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Research Article

Drug lag for antineoplastic and immunomodulating agent approvals in India compared with the US and EU approvals

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ABSTRACT

Background: There is a tremendous amount of research being conducted on development of new drugs for cancer therapies. The drug development of cancer therapies has dramatically increased over the past few decades. The present study was undertaken to assess the drug lag for new antineoplastic and immunomodulating agents in India compared with that in the United States (US) or European Union (EU).
Methods: The new drugs approved in the US, EU and India between 2011 and 2015 were identified and information was gathered primarily from the websites of regulatory agencies of the three regions. For the drug products identified, the drugs were classified into fourteen main Anatomical Therapeutic Chemical (ATC) groups, review classification and approval date. We assessed the absolute and relative drug lag for new antineoplastic and immunomodulating agents approved in the three regions (with the ATC code L).
Results: Of the 67 new antineoplastic and immunomodulating agents, 63 (94.02%) were approved in the United States, 58 (86.56%) in the European Union and 18 (26.86%) in India. The US was the first to approve 59 (88.05%) out of the 67 new antineoplastic and immunomodulating agents, the EU was the first to approve 7 (10.44%) and India was the first to approve 1 (1.49%). The median approval lag for India (18.36 months) was higher as compared to the United States (0 month) and European Union (6.02 months).
Conclusions: This study confirms that India lag behind the US and EU regions in terms of total number of new drug approvals for antineoplastic and immunomodulating agents. There is a substantial approval delay in India compared to the US and EU regions. Further detailed analyses are necessary to find the reasons and impacts of drug lag for new antineoplastic and immunomodulating agents in India.

Keywords: Drug lag, Oncology, Anticancer drug, European medicines agency (EMA), Drug development

INTRODUCTION

Drug development of cancer therapies has dramatically increased over the past few decades, in line with increasing understanding of the biological features of the disease and advances in technology.[1,2] Our recent analysis of drug approvals in the US, EU, or India showed upward trend of drug development and approvals for oncology drugs.[3,4] In all the three regions proportionately more number of drugs approved in the oncology therapeutic area.[3,4]

Delay in approval of drugs is an important issue with increasing burden of cancer related deaths in India. 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] Our previous analysis of drug approvals for antineoplastic agents showed substantial drug lag in India compared to the US and EU regions.[6]

There have been some recent reforms implemented by the Indian regulatory agency. One statutory board and a

committee have been framed called Drugs Technical Advisory Board (DTAB) and Drug Consultative Committee (DCC). DTAB comprises of technical experts who advises central and state governments on technical matters of drug regulation. The objective of present study was to assess the drug lag for new antineoplastic and immunomodulating agents approved in India (2011-2015), in comparison with the US and EU regions and to find the difference with respect to drug lag assessed in our previous study (1999-2011).[6]

METHODS

Data sources of new antineoplastic and immunomodulating and immunomodulating agent approvals

We obtained information about regulatory approval of new drugs in the US, EU, or India between 2011 and 2015 from the following publicly accessible databases:

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 approved drug.[9]

Information about name of approved drug, indication and date of issue of marketing approval was retrieved from the above sources. The definition of "new drug" included new molecular entities (NMEs) and new biologics. These analyses don't include generic drugs, biosimilar and supplemental approvals (e.g. additional indication, additional strength, new dosage form etc.) to new drugs. The information from the regulatory agencies online databases was entered and analysed using a Microsoft Excel worksheet (Microsoft Office 2010).

For the drug products identified the following features were recorded: International Non-proprietary Names (INN), the ATC code as per WHO Anatomical Therapeutic Chemical (ATC) classification[10], single or combination product and approval date. Further data were analysed for antineoplastic and immunomodulating drugs (with the ATC code L).

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 and immunomodulating agents in each region out of a total of new antineoplastic and immunomodulating 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 and immunomodulating 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 and immunomodulating agent in the three regions. For example, if the US was the first to approve an antineoplastic and immunomodulating agent in February 2011 and if India approved the same antineoplastic and immunomodulating agent in November 2011, 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 and immunomodulating agents approved in each region, and the median approval lag was calculated for each region.

