among the industrialized countries.

Although it has long been recognized that a significant drug lag exists in Japan, the issue has not been discussed much in the country until recently. Since the beginning of 2000, owing to the spread of information technology, Japanese patients have become more informed and aware of their diseases and therapeutic alternatives. They gradually came to realize that many drugs used in other countries are not available in Japan. And so, for the first time in many years, drug lag has become a publicly recognized

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issue in the country. As the public recognition of the issue has just recently begun, the drug lag situation in Japan has not been studied extensively. So we recently conducted a study to examine the approval status of 334 new chemical entities (NCEs) approved in the US, EU and Japan between 1999 and 2005 [6]. We found that out of 334 NCEs, 274 (82.6%) were approved in the US, 262 (78.4%) in EU and 181 (54.2%) in Japan. The mean approval lag was 13.5 months for the US, 13.2 months for EU and 46.3 months for Japan. Our findings indicated that the US was not far behind EU in terms of speed of drug approval, while a significant drug lag existed in Japan.

Biopharmaceuticals, which are drugs derived from biotechnology, have become the therapeutics of significance in the 21st century. In this regard, drug lag in biopharmaceuticals may be of great interest to both the public and health policymakers. However, as the history of biopharmaceuticals is relatively short, not many reports on the issue of biopharmaceutical drug lag have been published. Bienz-Tadmor studied 14 new biopharmaceuticals approved in the US, Europe or Japan between 1982 and 1992 [7]. All 14 new biopharmaceuticals were approved in Europe, while 11 out of 14 were approved in the US and 10 out of 14 were approved in Japan. In terms of "first approval country", Europe was the first approval country in 75% of the products, while US is the first approval country in 25%. None of these new products was first approved in Japan. After the Bienz-Tadmor study, very few international studies on the subject of drug lag in biopharmaceuticals have been reported. Although a series of studies on the approval of biopharmaceuticals in the US and EU was reported by the Tufts Center for the Study of Drug Development, these studies mainly focused on the trends in biopharmaceutical development [8–11].

The purpose of this report is to examine the approvals of new biopharmaceuticals in the three major pharmaceutical markets – US, EU and Japan – in order to clarify the drug lag situation in the three regions. In this report, biopharmaceuticals are defined as either proteins derived from recombinant DNA technology (rDNAs) or therapeutic monoclonal antibodies (mAbs). mAbs include those that are used for in vivo diagnostic use as well as in vivo therapeutic use.

2. Methods

All data in this report are based on information gathered as of 31 December, 2006.

2.1. Identification of new biopharmaceuticals

Information on new biopharmaceuticals approved in the US, EU or Japan between 1999 and 2006 were identified by their International Non-proprietary Names (INN) and gathered primarily through the following data sources. Vaccines were excluded from the study.

(1) US: "CDER Drug and Biologic Approval Report", Center for Drug Evaluation and Research (CDER), the U.S. Food and Drug Administration (FDA) (http://www.fda.gov/cder/rdmt/).
(2) EU: "European Public Assessment Report" (EPAR), Committee for Medicinal Products for Human Use (CHMP), European Medicine Agency (EMEA) (http://www.emea.europa.eu/htms/human/epar/eparintro.htm).
(3) Japan: "*Iyakuhin Iryo-kiki Joho-teikyo Homupēge* (Homepage for Information about Pharmaceuticals and Medical Devices)", Pharmaceuticals and Medical Devices Agency (PMDA) (http://www.info.pmda.go.jp/shinyaku/shinyaku_index.html) (in Japanese).

2.2. Determining the approval dates of new biopharmaceuticals approved in the US, EU and Japan

The approval dates of new biopharmaceuticals approved between 1999 and 2006 were determined at the time the new biopharmaceuticals were identified. If approval in any one of the three regions was made before 1999, the approval date in that region was determined using the "IMS R&D Focus" (IMS Health), which provided at least the year of approval [12]. Once it is confirmed that the biopharmaceutical was approved, the approval date was verified using the data sources described in Section 2.1.

2.3. Analysis of drug lag in biopharmaceuticals in the US, EU and Japan

In this study, we described and assessed the drug lag in the three regions in terms of the two meanings described in the introduction, i.e. "absolute drug lag" and "relative drug lag".

