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Research Article

Approval of antineoplastic agents in India: comparison with the US and EU regions

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ABSTRACT

Background: The antineoplastic drugs are prescribed for the treatment of cancer, which is an important cause of mortality in India; therefore, a drug lag in the availability of antineoplastic drugs is a direct threat to life. The present study was undertaken to assess the drug lag for new antineoplastic agents in India compared with that in the United States (US) or European Union (EU).
Methods: The new antineoplastic agents approved in the United States, European Union and India between 1999 and 2011 were identified and information was gathered primarily from the websites of regulatory agencies of the three regions. We assessed absolute and relative drug lag for new antineoplastic agents approved in the three regions.
Results: Of the 70 new antineoplastic agents, 64 (91.42%) were approved in the United States, 54 (77.14%) in the European Union and 44 (62.85%) in India. The US was the first to approve 59 (84.28%) out of the 70 new antineoplastic agents, the EU was the first to approve 9 (12.85%) and India was the first to approve 2 (2.85%). The median approval lag for India (26.35 months) was higher as compared to the United States (0 month) and European Union (7.3 months).
Conclusions: This study confirms that India's drug lag in the case of new antineoplastic agents is higher as compared to the US and EU. Further detailed analyses are necessary to find the reasons and impacts of drug lag for antineoplastic agents in India.

Keywords: Oncology, anticancer drug, marketing approval, drug lag, new drug development

INTRODUCTION

As per the International Agency for Research on Cancer (IARC) estimate for India about 635000 people died from cancer in 2008.[1] The recent nationally representative mortality survey in India has confirmed that more than 70% of fatal cancers occurring during the productive ages of 30-69 years.[2] The antineoplastic drugs are prescribed for the treatment of cancer, which is an important cause of mortality in India; therefore, a drug lag in the availability of antineoplastic drugs is a direct threat to life. The number of cancer related deaths in India is projected to increase because of improvement in the life expectancy and population growth.

Drug development of cancer therapies has dramatically increased over the past two decades, in line with increasing understanding of the biological features of the disease and advances in technology.[3-4] However, delay in approval of drugs is an important issue with increasing burden of cancer related deaths in India. Each country has specific regulatory controls that govern approval of new drugs; however, these controls often differ from country to country. Therefore, the time required for approval of a new drug may vary depending on each country's regulatory process. The United States (US) Food and Drug Administration (FDA) has done some reforms to improve the access to therapeutics for life-threatening disease by establishing accelerated approval regulations in 1992.[5]

There is a change in the regulatory environment after a system of product patents in India since 2005.[6] The main regulatory body for the Indian pharmaceutical industry is the Central Drugs Standard Control Organization (CDSCO). The Drug Controller General of India (DCGI) is the controlling body for the CDSCO. The office of the Drug Controller General of India is responsible for the approval of new drugs and clinical trials. The timeliness with which drug regulatory authorities approve new drugs

for marketing affects health care professionals and patients. A long approval process delays access to new medicines that may improve patients' health status.

The drug lag for antineoplastic drugs has not been studied extensively in India, and the factors associated with this problem and impacts of drug lag remain unknown. Therefore, identifying the actual status of the antineoplastic drug lag in India would provide important information that could be used in efforts to resolve this issue. Drug lag in India may be the result of three separate types of delay or a combination of these: delay in the start of development, delay in the progress of development and delay in review by regulatory authority.

The purpose of this study was to assess the drug lag for new antineoplastic agents approved in India, in comparison with the approval of new antineoplastic agents in developed regions like the US and European Union (EU).

METHODS

Data sources

New antineoplastic agents approved in the US, EU, or India between 1999 and 2011 were identified by their International Non-proprietary Names (INN), and information was gathered primarily from the following sources:

1. The US: The Center for Drug Evaluation and Research (CDER) New Molecular Entity (NME) and New Biological Approvals, US Food and Drug Administration (FDA),[7]
2. The EU: The European Public Assessment Report (EPAR), Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMA),[8]
3. India: The Central Drugs Standard Control Organization (CDSCO), List of drug approved for marketing in India.[9]

The list of approved drugs was available from 1999 through 31st December 2011 at the time of analysis of the data. Information about name of approved drug, indication and date of issue of marketing approval was retrieved from the above sources.