RESULTS

New antineoplastic and immunomodulating agents approved in the US, EU and India

We identified 67 new antineoplastic and immunomodulating agents approved either in the US, the EU, or India between 2011 and 2015. Of these 67 new antineoplastic and immunomodulating agents, 16 were mutually approved in the three regions. Total 17 new antineoplastic and immunomodulating agents were approved in India during the period of 2011 to 2015, with an average of 3.4 new antineoplastic and immunomodulating agents approved per year. For the same period a total of 54 new antineoplastic and immunomodulating agents were approved in the US, with an average of 10.8 antineoplastic and immunomodulating agents approved per year and in the EU a total of 54 new antineoplastic and immunomodulating agents were approved, with an average of 10.8 antineoplastic and immunomodulating agents approved per year. The year wise distribution of new antineoplastic and immunomodulating agents approved in the US, EU and India is shown in Figure 1.

Table 1: Absolute and relative drug lag of new antineoplastic and immunomodulating drugs for the US, EU and India (*n*= 67).

Drug lag	US	EU	India
Number of approvals	63 (94.02%)	58 (86.56%)	18 (26.86%)
Number of first approvals	59 (88.05%)	7 (10.44%)	1 (1.49%)
Median approval lag (months)	0 (*n*= 63)	6.02 (*n*= 58)	18.36 (*n*= 18)

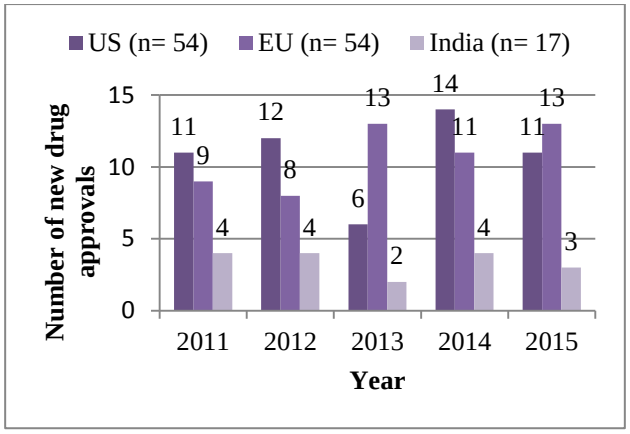


Figure 1: New antineoplastic and immunomodulating drugs approved in the US, EU and India, 2011-2015.

Analyses of drug lag

The absolute drug lags for the US, the EU and India are shown in Table 1. Of the 67 new antineoplastic and immunomodulating agents, 63 (94.02%) were approved in the US, 58 (86.56%) in the EU and 18 (26.86%) 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 (88.05%) out of the 67 new antineoplastic and immunomodulating agents, the EU was the first to approve 7 (10.44%) and India was the first to approve 1 (1.49%). The median approval lag for India (18.36 months) was higher as compared to the United States (0 month) and European Union (6.02 months). The distribution of approval lags for each region is shown in Figure 2. Although the approval lag was less than one year for most of the antineoplastic and immunomodulating agents for the US and the EU, India had a different distribution profile. The 11 new antineoplastic and immunomodulating agents were approved in India within first 24 months of drug lag interval and showed a wide distribution up to nearly 241 months (Figure 2).

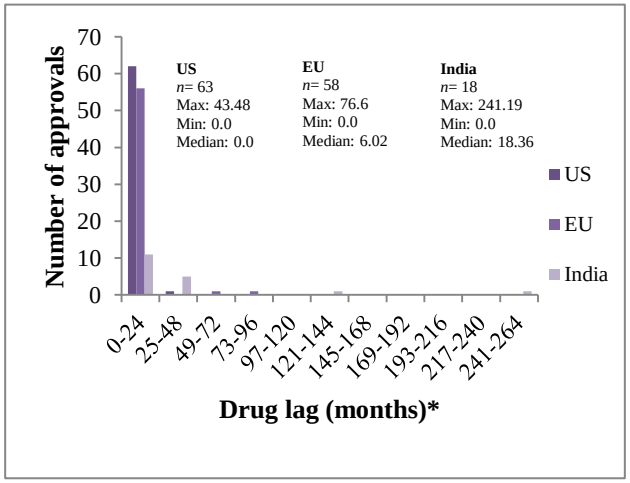
Table 2: Approval dates and indications of new antineoplastic and immunomodulating drugs approved either in the US, EU or India from 2011 through 2015 (*n*= 67).

