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Drug lag for cardiovascular drug approvals in India compared with the US and EU approvals

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ABSTRACT

Objective: Age-standardized burden of cardiovascular diseases is substantially higher in low and middle-income countries than in high-income countries. However, Indian patients are not getting access to the new cardiovascular drugs at the same time as patients in the developed nations. The objective of this study was to assess the drug lag for new cardiovascular drugs in India compared with that in the United States (US) or European Union (EU).

Methods: The information regarding approval of new cardiovascular drugs in the United States, European Union and India between 1999 and 2011 were obtained primarily from the online databases of regulatory agencies. The approval lag was obtained for all new cardiovascular drugs approved in each region, and the median approval lag was calculated for each region.

Results: Of the 75 new cardiovascular drugs, 61 (81.33%) were approved in the United States, 65 (86.66%) in the European Union and 56 (74.66%) in India. The US was the first to approve 35 (56.45%) out of the 75 new cardiovascular drugs, the EU was the first to approve 24 (38.71%) and India was the first to approve 3 (4.84%). The median approval lag for India (44.14 months) was substantially higher as compared to the United States (0 month) and European Union (2.99 months).

Conclusion: This study confirms that there is a substantial drug lag in approval of new cardiovascular drugs in India compared with the United States and European Union. The impact of drug lag on health outcomes remains to be established.

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1. Introduction

The last four decades has seen major advances in the prevention, diagnosis, and treatment of cardiovascular diseases (CVD). Mortality rates from cardiovascular diseases have declined significantly in western society.[1] This marked reduction in cardiovascular diseases and its consequences may be driven by the development and better utilization of drugs for cardiovascular diseases. Cardiovascular diseases will be the largest cause of death and disability by 2020 in India.[2] Global cardiovascular deaths are projected to increase from 17.1 million in 2004 to 23.4 million in 2030.[3] Age-standardized burden of cardiovascular diseases is substantially higher in low and middle-income countries than in

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high-income countries.[3] However, Indian patients are not getting access to the new medicines at the same time as patients in the developed nations. 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.

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. There is a change in the regulatory environment after a system of product patents in India since 2005.[4] 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 DCGI is responsible for the approval of new drugs and clinical trials.

Drug lag has been a debated issue in the United States (US) and Europe during the 1970s and 1980s.[5,6] However, the drug lag issue has not been addressed seriously in India. Because of increasing use of internet in India, many healthcare professionals and general public are now aware of the treatment options available in the developed regions. The drug lag prevents Indian patients from accessing new drugs at the same time as patients in the developed nations. Further, it may even delay the progress of clinical research in India. Therefore, identifying the actual status of the cardiovascular drug lag in India would provide important information that could be used in efforts to resolve this issue. The purpose of this study was to assess the drug lag for new cardiovascular drugs approved in India, in comparison with the approval of new cardiovascular drugs in the US and European Union (EU).

2. Methods

2.1. Data sources of new cardiovascular drug approvals

New cardiovascular drugs approved in the US, EU, or India between 1999 and 2011 were identified by their International Nonproprietary 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]

Information about name of approved drug, indication and date of issue of marketing approval was retrieved from the above sources. New cardiovascular drugs 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 and (b) combination drugs that do not include any new drugs.

2.2. 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 cardiovascular drugs in each region out of a total of new cardiovascular drugs 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 cardiovascular drugs 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 cardiovascular drug in the three regions. For example, if the US was the first to approve a cardiovascular drug in February 2010 and if India approved the same cardiovascular drug in December 2010, the approval lag for the US is 0, and the approval lag for India is 10 months.

The approval lag was obtained for all new cardiovascular drugs approved in each region, and the median approval lag was calculated for each region. In the European Union, the European Medicines Agency was established in 1993 to unify regulatory practice within the EU. The centralized procedure for marketing authorization of drugs throughout the EU went into operation in 1995. So, alternatively, we searched the Medicines and Healthcare products Regulatory Agency (MHRA) of United Kingdom (UK) approval date for the cardiovascular drugs for which EU approval date was not available. The UK approval dates were obtained from the electronic medicines compendium.[10] The new cardiovascular drugs for which approval dates were unknown were excluded from the calculation of median approval lag.