New antineoplastic agents were defined as drugs having an active ingredient that has never before been marketed in the US, EU or India in any form. The following drugs were excluded: (a) vaccines, (b) combination drugs that do not include any new drugs.

Analyses of drug lag

In this study, we assessed and described the drug lag in the three regions in terms of 'absolute drug lag' and 'relative drug lag'. In assessing absolute drug lag, we used as variables the number and the percentage of approved new antineoplastic agents in each region out of a total of new antineoplastic agents approved either in the three regions in the study period. In assessing relative drug lag, two variables were used; one variable was the number and percentage of first approvals in the regions out of a total of new antineoplastic agents approved either in the three regions in the study period, and the other variable was the approval lag against the first approval granted to each antineoplastic agent in the three regions. For example, if the US was the first to approve an antineoplastic agent in January 2006 and if India approved the same antineoplastic agent in October 2006, the approval lag for the US is 0, and the approval lag for India is 9 months.

The approval lag was obtained for all new antineoplastic agents approved in each region, and the median approval lag was calculated for each region. The new antineoplastic agents for which approval dates were unknown were excluded from the calculation of median approval lag.

Additionally, for the FDA approved drugs, the following information was collected: drug type (molecular-targeted agents/non-molecular-targeted agents), review type (standard/priority) and orphan drug status (yes/no). The molecularly targeted drugs were defined according to the National Cancer Institute fact sheet 'Targeted Cancer Therapies'.[10]

RESULTS

Analyses of new antineoplastic agents approved in the US, EU and India

We identified 70 new antineoplastic agents approved either in the US, the EU, or India between 1999 and 2011. Of these 70 new antineoplastic agents, 30 were mutually approved in the three regions. The US and the EU approved 26 antineoplastic agents that were not approved in India. The EU and India approved 6 antineoplastic agents that were not approved in the US. The US and India approved 16 antineoplastic agents that were not approved in the EU. Total 40 new antineoplastic agents were approved in India during the period of 1999 to 2011, with an average of 3.07 new antineoplastic agents approved per year. For the same period a total of 51 new antineoplastic agents were approved in the US, with an average of 3.92 antineoplastic agents approved per year and in the EU a total of 44 new antineoplastic agents were approved, with an average of 3.38 antineoplastic agents approved per year. The year wise distribution of new antineoplastic agents approved in the US, EU and India is shown in Figure 1.

Analyses of drug lag

The absolute drug lags for the US, the EU and India are shown in Table 1. Of the 70 new antineoplastic agents, 64 (91.42%) were approved in the US, 54 (77.14%) in the EU and 44 (62.85%) in India. The relative drug lags for the US, the EU and India are summarized in Table 1. The US was the first to approve 59 (84.28%) out of the 70 new antineoplastic agents, the EU was the first to approve