In assessing "absolute drug lag", we used as variables the number and the percentage of approved biopharmaceuticals in each region. Two sub-group analyses were conducted – one for rDNAs and mAbs, and another one for orphan and non-orphan biopharmaceuticals. All three regions have existing policies for orphan drug designation but these policies differ to some degree. In this study, orphan biopharmaceuticals are defined as those designated as orphan drugs in any of the three regions.

In assessing "relative drug lag," two variables were used. One variable is the number and percentage of first approvals in the regions. The other variable is the approval lag against the first approval granted to each biopharmaceutical in the three regions. For example, if the US was the first to approve a biopharmaceutical in April 2001 and EU approved the same biopharmaceutical in October 2001, the approval lag for the US is zero and the approval lag for EU is 6 months. The approval lag was obtained for all biopharmaceuticals approved in each region and the mean approval lag was calculated for each region.

Table 1
Sixty-five new biopharmaceuticals approved either in the US, EU or Japan between 1999 and 2006 (in the order of the US approval date)

Generic name (INN)	Description	US approval date	EU approval date	JP approval date
Interferon beta-1b	rDNA interferon	23-Jul-1993	30-Nov-1995	22-Sep-2000
Interferon beta-1a	rDNA interferon	17-May-1996	13-Mar-1997	26-Jul-2006
Insulin lispro	rDNA insulin	14-Jun-1996	30-Apr-1996	20-Jun-2001
Reteplase	rDNA tissue plasminogen activator	30-Oct-1996	9-Nov-2001	NA
Follitropin alfa	rDNA FSH	29-Sep-1997	20-Oct-1995	23-Jan-2006
Follitropin beta	rDNA FSH	29-Sep-1997	3-May-1996	11-Apr-2005
Rituximab	mAb pan B-cell	26-Nov-1997	2-Jun-1998	20-Jun-2001
Daclizumab	mAb CD25 (IL-2 receptor)	10-Dec-1997	26-Feb-1999	NA
Becaplermin	rDNA platelet derived growth factor	16-Dec-1997	29-Mar-1999	NA
Basiliximab	mAb IL-2	12-May-1998	9-Oct-1998	17-Jan-2002
Palivizumab	mAb respiratory syncytial virus	19-Jun-1998	13-Aug-1999	17-Jan-2002
Infliximab	mAb TNF-alfa	24-Aug-1998	13-Aug-1999	17-Jan-2002
Trastuzumab	mAb HER-2	25-Sep-1998	28-Aug-2000	4-Apr-2001
Etanercept	rDNA TNF receptor	2-Nov-1998	3-Feb-2000	19-Jan-2005
Thyrotropin alfa	rDNA TSH	30-Nov-1998	9-Mar-2000	NA
Denileukin difitox	rDNA IL-2 fusion protein	5-Feb-1999	NA	NA
Eptacog alfa (activated)	rDNA factor VIIa	25-Mar-1999	23-Feb-1996	10-Mar-2000
Moroctocog alfa	rDNA factor VIII	6-Mar-2000	13-Apr-1999	NA
Insulin glargine	rDNA insulin	20-Apr-2000	9-Jun-2000	16-Oct-2003
Gemtuzumab	mAb CD33	17-May-2000	NA	25-Jul-2005
Tenecteplase	rDNA tPA	2-Jun-2000	23-Feb-2001	NA
Insulin aspart	rDNA insulin	7-Jun-2000	7-Sep-1999	2-Oct-2001
Choriogonadotropin alfa	rDNA hCG	20-Sep-2000	2-Feb-2001	NA
Peginterferon alfa-2b	rDNA interferon, PEG	19-Jan-2001	25-May-2000	22-Oct-2004
Alemtuzumab	mAb CD52	7-May-2001	6-Jul-2001	NA
Nesiritide	rDNA brain natriuretic peptide	10-Aug-2001	NA	NA
Darbepoetin alfa	rDNA novel erthropoiesis stimulating protein	17-Sep-2001	8-Jun-2001	NA
Eptotermin alfa	rDNA ospeogenic protein-1	15-Oct-2001	17-May-2001	NA
Anakinra	rDNA IL-1 receptor antagonist	14-Nov-2001	8-Mar-2002	NA
Drotrecogin alfa (activated)	rDNA protein C	21-Nov-2001	22-Aug-2002	NA
Pegfilgrastim	rDNA G-CSF, PEG	31-Jan-2002	22-Aug-2002	NA
Ibritumomab tiuxetan	mAb pan B-cell	19-Feb-2002	16-Jan-2004	NA
Rasburicase	rDNA urate oxidase	12-Jul-2002	23-Feb-2001	NA
Dibotermin alfa	rDNA BMP-2	15-Jul-2002	9-Sep-2002	NA
Peginterferon alfa-2a	rDNA interferon, PEG	16-Oct-2002	20-Jun-2002	NA
Teriparatide	rDNA PTH	26-Nov-2002	10-Jun-2003	NA
Adalimumab	mAb TNF-alfa	31-Dec-2002	8-Sep-2003	NA
Alefacept	rDNA LFA-3-lg fusion protein and CD2 antagonist	30-Jan-2003	NA	NA
Pegvisomant	rDNA GH receptor antagonist, PEG	25-Mar-2003	13-Nov-2002	NA
Agalsidase beta	rDNA galactosidase-alfa	24-Apr-2003	3-Aug-2001	29-Jan-2004
Laronidase	rDNA alpha-L-iduronidase	30-Apr-2003	10-Jun-2003	20-Oct-2006
Omalizumab	mAb IgE	20-Jun-2003	25-Oct-2005	NA
Efalizumab	mAb CD11	27-Oct-2003	20-Sep-2004	NA
Cetuximab	mAb EGFR	12-Feb-2004	29-Jun-2004	NA
Bevacizumab	mAb VEGF	26-Feb-2004	12-Jan-2005	NA
Insulin glulisine	rDNA insulin	16-Apr-2004	27-Sep-2004	NA
Lutropin alfa	rDNA LH	8-Oct-2004	29-Nov-2000	NA
Natalizumab	mAb integrin	23-Nov-2004	27-Jun-2006	NA
Palifermin	rDNA keratinocyte growth factor	15-Dec-2004	25-Oct-2005	NA
Galsulfase	rDNA arylsulfatase B	31-May-2005	24-Jan-2006	NA
Insulin detemir	rDNA insulin	16-Jun-2005	1-Jun-2004	NA
Mecasermin	rDNA insulin-like growth factor-1	30-Aug-2005	NA	NA
Human hyaluronidase	rDNA hyaluronidase	2-Dec-2005	NA	NA
Mecasermin rinfabate	rDNA insulin-like growth factor-1	12-Dec-2005	NA	NA
Abatacept	rDNA CTLA4lg	23-Dec-2005	NA	NA
Alglucosidase alfa	rDNA alfa glucosidase	28-Apr-2006	29-Mar-2006	NA
Ranibizumab	mAb VEGF-A	30-Jun-2006	NA	NA
Idursulfase	rDNA iduronate-2-sulfatase	24-Jul-2006	NA	NA
Panitumumab	mAb EGFR	27-Sep-2006	NA	NA
Tasonermin	rDNA TNF-alfa	NA	13-Apr-1999	NA
Agalsidase alfa	rDNA galactosidase-alfa	NA	3-Aug-2001	20-Oct-2006
Epoetin delta	rDNA erythropoietin	NA	18-Mar-2002	NA
Human parathyroid hormone	rDNA PTH	NA	24-Apr-2006	NA

