

ORIGINAL ARTICLE

DRUG LAG FOR ANTIMICROBIAL AGENTS: COMPARISON OF THE US, EU AND INDIA APPROVALS

Kataria Bhaven C¹, Mehta Dimple S², Mehta Sanjay J³

¹Assistant Professor, ²Professor & Head, Pharmacology Department, ³Professor & Head, Microbiology Department, C.U. Shah Medical College, Surendranagar, Gujarat, India

Correspondence:

Dr. Bhaven C. Kataria, E-mail: drbkataria@gmail.com

ABSTRACT

Background: Antimicrobial resistance is a global problem and the need for new antimicrobial agents is greater in both developed and developing nations. However, there is a difference in timing of introduction of new antimicrobial agents between India and developed markets.

Aim: Assess the drug lag for new antimicrobial agents approved in the United States, European Union and India.

Materials and Methods: The new antimicrobial 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 antimicrobial agents approved in the three regions.

Results: Of the 70 new antimicrobial agents, 59 (84.28%) were approved in the United States, 59 (84.28%) in the European Union and 58 (82.85%) in India. The median approval lag for India (39.7 months) was substantially high as compared to the United States (0 month) and European Union (6.5 months).

Conclusion: This study confirms that India's drug lag in the case of new antimicrobial agents is quite substantial. Further detailed analyses are necessary to find the background factors and impacts of drug lag for antimicrobial agents in India.

Keywords: Drug approval, Drug lag, Regulatory authority, New drug development

INTRODUCTION

Numerous studies have shown that the frequency of multidrug-resistant isolates is increasing in India and throughout the world.¹⁻⁷ The emergence of multidrug-resistant bacteria has created a situation in which there are few or no treatment options for infections with certain microorganism. Antibiotic use has been increasing in India.⁸ The units of antibiotics sold have increased by about 40 per cent during the period of 2005-2009. In the same five-year period cephalosporins sales were increased by 60 per cent.⁹ The need for new antimicrobials is increasing as there is increasing the development of resistance by microorganism.

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. Drug lag has been a debated issue in the United States (US) and Europe during the 1970s and 1980s.¹⁰⁻¹¹ However, the drug lag issue has not been studied extensively 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 large multinational pharmaceutical companies primarily target major markets like the United States and Europe for sales of their new drugs. However, antimicrobial resistance, a global problem, is particularly pressing in developing countries where the infectious disease burden is high.¹² The drug options for treatment of infections are increasingly limited, there should not be much delay in the approval of new antimicrobial agents in India. Therefore, a study was undertaken to assess the drug lag for new antimicrobial agents approved in the US, European Union (EU) and India.

MATERIALS AND METHODS

New antimicrobial 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).¹³

2. The EU: The European Public Assessment Report (EPAR), Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMA).¹⁴

3. India: The Central Drugs Standard Control Organization (CDSCO), List of drug approved for marketing in India.¹⁵

The list of approved drugs was available from 1999 through 31st December 2011 for the US, EU and India. Information about name of approved drug, indication and date of issue of marketing approval was retrieved from the above sources. Then analyses were performed to categories new antimicrobial agents into antibacterial, antiviral, antifungal, and antiparasitic agents.

New antimicrobial agents were defined as chemical compounds that had not previously been approved by the FDA, EMA and CDSCO in any formulation, possess antimicrobial activity and were indicated to treat systemic infections. Combination agents (e.g., Artemether/Lumefantrine) were only considered new antimicrobial agents if ≥ 1 of the components had not been previously approved. Topical antimicrobials, antimicrobials for veterinary use, vaccines, antibodies, and immunomodulators were not considered new antimicrobial agents.

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 antimicrobial agents in each region out of a total of new antimicrobial agents approved either in the three regions in the study period. In assessing relative drug lag, the variable was the approval lag against the first approval granted to each antimicrobial agent in the three regions. For example, if the US was the first to approve an antimicrobial agent in January 2005 and if India approved the same antimicrobial agent in October 2005, 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 antimicrobial agents approved in each region, and the median approval lag was calculated for each region. The new antimicrobial agents for which approval dates were unknown were excluded from the calculation of median approval lag.