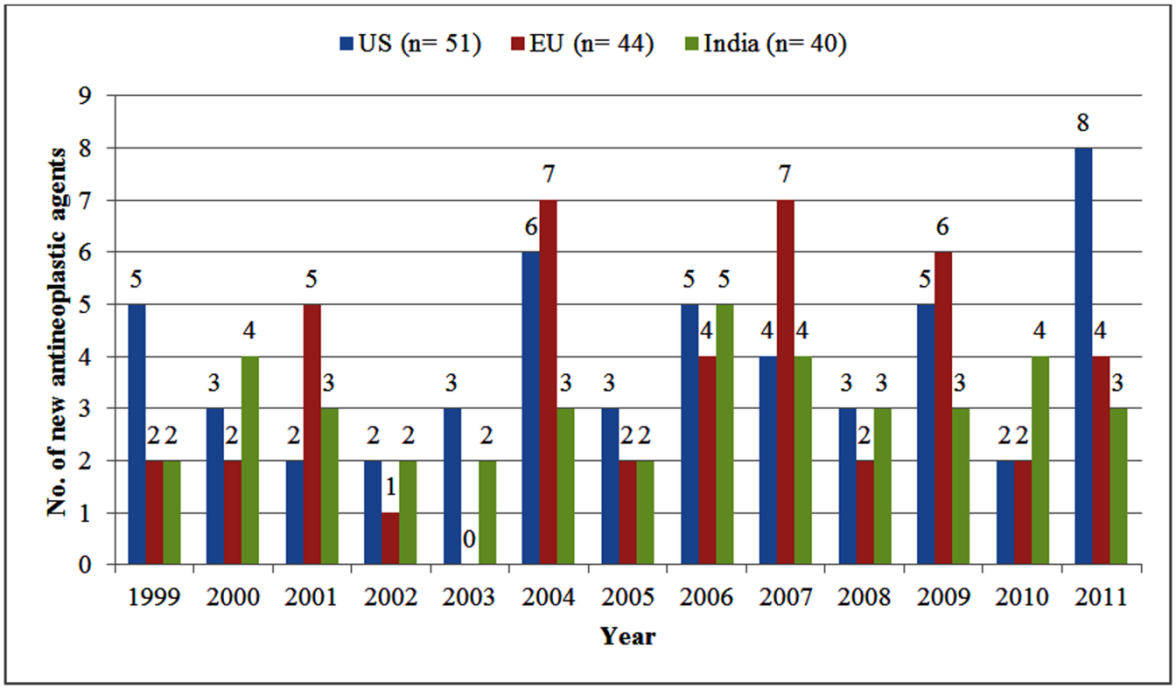

Figure 1: New antineoplastic agents approved in the US, EU and India, 1999-2011.

Table 1: Absolute and relative drug lag of new antineoplastic agents for the US, the EU and India (*n*= 70).

	US	EU	India
Number of approvals	64 (91.42%)	54 (77.14%)	44 (62.85%)
Number of first approvals	59 (84.28%)	9 (12.85%)	2 (2.85%)
Median approval lag (months)	0 (*n*= 61)	7.3 (*n*= 50)	26.35 (*n*= 40)

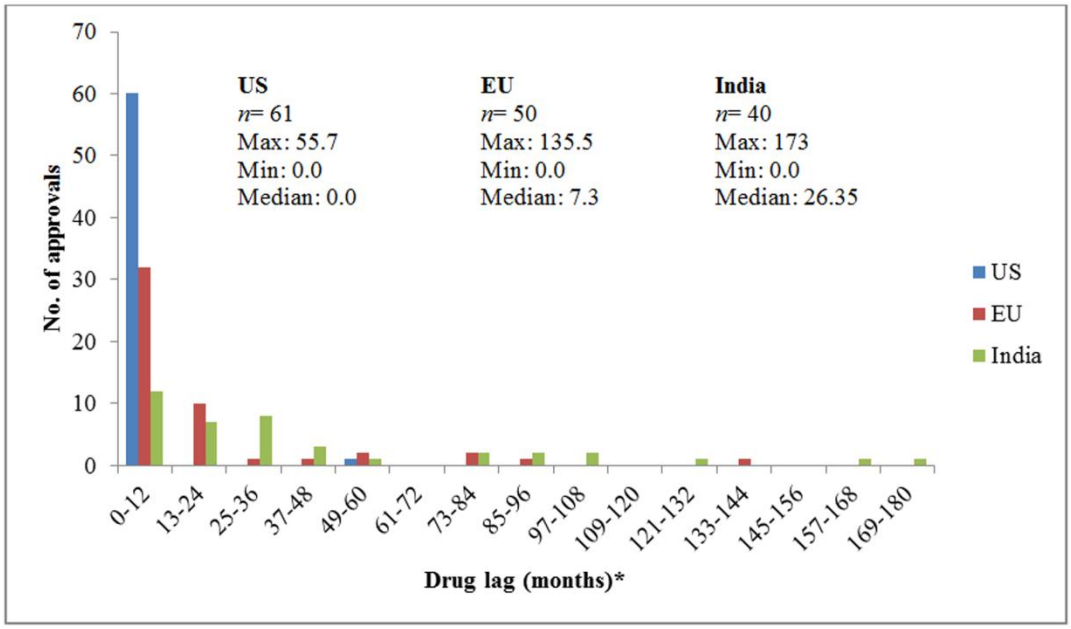

Figure 2: Distribution of drug lag for new antineoplastic agents approved in the US, EU and India.
*The distribution is shown in 12-month interval.