Table 1 (*continued*)

Generic name (INN)	Description	US approval date	EU approval date	JP approval date
Trafermin	rDNA basic fibroblast growth factor	NA	NA	4-Apr-2001
Tocilizumab	mAb IL-6 receptor	NA	NA	11-Apr-2005

rDNA, proteins derived from recombinant DNA technology; mAb, monoclonal antibody; NA, not approved. Data as of 31 December, 2006.

2.4. Approval status of biopharmaceuticals based on the licensor's nationality

We also investigated the status of approval of biopharmaceuticals in the three regions based on the nationalities of the licensors. In this regard, information about the identity and nationality of the licensor of each biopharmaceutical was obtained from the 'Licensor' field of 'IMS R&D Focus'. Licensors are defined as the current patent holders who developed or are developing the product, as of 31 December, 2006. Nationality was determined on basis of where corporate headquarters of the licensor is located.

2.5. Development status of unapproved biopharmaceuticals in the US, EU and Japan

For biopharmaceuticals which were not approved in any region at the time of this study, the development status was examined through information gathered from "IMS R&D Focus" and other public sources, such as the website of Japan Pharmaceutical Manufactures Association (JPMA) "New drugs under development" (http://www.okusuri.org/chikeninfo/html/shinyaku.htm). In this study, the term "Development" includes preclinical development and clinical phases I, II, and III.