Generic name (INN)	Indication	US approval date	EU approval date	India approval date
Abiraterone acetate	Metastatic castration-resistant prostate cancer	28-Apr-2011	5-Sep-2011	16-Dec-2011
Afatinib	Non-small-cell lung cancer (NSCLC) with epidermal-growth-factor-receptor (EGFR) mutation(s)	12-Jul-2013	25-Sep-2013	NA
Aflibercept	Metastatic colorectal cancer	18-Nov-2011	1-Feb-2013	NA
Apremilast	Active psoriatic arthritis	21-Mar-2014	15-Jan-2015	NA
Asparaginase Erwinia chrysanthemi	Acute lymphoblastic leukemia (ALL)	18-Nov-2011	NA	NA
Axitinib	Advanced renal-cell carcinoma (RCC)	27-Jan-2012	3-Sep-2012	18-Sep-2014
Azacitidine	Myelodysplastic syndromes	19-May-2004	17-Dec-2008	23-Jul-2014
Belatacept	Prophylaxis of graft rejectionin adults receiving a renal transplant	15-Jun-2011	17-Jun-2011	NA
Belimumab	Active, auto-antibody-positive systemic lupus erythematosus	9-Mar-2011	13-Jul-2011	NA
Blinatumomab	Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)	3-Dec-2014	23-Nov-2015	NA
Bosutinib monohydrate	Philadelphia-chromosome-positive chronic myelogenous leukaemia	4-Sep-2012	27-Mar-2013	NA
Brentuximab vedotin	Relapsed or refractory CD30+ Hodgkin lymphoma (HL)	19-Aug-2011	25-Oct-2012	NA
Cabazitaxel	Hormone-refractory metastatic prostate cancer	17-Jun-2010	17-Mar-2011	16-Nov-2011
Cabozantinib	Progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma	29-Nov-2012	21-Mar-2014	NA
Carfilzomib	Multiple myeloma	20-Jul-2012	19-Nov-2015	NA
Ceritinib	Anaplastic lymphomakinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer	29-Apr-2014	6-May-2015	13-Jan-2015
Cobimetinib hemifumarate	Unresectable or metastatic melanoma with a BRAF V600 mutation	10-Nov-2015	20-Nov-2015	NA
Crizotinib	Anaplastic-lymphoma-kinase (ALK)-positive	26-Aug-2011	23-Oct-2012	16-Dec-2011