Table 2: Approval dates and characteristics of new antineoplastic agents approved either in the US, EU or India from 1999 through 2011 (*n*= 70).

Generic name (INN)	US approval date	EU approval date	India approval date	Review Type[§] (Standard/Priority)	Orphan[§] (Yes/No)	Molecularly targeted agent[§] (Yes/No)
Cabazitaxel	17-Jun-2010	17-Mar-2011	16-Nov-2011	P[a]	No	No
Abiraterone acetate	28-Apr-2011	5-Sep-2011	16-Dec-2011	P	No	No
Crizotinib	26-Aug-2011	NA*	16-Dec-2011	P	No	Yes
Nilotinib	29-Oct-2007	19-Nov-2007	10-Jul-2010	S[¶]	Yes	Yes
Irinotecan	14-Jun-1996	NA	31-Aug-2010	P	No	No
Pazopanib	19-Oct-2009	14-Jun-2010	16-Oct-2010	S	No	Yes
Temsirolimus	30-May-2007	19-Nov-2007	11-Dec-2010	P	Yes	Yes
Trabectedin	NA	17-Sep-2007	30-Mar-2009	-	-	-
Decitabine	2-May-2006	NA	25-Apr-2009	S	Yes	No
Bendamustine	20-Mar-2008	NA	16-May-2009	P	Yes	No
Doxifluridine	NA	NA	31-Jan-2008	-	-	-
Temoporfin	NA	24-Oct-2001	8-Jul-2008	-	-	-
Ixabepilone	16-Oct-2007	NA	13-Sep-2008	P	No	No
Sunitinib	26-Jan-2006	19-Jul-2006	10-Apr-2007	P	No	Yes
Lenalidomide	27-Dec-2005	14-Jun-2007	16-May-2007	P	Yes	No
Lapatinib	13-Mar-2007	10-Jun-2008	24-Jul-2007	P	No	Yes
Sorafenib	20-Dec-2005	19-Jul-2006	31-Jul-2007	P	Yes	Yes
Cetuximab	12-Feb-2004	29-Jun-2004	17-Aug-2006	P	No	Yes
Pemetrexed	4-Feb-2004	20-Sep-2004	21-Aug-2006	P	Yes	No
Paclitaxel	29-Dec-1992	19-Jul-1999	23-Aug-2006	P	Yes	No

Dasatinib	28-Jun-2006	20-Nov-2006	30-Aug-2006	P	Yes	Yes
Fulvestrant	25-Apr-2002	10-Mar-2004	30-Aug-2006	S	No	Yes
Bortezomib	13-May-2003	26-Apr-2004	18-May-2005	P	Yes	Yes
Erlotinib	18-Nov-2004	19-Sep-2005	13-Jul-2005	P	No	Yes
Gefitinib	5-May-2003	24-Jun-2009	17-Feb-2004	P	No	Yes
Everolimus	30-Mar-2009	3-Aug-2009	30-Aug-2004	P	No	Yes
Gemcitabine	15-May-1996	22-Jun-1996	1-Sep-2004	P	No	No
Anastrozole	27-Dec-1995	11-Aug-1995	10-Feb-2003	S	No	Yes
Cladribine	26-Feb-1993	14-Apr-2004	9-Sep-2003	P	Yes	No
Bicalutamide	4-Oct-1995	5-Apr-1995	7-Mar-2002	S	No	No
Gemtuzumab	17-May-2000	NA	12-Sep-2002	P	Yes	Yes
Vinorelbine	23-Dec-1994	A**	17-Jan-2001	P	No	No
Exemestane	21-Oct-1999	16-Dec-1998	18-Oct-2001	S	Yes	Yes
Imatinib	10-May-2001	7-Nov-2001	9-Dec-2001	P	Yes	Yes
Temozolomide	11-Aug-1999	26-Jan-1999	17-Jan-2000	P	Yes	No
Rituximab	26-Nov-1997	2-Jun-1998	10-Jul-2000	S	No	Yes
Trastuzumab	25-Sep-1998	28-Aug-2000	10-Jul-2000	S	No	Yes
Capecitabine	30-Apr-1998	2-Feb-2001	12-Oct-2000	P	No	No
Topotecan	28-May-1996	12-Nov-1996	15-Jun-1999	P	No	No
Fludarabine	18-Apr-1991	11-Aug-1994	26-Jun-1999	P	Yes	No
Vandetanib	4-Jun-2011	NA	NA	P	No	Yes
Vemurafenib	17-Aug-2011	NA	NA	P	No	Yes