The status of development was classified into 'Pre-registration', 'Development', 'Discontinued' and 'No Development'.

3. Results

3.1. Identified new biopharmaceuticals

By perusing the sources mentioned in Section 2.1 we have identified 65 new biopharmaceuticals approved in the US, EU and Japan between 1999 and 2006, as shown in Table 1. These new biopharmaceuticals were classified into rDNAs (47) and mAbs (18).

3.2. Absolute drug lag

The absolute drug lag in the US, EU and Japan is summarized in Table 2.

Out of the 65 new biopharmaceuticals approved, 59 (90.8%) were approved in the US, 52 (80.0%) in EU and 22 (33.8%) in Japan. Out of 47 rDNAs, 42 (89.4%) were approved in US, 38 (80.9%) in EU and 15 (31.9%) in Japan. Out of 18 mAbs, 17 (94.4%) were approved in the US, 14 (77.8%) in EU and 7 (38.9%) in Japan.

Eighteen biopharmaceuticals had orphan drug designations in the US, EU or Japan. Out of these 18 orphan biopharmaceuticals, 16 (88.9%) were approved in the US, 13 (72.2%) in EU and 12 (66.7%) in Japan. Out of 47 non-orphan biopharmaceuticals, 43 (91.5%) were approved in the US, 39 (83.0%) in EU and 10 (21.3%) in Japan.

3.3. Relative drug lag

The relative drug in the US, EU and Japan is summarized in Table 3.

The US was the first to approve 43 (66.2%) out of 65 new biopharmaceuticals, EU was the first for 20 (30.8%) and Japan was the first for 2 (3.1%). The mean approval lag for the US, EU and Japan was 3.7 months (0.3 years), 7.5 months (0.6 years) and 52.6 months (4.4 years), respectively. The distribution of approval lag in each region is shown in Fig. 1. Since many of the first approvals were

Table 2
Absolute drug lag – the number of new biopharmaceuticals approved

	US (%)	EU (%)	Japan (%)
All biopharmaceuticals ($n = 65$)	59 (90.8)	52 (80.0)	22 (33.8)
rDNAs ($n = 47$)	42 (89.4)	38 (80.9)	15 (31.9)
mAbs ($n = 18$)	17 (94.4)	14 (77.8)	7 (38.9)
Orphan ($n = 18$)	16 (88.9)	13 (72.2)	12 (66.7)
Non-orphan ($n = 47$)	43 (91.5)	39 (83.0)	10 (21.3)

Table 3
Relative drug lag – the number of first approval and approval lag

	US		EU		Japan	
	First approval	Approval lag	First approval	Approval lag	First approval	Approval lag
All biopharmaceuticals ($n = 65$)	43 (66.2%)	3.7 m (0.3y)	20 (30.8%)	7.5 m (0.6y)	2 (3.1%)	52.6 m (4.4y)
rDNAs ($n = 47$)	26 (55.3%)	5.2 m (0.4y)	20 (42.6%)	5.6 m (0.5y)	1 (2.1%)	59.6 m (5.0y)
mAbs ($n = 18$)	17 (94.4%)	0 m (0y)	0 (0%)	12.9 m (1.1y)	1 (5.6%)	37.7 m (3.1y)
Orphan ($n = 18$)	12 (66.7%)	3.9 m (0.3y)	5 (27.8%)	7.2 m (0.6y)	1 (5.6%)	51.0 m (4.2y)
Non-orphan ($n = 47$)	31 (66.0%)	3.7 m (0.3y)	15 (31.9%)	7.7 m (0.6y)	1 (2.1%)	54.6 m (4.5y)

obtained in the US, the distribution was centered to 0 and dispersed between 0 and 46.3 months. EU showed a similar pattern as in the US and the distribution of approval lag in this region dispersed between 0 and 60.4 months. The approval lag for Japan dispersed in a wider range, between 0 and 123.3 months (10.3 years).

As for approval of the 47 rDNAs, the US was first to approve 26 (55.3%), EU for 20 (42.6%) and Japan for 1 (2.1%). As for the 18 mAbs, the US was first to approve 17 (94.4%), EU for 0 (0%) and Japan for 1 (2.1%).