RESULTS

We identified 70 new antimicrobial agents approved either in the US, the EU, or India between 1999 and 2011. Of these 70 new antimicrobial agents, 20 were mutually approved in the three regions. The US and the EU approved 12 antimicrobial agents that were not

approved in India. The EU and India approved 11 antimicrobial agents that were not approved in the US. The US and India approved 11 antimicrobial agents that were not approved in the EU.

Absolute drug lag

The absolute drug lags for the US, the EU and India are shown in Table 1. Of the 70 new antimicrobial agents, 59 (84.28%) were approved in the US, 59 (84.28%) in the EU and 58 (82.85%) in India.

Table 1: Absolute and Relative Drug Lag of New Antimicrobial Agents for the US, the EU and India (n= 70)

	US	EU	India
Approvals	59 (84.28)	59 (84.28)	58 (82.85)
Median approval lag (months)	0 (n= 38)	6.5 (n= 32)	39.7 (n= 55)

(Figure in parenthesis shows percentage)

Table 2: Distribution of Different Types of Antimicrobial Agents Approved in the US, EU and India

	No. of Approvals		
	US	EU	India
Antibacterials	13	6	23
Antivirals	19	20	22
Antiparasitics	3	1	7
Antifungals	5	5	5

Total 57 new antimicrobial agents were approved in India during the period of 1999 to 2011, with an average of 4.38 new antimicrobial agents approved per year. Out of these total 57 new antimicrobial agents, 23 (40.35%) were antibacterials, 22 (38.59%) were antivirals, seven (12.28%) were antiparasitics and five (8.77%) were antifungals (Table 2). For the same period total 40 new antimicrobial agents were approved in the US, with an average of 3.07 antimicrobial agents approved per year and in the EU total 32 new antimicrobial agents were approved, with an average of 2.46 antimicrobial agents approved per year.

Relative drug lag

The relative drug lags for the US, the EU and India are summarized in Table 1. The median approval lag for India (39.7 months) was substantially high as compared to the United States (0 month) and European Union (6.5 months). The distributions of approval lags for each region are shown in Figure 1. Although the approval lag was less than 1 year for most of the antimicrobial agents for the US and the EU, India had a different distribution profile. The ten new antimicrobial agents were approved in India within first 12 months of drug lag interval and showed a wide distribution up to nearly 215 months (Figure 1).

Overall number for approval of new antimicrobial agents was higher in India as compared to the US and EU during 1999-2011 (40 for US, 32 for EU and 57 for India). But this trend is declining in last two years

(Figure 2). In last two years, four new antimicrobials were approved in the US and five in the EU while in India only two new antimicrobials were approved. One anti-HIV agent (Raltegravir) was approved in 2010 and one antimalarial agent (Arterolane/Piperaquine) was approved in 2011 in India. Out of four new antimicrobial agents approved in the US in last two years, three were antiviral agents (Rilpivirine, Boceprevir and Telaprevir) and one was antibacterial agent (Ceftaroline). Of the five new antimicrobial agents approved in the EU in last two years, three were antiviral agents (Rilpivirine, Boceprevir and Telaprevir),

one was antibacterial agent (Telavancin) and one was antimalarial agent (Piperaquine/Dihydroartemisinin). Overall higher number for approval of new antimicrobial agents in India during the period of 1999 to 2011 indicates that the Indian pharmaceutical companies took the advantage of process patent in India before 2005 and introduced generic copies of new antimicrobial agents developed by the foreign multinational companies. However, there is a substantial delay in approval of these antimicrobial agents in India as indicated by the relative drug lags for the US, EU and India (Table 1).