Ipilimumab	25-Mar-2011	13-Jul-2011	NA	P	Yes	Yes
Brentuximab vedotin	19-Aug-2011	NA	NA	P	Yes	Yes
Ruxolitinib	16-Nov-2011	NA	NA	P	Yes	Yes
Asparaginase Erwinia Chrysanthem	18-Nov-2011	NA	NA	P	Yes	No
Eribulin	15-Nov-2010	17-Mar-2011	NA	P	No	No
Pralatrexate	24-Sep-2009	NA	NA	P	Yes	Yes
Romidepsin	5-Nov-2009	NA	NA	S	Yes	Yes
Ofatumumab	26-Oct-2009	19-Apr-2010	NA	P	Yes	Yes
Plerixafor	15-Dec-2008	31-Jul-2009	NA	P	Yes	No
Degarelix	24-Dec-2008	17-Feb-2009	NA	S	No	No
Vorinostat	6-Oct-2006	NA	NA	P	Yes	Yes
Panitumumab	27-Sep-2006	3-Dec-2007	NA	P	No	Yes
Nelarabine	28-Oct-2005	22-Aug-2007	NA	P	Yes	No
Azacitidine	19-May-2004	17-Dec-2008	NA	P	Yes	No
Clofarabine	28-Dec-2004	29-May-2006	NA	P	Yes	No
Bevacizumab	26-Feb-2004	12-Jan-2005	NA	P	No	Yes
Abarelix	25-Nov-2003	NA	NA	P	No	No
Oxaliplatin	9-Aug-2002	A	A	P	No	No
Triptorelin	15-Jun-2000	A	A	S	No	No
Arsenic trioxide	25-Sep-2000	5-Mar-2002	A	P	Yes	No
Alitretinoin	2-Feb-1999	11-Oct-2000	NA	P	Yes	Yes
Epirubicin	15-Sep-1999	A	A	P	Yes	No

Bexarotene	29-Dec-1999	29-Mar-2001	NA	P	Yes	Yes
5-Aminolevulinic acid	NA	7-Sep-2007	NA	-	-	-
Vinflunine	NA	21-Sep-2009	NA	-	-	-
Alemtuzumab	7-May-2001	6-Jul-2001	NA	S	No	Yes
Catumaxomab	NA	20-Apr-2009	NA	-	-	-
Anagrelide	14-Mar-1997	16-Nov-2004	NA	P	Yes	No

* NA: Not approved, **A: Available, but approval date is not known, [§]Characteristics for the FDA approved drugs

[a]P-Priority review drug, [¶]S-Standard review drug

9 (12.85%) and India was the first to approve 2 (2.85%). The median approval lag for India (26.35 months) was higher as compared to the United States (0 month) and European Union (7.3 months). The distribution of approval lags for each region are shown in Figure 2. Although the approval lag was less than one year for most of the antineoplastic agents for the US and the EU, India had a different distribution profile. The 12 new antineoplastic agents were approved in India within first 12 months of drug lag interval and showed a wide distribution up to nearly 173 months (Figure 2).

The relative drug lag was assessed for the 30 'mutually approved new antineoplastic agents'. The US was the first to approve 25 (83.33%) out of the 30 mutually approved new antineoplastic agents, the EU was the first to approve 4 (13.33%) and India was the first to approve 1 (3.33%). Again the median approval lag for India (27.15 months) was higher as compared to the United States (0 month) and European Union (7.3 months) for the mutually approved new antineoplastic agents.

The approval dates and characteristics of new antineoplastic agents approved either in the US, EU or India is shown in Table 2. Of the 64 new antineoplastic agents that were approved by the FDA, 51 (79.68%) were priority review drugs; 13 (20.31%) were standard review drugs; 33 (51.56%) received orphan drug status; 34 (53.12%) were molecularly targeted drugs and 30 (46.88%) were non-molecularly targeted drugs.