As for the 18 orphan biopharmaceuticals, the US was first to approve 12 (66.7%), EU for 5 (27.8%) and Japan for 1 (5.6%). The mean approval lag for the US, EU and Japan was 3.9 months (0.3 years), 7.2 months (0.6 years) and 51.0 months (4.2 years), respectively.

The products in which Japan came in as the first approval country are trafermin (rDNAs, non-orphan) and tocilizumab (mAbs, orphan). But neither of these two biopharmaceuticals was approved in the US and EU.

3.4. Approval status based on the licensor's nationality

In terms of the licensors' nationalities, the US was again in the lead, with US companies being the licensors of 42 (64.6%) out of 65 biopharmaceuticals. European companies were the licensors of 21 (32.3%) biopharmaceuticals and Japanese companies were the licensors of 2 (3.1%) biopharmaceuticals. The 2 Japanese companies' biopharmaceutical products are tocilizumab, developed and licensed by Chugai, and denileukin difitox, which Eisai acquired from Ligand (a US biotech company) in September 2006. Eisai's acquisition covers exclusive worldwide rights including intellectual property and licenses.

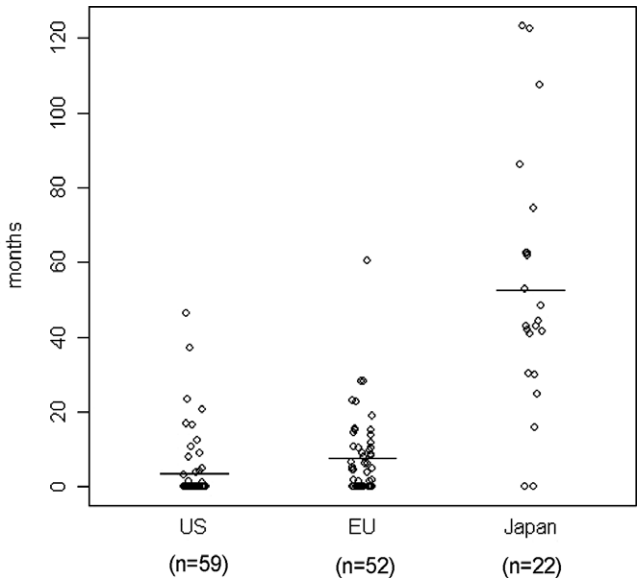

Fig. 1. Distribution of approval lag of new biopharmaceuticals in the US, EU and Japan. Note: The number of first approval with 0 approval lag is 43 in the US, 20 in EU and 2 in Japan.

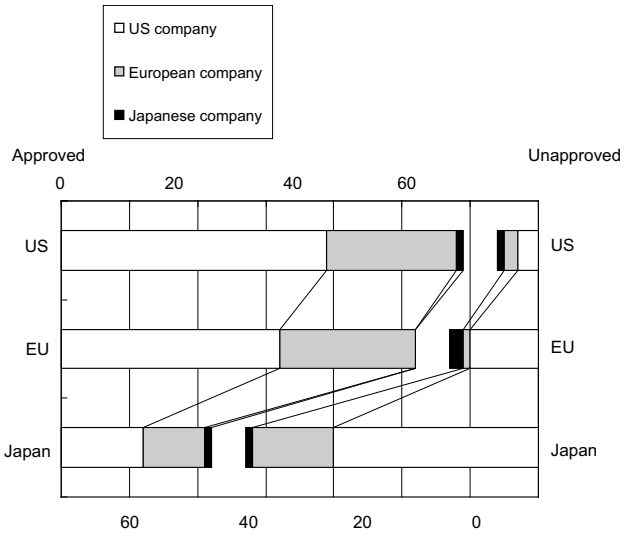

Fig. 2. Number of approved and unapproved biopharmaceuticals in the US, EU or Japan by licensor's nationality. Approved: authorized for marketing by the regulatory agency in the Region. Unapproved: not yet authorized for marketing by the regulatory agency in the Region. Source: IMS R&D Focus (accessed March 2007) Reprint with permission.