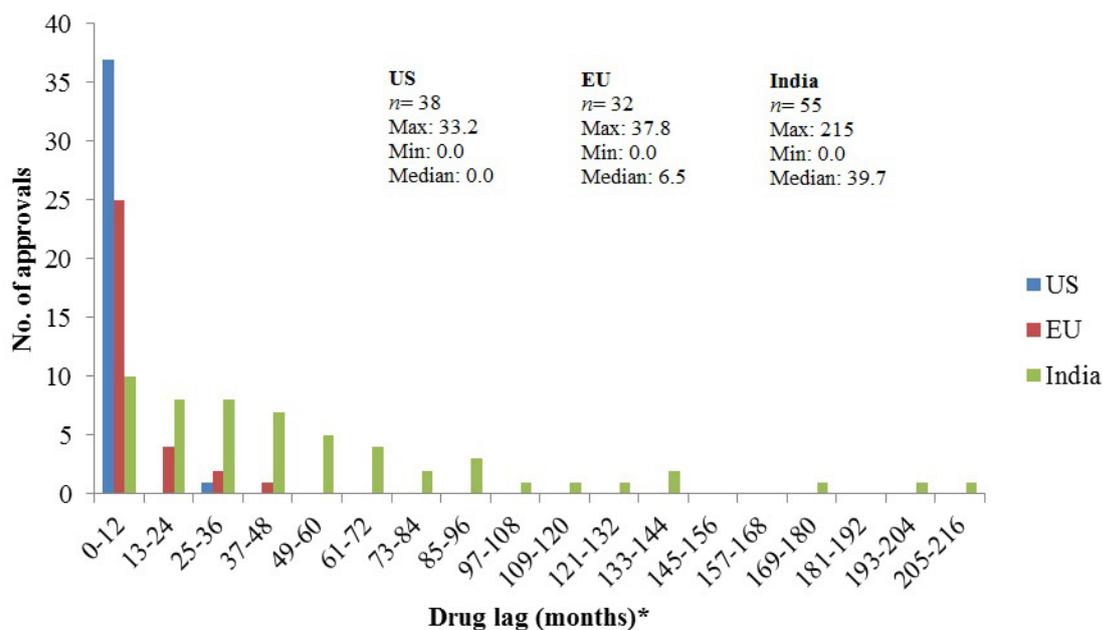


Figure 1: Distribution of drug lag for new antimicrobial agents approved in the US, EU and India
*The distribution is shown in 12-month interval