	advanced non-small-cell lung cancer (NSCLC)			
Dabrafenib	Unresectable or metastatic melanoma with a BRAF V600 mutation	29-May-2013	26-Aug-2013	NA
Daratumumab	Multiple myeloma	16-Nov-2015	NA	NA
Decitabine	Newly diagnosed de novo or secondary acute myeloid leukaemia (AML)	2-May-2006	20-Sep-2012	25-Apr-2009
Degarelix	Advanced hormone dependent prostate cancer	24-Dec-2008	17-Feb-2009	19-Jan-2012
Dinutuximab	High-risk neuroblastoma	10-Mar-2015	14-Aug-2015	NA
Elotuzumab	Multiple myeloma	30-Nov-2015	NA	NA
Enzalutamide	Mmetastatic castration resistant prostate cancer	31-Aug-2012	21-Jun-2013	18-Dec-2015
Eribulin	Locally advanced or metastatic breast cancer	15-Nov-2010	17-Mar-2011	27-Jan-2012
Everolimus	Ttuberous sclerosis complex (TSC), advanced breast cancer, Renal Cell Pancreatic Neoplasms	30-Mar-2009	3-Aug-2009	21-Mar-2013
Fingolimod hydrochloride	Multiple sclerosis	21-Sep-2010	17-Mar-2011	NA
Ibrutinib	Mantle cell lymphoma (MCL), Chronic lymphocytic leukaemia (CLL), Waldenstrms macroglobulinaemia (WM)	12-Feb-2014	21-Oct-2014	7-Oct-2015
Idelalisib	Chronic lymphocytic leukaemia (CLL), follicular lymphoma (FL)	23-Jul-2014	18-Sep-2014	NA
Ipilimumab	Advanced (unresectable or metastatic) melanoma	25-Mar-2011	13-Jul-2011	NA
Lenvatinib mesylate	Differentiated (papillary/follicular/Hrthle cell) thyroid carcinoma (DTC)	13-Feb-2015	28-May-2015	NA
Lipegfilgrastim	Reduction in the duration of neutropenia and the incidence of febrile neutropenia	NA	25-Jul-2013	NA
Mepolizumab	Eosinophilic asthma	4-Nov-2015	2-Dec-2015	NA
Necitumumab	Metastatic squamous non-small cell lung cancer (NSCLC)	24-Nov-2015	NA	NA
Nintedanib	Idiopathic Pulmonary Fibrosis (IPF)	15-Oct-2014	21-Nov-2014	NA
Nivolumab	Locally advanced or metastatic squamous non-small cell lung cancer (NSCLC)	22-Dec-2014	19-Jun-2015	NA
Obinutuzumab	Chronic lymphocytic leukaemia (CLL)	1-Nov-2013	23-Jul-2014	NA
Olaparib	High grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer	19-Dec-2014	16-Dec-2014	NA
Omacetaxine mepesuccinate	Chronic- or accelerated-phase chronic myeloid leukemia (CML)	26-Oct-2012	NA	NA
Panobinostat lactate anhydrous	Multiple myeloma	23-Feb-2015	28-Aug-2015	NA
Pegaspargase	Acute lymphoblastic leukemia (ALL)	1-Feb-1994	NA	7-Mar-2014
Peginterferon beta-1a	Relapsing remitting multiple sclerosis	15-Aug-2014	18-Jul-2014	NA
Pembrolizumab	Advanced (unresectable or metastatic) melanoma	4-Sep-2014	17-Jul-2015	NA
Pertuzumab	Metastatic breast cancer and neoadjuvant treatment of breast cancer	8-Jun-2012	4-Mar-2013	NA
Pidotimod	For infections of the respiratory system in secondary and primary immunodeficiency with alteration in maturation of T cells	NA	NA	11-Feb-2011
Pirfenidone	Mild to moderate idiopathic pulmonary fibrosis	15-Oct-2014	28-Feb-2011	NA
Pixantrone dimaleate	Non-Hodgkin B-cell lymphomas (NHL)	NA	10-May-2012	NA
Plerixafor	Lymphoma or multiple myeloma for autologous transplantation	15-Dec-2008	31-Jul-2009	31-Jan-2012
Pomalidomide	Multiple myeloma	8-Feb-2013	5-Aug-2013	NA
Ponatinib	Chronic myeloid leukaemia (CML), Philadelphia-chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL)	14-Dec-2012	1-Jul-2013	NA
Ramucirumab	Advanced gastric cancer or gastro-oesophageal junction adenocarcinoma	21-Apr-2014	19-Dec-2014	NA