DISCUSSION

The percentage of approval of new antineoplastic agents was more than 90% for the US and almost 80% for the EU, 44 (62.85%) of the 70 new antineoplastic agents were approved in India. Thus, India is behind in comparison to the US and EU regions in terms of absolute drug lag. The US was the first to approve the majority of the new antineoplastic agents, and the EU was slightly delayed (Median approval lag: 7.3 months). But, the considerable delay was observed for India in approval of new antineoplastic agents. The median approval lag for India (26.35 months) was more than 2 years longer than that for the US (0 month) and 1.5 years longer than that for the EU (7.3 months). While our study showed that the US was first to approve majority of the new antineoplastic agents, the relative drug lag for EU was not so high. Therefore, it can be assumed that the drug lag in the EU was simply a slight delay in approval, which may be attributed to a delay in the start of development and may be a slightly longer review period.

The US FDA has given New Molecular Entity (NME) status for thalidomide in 1998. However, we excluded thalidomide from our analysis as its old drug approved for multiple myeloma by the US FDA and EMA.[7-8] Thalidomide was withdrawn due to its association with foetal malformation. In 2002, thalidomide was made available again in India. Marketing authorisation for gemtuzumab and pralatrexate was refused by EMA.[8] Both these drugs are approved by the US FDA. In 2009, Merck Sharp & Dohme Ltd has notified EMA to withdraw its application for a centralised marketing authorisation for the medicine vorinostat.[11]

Due to the limitations of this study, it is not possible to make an analysis of the possible reasons behind these delays. However, delay in the start of development, delay in the progress of development and delay in review by the regulatory authority could be possible reasons behind these delays in approval of antineoplastic agents in India. Besides, delay in review by the regulatory authority, this study suggests that the drug lag may be associated with delays in the initiation of drug development in India. One possible reason for the delays may be that pharmaceutical companies believe that simultaneously conducting registration trials in India and in the US or EU is a risk. As per World Trade Organisation (WTO), from the year 2005, India granted product patent recognition to all new chemical entities (NCEs).[6] Though, many foreign multinational corporations (MNCs) are not taking risk to launch their patented new drugs in India simultaneously with the developed markets. The questions on India's intellectual property (IP) regime are raised after Bayer has lost a landmark drug ruling in India, forcing it to grant a compulsory licence for its cancer treatment Sorafenib (Nexavar) to the Indian company, Natco Pharma.[12] To resolve delays in the initiation of drug development in India, pharmaceutical companies should make an effort to enrol Indian patients in international registration trials. For majority of new drugs, drug development is being performed in the US and the EU concurrently, and the integrated data package may be used for new drug applications (NDAs) in the US and the EU. Thus, it was not surprising that there was a little time gap in new drug approvals between the US and the EU.

Compared with the US and the EU, a striking drug lag was observed for approval of new antineoplastic agents in India. This may be because the US or Europe based companies were not interested to introduce the new antineoplastic agents through their subsidiaries in India due to relaxed patent law in India before 2005. The majority of large multinational pharmaceutical companies have presence in India and they may try to introduce their new products in India, simultaneously with other markets. Now, because of product patent in India, the Indian pharmaceutical companies can't introduce patented drugs developed by the foreign multinational corporations (MNCs). With the introduction of product patents, Indian companies will have to shift the area of focus from process development to developing new drug products.

Drug development is becoming increasingly globalised and to conduct the clinical trials in India is relatively economical as compared to other developed markets. However, there is a need to improve the regulatory processes in India to enhance the clinical trial and new drug approvals. The Indian regulatory authority has to

initiate some measures to reduce this delay in approval. The Japanese government has initiated various direct and indirect measures to reduce drug lag in Japan.[13] There is an urgent need to increase the human resources and improvement in the regulatory processes in India.

In conclusion, our analysis confirms that India's drug lag in the case of new antineoplastic agents is quite substantial. The drug lag in India may be attributed to a delay in the start of development, a delay in the progress of development, late submission of NDA and a delay in review by the regulatory authority. Further detailed analyses are necessary to find the background factors responsible for delay in approval in India and assess the impacts of drug lag for antineoplastic agents. To reduce this delay, combined efforts are required by the Indian regulatory agency and pharmaceutical companies.

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