Additionally, for the FDA approved drugs, the information about review type (standard/priority/orphan drug status) was obtained from the FDA online database.[7]

3. Results

3.1. New cardiovascular drugs approved in the US, EU and India

We identified 75 new cardiovascular drugs approved either in the US, the EU, or India between 1999 and 2011. Of these 75 new cardiovascular drugs, 35 were mutually approved in the three regions. The US and the EU approved 19 cardiovascular drugs that were not approved in India. The EU and India approved 14 cardiovascular drugs that were not approved in the US. The US and India approved 10 cardiovascular drugs that were not approved in the EU. Total 54 new cardiovascular drugs were approved in India during the period of 1999—2011, with an average of 4.15 new cardiovascular drugs approved per year. For the same period a total of 34 new cardiovascular drugs were approved in the US, with an average of 2.61 cardiovascular drugs approved per year and in the EU a total of 23 new cardiovascular drugs were approved, with an average of 1.76 cardiovascular drugs approved per year. The year wise distribution of new cardiovascular drugs approved in the US, EU and India is shown in Fig. 1.
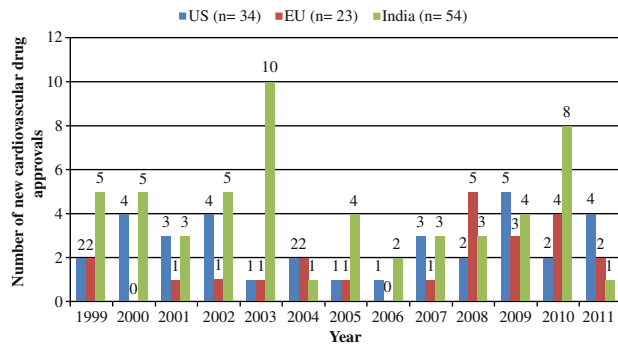
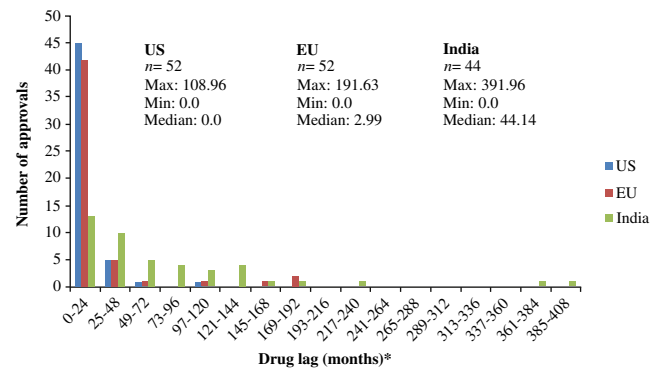**Fig. 1** − **New cardiovascular drugs approved in the US, EU and India, 1999−2011.**

Fig. 2 − **Distribution of drug lag for new cardiovascular drugs approved in the US, EU and India. *The distribution is shown in 24-month interval.**

3.2. Analyses of drug lag

The absolute drug lags for the US, the EU and India are shown in Table 1. Of the 75 new cardiovascular drugs, 61 (81.33%) were approved in the US, 65 (86.66%) in the EU and 56 (74.66%) 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 35 (56.45%) out of the 75 new cardiovascular drugs, the EU was the first to approve 24 (38.71%) and India was the first to approve 3 (4.84%). The median approval lag for India (44.14 months) was substantially higher as compared to the United States (0 month) and European Union (2.99 months). The distributions of approval lags for each region are shown in Fig. 2. Although the approval lag was less than 24 months for most of the cardiovascular drugs for the US and the EU, India had a different distribution profile. The 13 new cardiovascular drugs were approved in India within first 24 months of drug lag interval and showed a wide distribution up to nearly 400 months (Fig. 2).

The relative drug lag was assessed for the 35 'mutually approved new cardiovascular drugs'. The US was the first to approve 24 (68.57%) out of the 35 mutually approved new cardiovascular drugs, the EU was the first to approve 11 (31.43%) and India was not the first to approve any mutually approved new cardiovascular drugs. Again the median approval lag for India (45.46 months) was substantially higher as compared to the United States (0.0 month) and European Union (8 months) for the mutually approved new cardiovascular drugs.