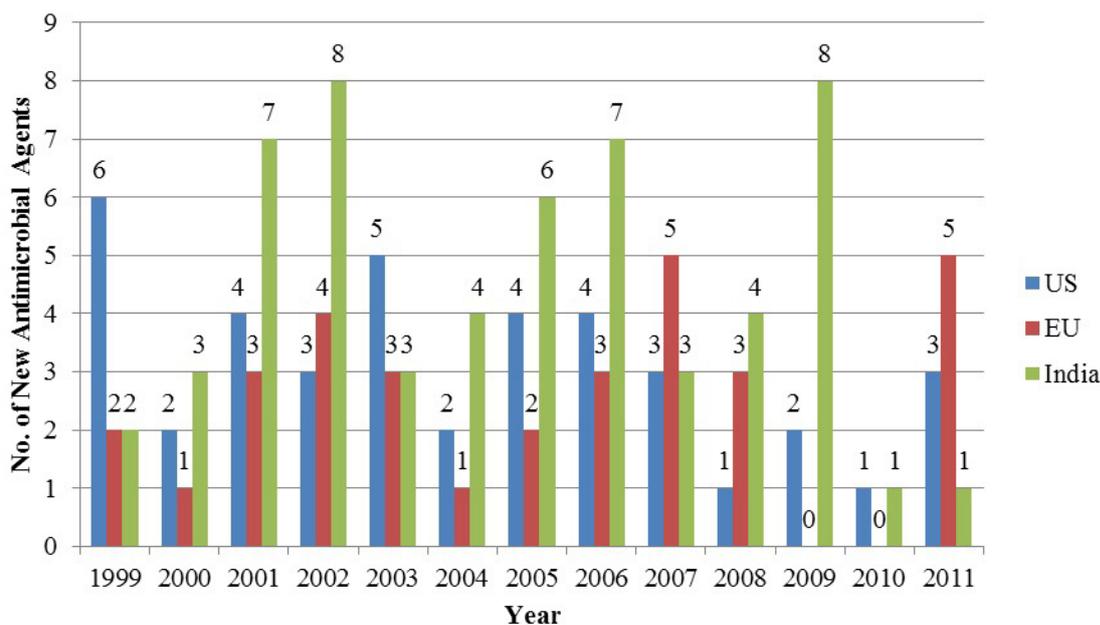


Figure 2: New antimicrobial agents approved in the US, EU and India, 1999-2011

Out of total 57 new antimicrobial agents approved in India during the period of 1999 to 2011, antibacterial group was top with a total approval of 23 for new antibacterial agents. However, no single approval for antibacterial agent in last two years in India shows a declining trend of antibacterial drug development. In the US and EU, the number for approval of antiviral agents was higher as compared to the approvals for antibacterial agents (Table 2). Gatifloxacin was approved by the US FDA in Dec 1999, but after reports of safety issues Gatifloxacin tablets, injections, and oral suspension, were withdrawn from sale in 2008.¹⁶⁻¹⁷

The US approved one antimicrobial agent (Ceftaroline) that was not approved either by the EU or India; The EU approved one antimicrobial agent (Piperaquine/Dihydroartemisinin) that was not approved by the US or India; and India approved eight antimicrobial agents (Arterolane/Piperaquine, Artesunate/Amodiaquine, Balofloxacin, Pazufloxacin, Faropenem, β -arteether, Cefetamet pivoxil and Bulaquine) that were not approved by the US or the EU. Of the 12 antimicrobial agents that were not approved in India, four antimicrobial agents were antibacterials (Ceftaroline, Telavancin, Telithromycin and Quinupristin/Dalfopristin), one was antiparasitic agent (Piperaquine/Dihydroartemisinin) and seven antimicrobial agents were antivirals.

Of the 22 new antiviral agents approved in India from 1999 through 2011, 12 antiviral agents were anti-HIV agents (Raltegravir, Darunavir, Maraviroc, Atazanavir, Emtricitabine, Tenofovir, Abacavir, Indinavir, Efavirenz, Nelfinavir, Nevirapine and Didanosine). Of the 19 new antiviral agents approved in the US from 1999 through 2011, 12 antiviral agents were anti-HIV agents (Raltegravir, Etravirine, Maraviroc, Raltegravir, Darunavir, Tipranavir, Enfuvirtide, Atazanavir, Emtricitabine, Tenofovir, Lopinavir/Ritonavir and Amprenavir). Two new anti-Hepatitis C agents (Boceprevir and Telaprevir) were approved in the US and EU in 2011.

DISCUSSION

The percentage of approval of new antimicrobial agents was more than 80% for the US, EU and India. Thus, there was no big difference among the three regions in terms of absolute drug lag. The US was the first to approve the majority of the new antimicrobial agents, and the EU was slightly delayed (Median approval lag: 6.5 months). But, the considerable delay was observed for India in approval of new antimicrobial agents. The median approval lag for India (39.7 months) was 3.3 years longer than that for the US (0 month) and 2.76 years longer than that for the EU (6.5 months). While our study showed that the US was first to approve majority of new antimicrobial 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. Due to the limitations of this study, it is not possible to make an analysis of the possible reasons behind these delays.

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 antimicrobial agents in India. This may be because the US or Europe based companies were not interested to introduce these new antimicrobial agents through their subsidiaries in India due to relaxed patent law in India before 2005. The drug lag for antibacterials like Meropenem and Imipenem was 5.6 years and 17.9 years, respectively. Although we have not assessed the impacts of drug lag in India for antimicrobial agents, it is obvious that many lives would have been saved by reducing the drug lag in India. The infectious disease burden in India is among the highest in the world.¹⁸ Resistance of common gram-positive and gram-negative bacteria to the least expensive antibiotics is common in both India and the United States.¹⁹ Therefore, the need for antimicrobial agent is as important in India as in the US or Europe.

There is a change in the regulatory environment after a system of product patents in India since 2005.²⁰ 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). Antimicrobial drug development is a risky and unpredictable process.²¹ 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.

CONCLUSION

The new antimicrobial agents' approval data of the three regions confirm that India's drug lag in the case of new antimicrobial agents is quite substantial. The drug lag in India may be attributed to a longer regulatory review period, late submission of NDA or a delay in the start of development. Further detailed analyses are necessary to find the background factors responsible for drug lag in India and assess the impacts of drug lag for antimicrobial agents.

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