Fig. 2 shows the number of approved and unapproved biopharmaceuticals in the US, EU and Japan classified by the licensor's nationality. While Switzerland is not an EU member state, Swiss companies were included among the European companies in this study. The authors found that the US generally approved biopharmaceuticals irrespective of the licensor's nationality. Out of the 42 biopharmaceuticals of which the US companies are the licensors, 39 (92.9%) were approved in the US, and out of the 21 biopharmaceuticals of which European companies are the licensors, 19 (90.5%) were approved in the US. In EU, almost all (20/21, 95.2%) the biopharmaceuticals of which European companies are the licensors were approved. On the other hand, relatively lower percentage (32/42, 76.2%) of biopharmaceuticals of which the US companies are the licensors was approved in EU. In Japan, 12 (28.6%) out of 42 US companies' products and 9 (42.9%) out of 21 European companies' products were approved. Of the 2 Japanese companies' products approved, one (denileukin difitox) was approved only in the US and the other one (tocilizumab) was approved only in Japan. Neither of the 2 Japanese products was approved in EU.

3.5. Development status of unapproved biopharmaceuticals in the US, EU and Japan

Fig. 3 shows the development status of unapproved biopharmaceuticals in each region. In the US, all but one product (5/6) (agalsidase alfa, whose development was discontinued) are either in development or pre-registration phase. In EU, 9 out of 13 unapproved biopharmaceuticals are in pre-registration phase and 2 are in development phase. Only one product (human hyaluronidase) is not in

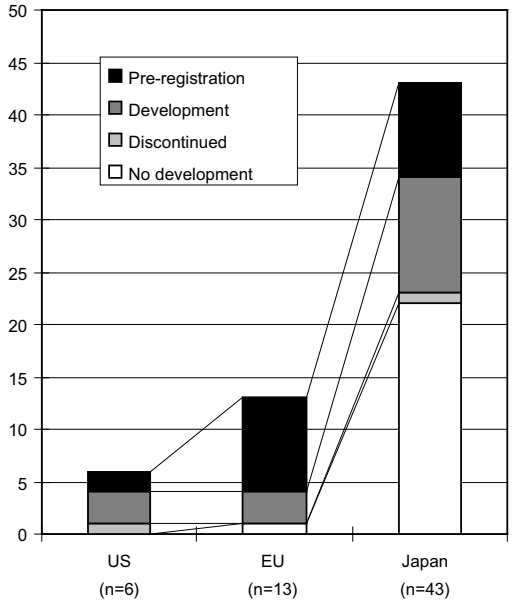

Fig. 3. Development status of unapproved biopharmaceuticals in the US, EU and Japan. Source: IMS R&D Focus (accessed March 2007) Reprint with permission.

development in EU. In Japan, 9 (20.9%) out of 43 unapproved biopharmaceuticals are in pre-registration phase, 11 (25.6%) are in development phase, while about half (22 out of 43, 51.2%) are not in development.

4. Discussion

The drug lag in Japan, one of the largest drug markets, has not been discussed in the international arena. Our examination of the new biopharmaceuticals approved in the US, EU and Japan between 1999 and 2006 revealed two major findings, i.e., (1) that the US is ahead of the two other regional markets (EU and Japan) in approvals of biopharmaceuticals, and (2) that there is a significant drug lag in Japan.

4.1. The US outperforms the EU in biopharmaceuticals approval

Overall, the US outperformed the EU both in terms of absolute drug lag and relative drug lag. Of the 65 new biopharmaceuticals approved during the study period, 59 (90.8%) were approved in the US, while 52 (80.0%) were approved in EU. The US was the first to approve 43 (66.2%) out of the 65 new biopharmaceuticals, while EU was the first in 20 (30.8%). The mean approval lag was 3.7 months (0.3 years) for the US and 7.5 months (0.6 years) for EU. In particular, the US leads in the approvals of mAbs. 17 (94.4%) out of 18 mAbs were approved in the US and these are all the first approvals.

While our study showed that the US is ahead of the EU in approvals, the biopharmaceutical drug lag for EU was not so big. In fact, the approval percentage of biopharmaceuticals in the EU is also relatively high, and the relative delay between EU and US was less than 4 months. We also noted that development programs for almost all (12/13) of the unapproved biopharmaceuticals in EU are underway. Therefore, it could be surmised that the drug lag in EU was simply a slight delay in approval, which may be attributed to a delay in the start of development, a slightly longer development period and may be a slightly longer review period. Due to the limitations of this study, it is not possible to make an in-depth analysis of the reasons behind these delays. However, we surmised that one factor that may be affecting this slight delay in EU might be the nationality of the licensor of the product. For example, in the US, biopharmaceuticals are approved irrespective of the licensor's nationality. On the other hand, in the EU, we observed a relatively lower percentage of approvals for US companies' biopharmaceutical products (32/42, 76.2%), implying that for most of the unapproved biopharmaceuticals in EU, the licensors are US biotech companies. Therefore, one of the reasons that we can attribute to the delay in approvals of biopharmaceuticals in EU may be due to the necessity of licensing negotiation between the US biotech companies and the applicants in EU.