The approval dates and characteristics of new cardiovascular drugs approved either in the US, EU or India is shown in

Table 2. Of the 61 new cardiovascular drugs that were approved by the FDA, 14 were priority review drugs; 46 were standard review drugs; 6 received orphan drug status and the US review type status was not available for one drug.

4. Discussion

The percentage of approval of new cardiovascular drugs was more than 80% for the US and EU, 56 (74.66%) of the 75 new cardiovascular drugs were approved in India. Thus, India is slightly 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 cardiovascular drugs, and the EU was slightly delayed (Median approval lag: 2.99 months). But, the substantial delay was observed for India in approval of new cardiovascular drugs. The median approval lag for India (44.14 months) was almost four years longer than that for the US and EU. While our study showed that the US was first to approve majority of the new cardiovascular drugs, 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.

A possible reason for the delays in approval of new cardiovascular drugs in India 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 Organization (WTO), from the year 2005, India granted product patent recognition to all new chemical entities (NCEs). Though, many foreign multinational corporations (MNCs) are not taking risk to launch their patented new drugs in India simultaneously with the developed markets. To resolve delays in the initiation of drug development in India, pharmaceutical companies should make an effort to enroll 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.

Table 1 − Absolute and relative drug lag of new cardiovascular drugs for the US, EU and India (n = 75).			
	US	EU	India
Number of approvals	61 (81.33%)	65 (86.66%)	56 (74.66%)
Number of first approvals	35 (56.45%)	24 (38.71%)	3 (4.84%)
Median approval lag (months)	0 (n = 52)	2.99 (n = 52)	44.14 (n = 44)