Regorafenib	Metastatic colorectal cancer, Metastatic gastrointestinal stromal tumors (GIST)	27-Sep-2012	26-Aug-2013	1-Jul-2014
Ruxolitinib	Disease-related splenomegaly or symptoms in adult patients with myelofibrosis	16-Nov-2011	23-Aug-2012	28-Jan-2013
Secukinumab	Moderate to severe plaque psoriasis	21-Jan-2015	15-Jan-2015	NA
Siltuximab	Multicentric Castlemans disease	23-Apr-2014	22-May-2014	NA
Sonidegib diphosphate	Locally advanced basal cell carcinoma (BCC)	24-Jul-2015	14-Aug-2015	NA
Tegafur /Gimeracil/Oteracil	Advanced gastric cancer	NA	14-Mar-2011	NA
Teriflunomide	Relapsing-remitting multiple sclerosis	12-Sep-2012	26-Aug-2013	NA
Tipiracil hydrochloride/Trifluridine	Metastatic colorectal cancer	22-Sep-2015	NA	NA
Tofacitinib citrate	Active rheumatoid arthritis	6-Nov-2012	Refused	NA
Trametinib	Unresectable or metastatic melanoma with a BRAF V600 mutation	29-May-2013	30-Jun-2014	NA
Trastuzumab emtansine	HER2-positive, unresectable locally advanced or metastatic breast cancer	22-Feb-2013	15-Nov-2013	NA
Vandetanib	Medullary thyroid cancer	6-Apr-2011	17-Feb-2012	NA
Vedolizumab	Ulcerative colitis, Crohn's disease	20-May-2014	22-May-2014	NA
Vemurafenib	BRAF-V600-mutation-positive unresectable or metastatic melanoma	17-Aug-2011	17-Feb-2012	19-Oct-2012
Vismodegib	Advanced basal-cell carcinoma	30-Jan-2012	12-Jul-2013	NA

INN: international nonproprietary name, NA: not available



*The distribution is shown in 24-month interval.

Figure 2: Distribution of drug lag for new antineoplastic and immunomodulating drugs approved in the US, EU and India.

The relative drug lag was assessed for the 16 mutually approved new antineoplastic and immunomodulating agents. The US was the first to approve all (100%) mutually approved new antineoplastic and immunomodulating agents. Again the median approval lag for India (18.36 months) was higher as compared to the United States (0 month) and European Union (8.6 months) for the mutually approved new antineoplastic and immunomodulating agents.

The approval dates and indications of new antineoplastic and immunomodulating agents approved either in the US, EU or India is shown in Table 2.

DISCUSSION

There is a substantial decrease in total number of new drug approvals in India between 2011 and 2015 compared to the US and EU regions. The percentage of approval of new antineoplastic and immunomodulating agents was 94.02% for the US and 86.56% for the EU and 18 (26.86%) of the 67 new antineoplastic and immunomodulating agents were approved in India. The percentage of approval of new antineoplastic and immunomodulating agents was 62.85% (44) for India during the period of 1999 to 2011.[6] The US was the first to approve the majority of the new antineoplastic and immunomodulating agents (88.05%), and the EU was slightly delayed (Median approval lag: 6.02 months). The median approval lag for India (18.36 months) was slightly less compared to the previous analysis (26.35 months).[6] While our study showed that the US was first to approve majority of the new antineoplastic and immunomodulating agents, the relative drug lag for EU was not so high (Median approval lag for 2011-2015: 6.02 months and Median approval lag for 1999-2011: 7.3 months).[6] 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.

Tofacitinib citrate approval was refused by the Committee for Medicinal Products for Human Use (CHMP) of EMA.[11] The CHMP had major concerns about the overall safety profile of tofacitinib citrate. Pidotimod has been approved by the Indian regulatory agency for infections of the respiratory system in secondary and primary immunodeficiency with alteration

in maturation of T cells while it is still not approved by the US and EU regulatory agencies.

The data for absolute drug lag showed that there is a lack of interest to launch new products by the foreign multinational corporations (MNCs) as number of approvals are very less in India (n=18) compared to the US (n=63) and the EU (n=58) regions. Drug development is becoming increasingly globalised and to conduct the clinical trials in India is relatively economical as compared to other developed markets. However, commercial gain possibly less in India compared to the developed markets could be one of the reasons why foreign multinational corporations are not taking interest to launch their new drugs in India. 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.

Our analysis confirms that India's drug lag in the case of new antineoplastic and immunomodulating agents is quite substantial. There is a decrease in the total number of approvals [18 (26.86%) Vs. 44 (62.85%)] compared to the previous analysis for the period of 1999 to 2011. 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 and immunomodulating agents. To reduce the absolute and relative drug lag of new antineoplastic and immunomodulating drugs, combined efforts are required by the Indian regulatory agency and pharmaceutical companies.

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