4.2. A significant drug lag for biopharmaceuticals in Japan

Compared with the US and EU, we observed a significant drug lag for biopharmaceuticals in Japan. In terms of absolute drug lag, only 22 (33.8%) out of 65 new biopharmaceuticals were available in Japan. Also, in terms of relative drug lag, the mean approval lag for Japan was 4.4 years, which means that approval of new biopharmaceuticals is delayed in Japan by 4.1 years from the US and 3.5 years from EU. In terms of first approval, Japan was the first approval country in only 2 products. With regard to development status of unapproved biopharmaceuticals, 22 (51.2%) out of 43 unapproved biopharmaceuticals were not in development in Japan. In summary, one in three new biopharmaceuticals was approved with about 4 years delay, one in three was in development, and one in three was not in development in Japan.

As mentioned earlier in this report, our separate study of the approval of NCEs (NCEs includes new biopharmaceuticals in this study) showed that 54.2% of the total NCEs approved in the three regions were approved in Japan. Although the period covered in the NCE study (i.e., between 1999 and 2005) was slightly different, the drug lag for biopharmaceuticals in Japan is considered far more serious.

As in the EU situation, we surmised that a major factor affecting the drug lag in Japan might be attributed to the licensors' nationality. Japan was the licensor in only 2 products and one of these products (denileukin difitox) was in fact developed by a US company and acquired by a Japanese company (Eisai Co., Ltd.). The other product, tocilizumab, was the only product that originated in Japan

and the Japanese company, Chugai, succeeded in obtaining first in the world approval in the orphan indication (Catsleman's disease) in Japan. It is also worthwhile to note that historically, breweries or other non-pharmaceutical companies with fermentation technology have been the ones who are active in generating biopharmaceuticals in Japan. In contrast, Japanese pharmaceutical companies have not been very much interested in biopharmaceutical development. So only a limited number of Japanese pharmaceutical companies have generated biopharmaceuticals while others are still hesitant to invest in expertise and resources needed for biopharmaceuticals development. So while Japan is one of the major drug markets in the world, it is still way behind US and EU in generating new biopharmaceuticals. In a separate study that we are conducting, the percentage of NCEs that is licensed by Japan is about 14% (unpublished data). This means that Japan's performance in generating biopharmaceuticals is weaker than that in field of chemical compounds.

The lack of expertise in originating new biopharmaceuticals may be related to the lack of interest to undertake development, go through the review process and manufacture biopharmaceuticals. If a promising candidate is found outside Japan, for example, the foreign company (which is developing the product) could license its subsidiary in Japan so that development of the product could be carried out in Japan and the filing of an NDA for the product could be made in Japan. However, if the foreign company developing the product has no subsidiary in Japan or if the Japanese subsidiary does not have the expertise to undertake such development, then another Japanese company may be licensed by the foreign company to develop and file an NDA for the product in Japan. Unless the required expertise and resources are available to undertake such development, go through the review process and manufacture the product, the prospect of licensing promising biopharmaceutical candidates may not appeal to Japanese companies. And even if a Japanese company might be interested in licensing a product, negotiating for such license is often an expensive and time-consuming endeavor, leading to a further delay in the start of development. Unfortunately, this kind of situation is contributing to increase the drug lag in Japan.

As we have explained above, a major factor affecting drug lag for biopharmaceuticals in Japan is the lack of expertise and/or licensing opportunities for new products. However, there are many other factors causing the drug lag in the country. One of these is the slow and costly clinical trials in Japan. Another factor may be regulation of drug prices in the country. Also, it may be important to discuss the differences among drug categories such as rDNAs/mAbs and orphan/non-orphan drugs as these differences may also be contributing factors in the drug lag. A comparison between therapeutic areas was not investigated in this study, but we think it is also an area that is worth considering for study. The authors are currently collecting and analyzing more data not only for biopharmaceuticals but also for other NCEs approved in the US, EU and Japan, in order to further investigate the drug lag situation in Japan and attempt to develop suggestions to narrow the gap between Japan and the US/EU.

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