Table 2 – Approval dates and characteristics of new cardiovascular drugs approved either in the US, EU or India from 1999 through 2011 (n = 75).					
Generic name (INN)	Indication	US approval date	EU approval date	India approval date	US review classification
Azilsartan medoxomil	Hypertension	25-Feb-2011	7-Dec-2011	NA	S
Rivaroxaban	Venous thromboembolism	1-Jul-2011	30-Sep-2008	30-Jan-2010	S
Ticagrelor	Acute coronary syndrome	20-Jul-2011	3-Dec-2010	NA	S
Icatibant acetate	Hereditary angioedema	25-Aug-2011	11-Jul-2008	NA	P,O
Polidocanol	Varicose veins	30-Mar-2010	NA	NA	S
Dabigatran etexilate	Venous thromboembolism	19-Oct-2010	18-Mar-2008	12-Dec-2011	P
Tolvaptan	Inappropriate ADH Syndrome	19-May-2009	3-Aug-2009	NA	S
Dronedarone	Atrial fibrillation	1-Jul-2009	26-Nov-2009	8-Apr-2010	P
Prasugrel	Acute coronary syndrome	10-Jul-2009	23-Feb-2009	13-Apr-2010	P
Pitavastatin	Dyslipidemias	3-Aug-2009	NA	14-Jan-2005	S
Ecallantide	Hereditary angioedema	1-Dec-2009	NA	NA	P,O
Regadenoson	Myocardial Perfusion Imaging	10-Apr-2008	6-Sep-2010	NA	S
Clevidipine	Hypertension	1-Aug-2008	NA	NA	S
Aliskiren	Hypertension	5-Mar-2007	22-Aug-2007	8-Jun-2007	S
Ambrisentan	Pulmonary arterial hypertension	15-Jun-2007	21-Apr-2008	24-May-2010	P,O
Nebivolol[a]	Hypertension	17-Dec-2007	4-Jan-1999	12-Jul-2002	S
Ranolazine	Angina pectoris	27-Jan-2006	9-Jul-2008	14-Jun-2007	S
Conivaptan	Inappropriate ADH Syndrome	29-Dec-2005	NA	NA	S
Omega-3-acid ethyl esters[a]	Hypertriglyceridaemia	10-Nov-2004	22-Jul-2001	NA	S
Iloprost	Pulmonary arterial hypertension	29-Dec-2004	16-Sep-2003	NA	P,O
Rosuvastatin[a]	Dyslipidemias	12-Aug-2003	21-Mar-2003	12-Sep-2003	S
Olmesartan medoxomil[a]	Hypertension	25-Apr-2002	22-May-2003	21-Jul-2005	S
Treprostinil	Pulmonary arterial hypertension	21-May-2002	NA	NA	P,O
Eplerenone[a]	Hypertension	27-Sep-2002	21-Sep-2004	10-Jun-2005	S
Ezetimibe	Dyslipidemias	25-Oct-2002	1-Oct-2002	18-Dec-2003	S
Nesiritide	Acutely decompensated heart failure	10-Aug-2001	NA	NA	S
Bosentan	Pulmonary arterial hypertension	20-Nov-2001	15-May-2002	23-Jun-2009	S,O
Fondaparinux	Venous thromboembolism	7-Dec-2001	21-Mar-2002	22-Oct-2003	P
Colesevelam	Hypercholesterolemia	26-May-2000	10-Mar-2004	NA	S
Argatroban	Anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia	30-Jun-2000	A	NA	S
Tinzaparin[a]	Venous thromboembolism	14-Jul-2000	20-Nov-1997	A	S
Bivalirudin	In patients with unstable angina undergoing PTCA	15-Dec-2000	20-Sep-2004	25-Aug-2005	S
Cilostazol[a]	Intermittent claudication	15-Jan-1999	21-Mar-2000	23-Jan-2003	S
Dofetilide	Atrial fibrillation	1-Oct-1999	29-Nov-1999	NA	S
Vernakalant	Atrial fibrillation	NA	1-Sep-2010	NA	
Ivabradine	Angina pectoris	NA	25-Oct-2005	3-Jul-2008	
Apixaban	Venous thromboembolism	NA	18-May-2011	NA	
Eptifibatide	Acute coronary syndrome	18-May-1998	1-Jul-1999	25-Aug-1999	P
Tenecteplase	Myocardial infarction	2-Jun-2000	23-Feb-2001	A	–
Laropiprant/ Nicotinic acid	Dyslipidemias	NA	3-Jul-2008	26-Mar-2010	
Conestat alfa	Hereditary angioedema	NA	28-Oct-2010	NA	
Sarpogrelate	Chronic arterial occlusion	NA	NA	16-Jan-2010	
Levosimendan	Acutely decompensated heart failure	NA	NA	30-Apr-2010	
Nadolol[a]	Angina pectoris	10-Dec-1979	24-Nov-1995	20-Aug-2010	S
Perindopril[a]	Hypertension	30-Dec-1993	28-Feb-2007	16-May-2009	S
Chlorthalidone	Hypertension	7-Apr-1960	A	3-Oct-2009	P
Acipimox[a]	Dyslipidemias	NA	2-May-2003	26-Nov-2009	
Nicardipine[a]	Hypertension	21-Dec-1988	15-May-1998	7-Apr-2008	S
Eprosartan[a]	Hypertension	22-Dec-1997	23-Aug-1999	11-Oct-2008	S
Moxonidine[a]	Hypertension	NA	15-Sep-1997	27-Feb-2007	
Cholestyramine[a]	Hypercholesterolemia	3-Aug-1973	25-Jul-1988	30-Mar-2006	S
Bemiparin	Venous thromboembolism	NA	A	8-Jun-2006	
Imidapril	Hypertension	NA	A	23-Feb-2004	
Metolazone	Hypertension	27-Nov-1973	A	23-Apr-2003	S
Torsemide	Hypertension	23-Aug-1993	NA	9-Jun-2003	S
Bendroflumethiazide	Hypertension	7-Dec-1959	A	24-Jul-2003	S
Tirofiban[a]	Acute coronary syndrome	14-May-1998	15-Jul-1999	12-Aug-2003	P
Trandolapril[a]	Hypertension	26-Apr-1996	25-Nov-1992	3-Oct-2003	S

Table 2 – (continued)

Generic name (INN)	Indication	US approval date	EU approval date	India approval date	US review classification
Fluvastatin[a]	Dyslipidemias	31-Dec-1993	23-Aug-1993	25-Nov-2003	S
Fosinopril	Hypertension	16-May-1991	A	10-Jan-2002	S
Lercanidipine	Hypertension	NA	22-Mar-1996	7-May-2002	
Quinapril[a]	Hypertension	19-Nov-1991	3-Aug-1990	19-Sep-2002	S
Telmisartan	Hypertension	10-Nov-1998	16-Dec-1998	25-Nov-2002	S
Triflusal	Prophylaxis of thromboembolic disorders	NA	A	17-Jan-2001	
Clopidogrel	ACS, MI, PVD, Stroke	17-Nov-1997	15-Jul-1998	22-Feb-2001	P
Valsartan[a]	Hypertension	23-Dec-1996	31-Oct-1997	10-Dec-2001	S
Trapidil	Adjunct in angioplasty	NA	A	11-May-2000	
Cerivastatin	Dyslipidemias	26-Jun-1997	A	11-May-2000	S
Irbesartan	Hypertension	30-Sep-1997	27-Aug-1997	26-Jun-2000	S
Candesartan[a]	Hypertension	4-Jun-1998	15-Dec-1998	31-Aug-2000	S
Pravastatin[a]	Dyslipidemias	31-Oct-1991	31-Oct-1997	20-Dec-2000	S
Doxazosin	Hypertension	2-Nov-1990	A	11-Mar-1999	S
Milrinone[a]	Acutely decompensated heart failure	31-Dec-1987	11-Oct-1989	17-May-1999	S
Atorvastatin[a]	Dyslipidemias	17-Dec-1996	8-Sep-1997	17-Sep-1999	P
Fenofibrate[a]	Dyslipidemias	31-Dec-1993	1-Nov-1993	22-Dec-1999	S

INN: international nonproprietary name, NA: not available, A: available, but approval date is not known, ADH: antidiuretic hormone, PTCA: percutaneous transluminal coronary angioplasty, ACS: acute coronary syndrome, MI: myocardial infarction, PVD: peripheral vascular diseases, P: Priority review drug, S: Standard review drug, O: Orphan drug.
a UK approval date.

There are examples of some contradictory approvals by the FDA and EMA. European Medicines Agency did not authorize nesiritide, awaiting longer-term data on renal side effects and mortality and a large randomized study. However, nesiritide was approved by the FDA in 2001 with similar data.[7] There was criticism about pro industry culture in the FDA that favored drug approval than its European counterparts. One of the reasons that might contribute to this culture is the prescription drug user fee act of FDA, which has allowed industry sources to direct funding to the FDA to help speed new drug approval.[11] The average approval time dropped from 27 months in 1993, when user fees were instituted, to 19 months in 2001.[12] The FDA didn't approve a new combination of niacin and laropiprant, an agent to prevent flushing. However, the same combination is approved by the EMA and DCGI.

In August 2001, cerivastatin was removed from the world market because of a higher risk of rhabdomyolysis associated with its use in comparison with other statins.[13] Safety-based withdrawals of drugs or their labels, however, show a beneficial aspect of the drug lag. A typical example is Rofecoxib, which was withdrawn from the market because of its association with cardiovascular problems in September 2004.[14] In the area of psychiatric drugs, the black box warnings of antidepressants for children[15] and of antipsychotics for the elderly with dementia[16] are cases where the drug lag has helped patients to avoid exposure to potentially harmful drugs. The general public as well as most healthcare professionals believe that the drug lag is always bad for patients, but its impact on health outcomes is unknown.

A study of the therapeutic significance of the drug lag in the USA in the 1970s[17] showed that only 14% of 198 drugs reviewed offered a potential therapeutic advance, whereas 75% appeared to offer little or no advance. There is a large gap between India and the west with regard to timing of approval of new cardiovascular drugs. This may be because the US or Europe based companies were not interested to introduce the new cardiovascular drugs 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 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. However, there is a need to improve the regulatory processes in India to enhance the clinical trials 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.[18] There is an urgent need to increase the human resources and improvement in the regulatory processes in India.

Due to the limitations of this study, it is not possible to make an analysis of the possible reasons behind the delays in approval of new cardiovascular drugs in India. 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 this lag in approval of cardiovascular drugs in India.

In conclusion, this study confirms that there is still a large gap between India and the West with regard to access to new cardiovascular drugs. 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. The impact of the drug lag on health outcomes remains to be established. To reduce drug lag, combined efforts are required by the Indian regulatory agency and pharmaceutical companies.

Conflicts of interest

All authors have none to declare.

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