

# An evaluation of drug lag for new drugs approved by the Indian regulator relative to the United States, European Union, and Japanese regulatory agencies: A 15-year analysis (2004–2018)

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## Abstract

**Background:** The approval process of every drug regulatory agency differs, and hence, the time required for the approval of a new drug varies. This results in a drug lag and India is no exception to this phenomenon. A drug lag precludes Indian patients from accessing new medicines at the same time as they are approved elsewhere. Against this backdrop, we assessed the absolute and relative drug lags of the Indian regulator relative to three regulators in mature markets, namely United States (US), European Union (EU), and Japan.

**Methods:** International nonproprietary names were used to identify new drugs. Their dates of approval (2004-2018) from the online database of four regulatory agencies were identified. Both absolute and relative drug lags were calculated for India as compared to US, EU, and Japan as well for all the agencies relative to the Indian regulator.

**Results:** We identified a total of 453, 473, 424, and 472 new drugs approved over the study period in India, US, EU, and Japan, respectively. The absolute drug lag of Central Drugs Standard Control Organization (CDSCO) was 19 and 18 relative to the US Food and Drug Administration (FDA) and Japan Pharmaceuticals and Medical Devices Agency (PMDA), respectively. The relative drug lag for the CDSCO *vis-a-vis* the US FDA, European Medicines Agency, and PMDA was 43.2 (2.1–1287.8), 25.6 (0.03–1310.5), and 30.3 (1.2–1242) months, respectively.

**Conclusion:** Our study shows a significant drug lag between India and other three developed nations (US, EU, and Japan). However, in some therapeutic areas, Indian regulator has proactively approved new drugs much before other agencies. The New Drugs and Clinical Trials Rule of 2019 has brought hope for reduction in drug lag in the near future.

**Keywords:** Absolute drug lag, Central Drugs Standard Control Organization, European Medicines Agency, Pharmaceuticals and Medical Devices Agency, relative drug lag, United States Food and Drug Administration

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## INTRODUCTION

A drug lag is defined as the delay in making a drug available in a certain market/country relative to another region/country.<sup>[1]</sup> This lag can be of two types: relative and absolute. The metric for the former is time, i.e., the delay (months/years) in introduction of the drug between one country and another. Absolute drug lag is measured as the actual numbers or the quantity of drugs available – a comparison of the total number of new drug approvals in different countries in a defined time period.<sup>[2]</sup>

Several studies beginning with the first one conducted in 1970 by Wardell<sup>[3]</sup> have brought to the fore the challenges presented by a drug lag.<sup>[4]</sup> In India, for example, Kataria *et al.* evaluated 75 new cardiovascular drug approvals between 1999 and 2011 and compared three regulators – the United States Food and Drug Administration (US FDA), European Union (EU), and the Indian regulator, the Central Drugs Standard Control Organization (CDSCO). They found a mixed pattern of approval across the regulators. Regulators in the US and EU approved 19 drugs not approved in India, EU and CDSCO approved 14 drugs not approved in the US, and US and CDSCO approved 10 drugs not approved in the EU. The relative drug lag in India ranged from 24 to approximately 400 months.<sup>[5]</sup>

The presence of a drug lag significantly hampers access to new drugs for patients and adds to the already existing burden of disability-adjusted life years (DALYS), where India's global contribution is a fifth.<sup>[1]</sup> To cite an example, bedaquiline for multidrug-resistant tuberculosis that was accorded approval by the US FDA on December 28, 2012, received the CDSCO approval only on January 14, 2015.<sup>[6]</sup> The impact of a drug lag is greater in India because of a higher disease burden,<sup>[7]</sup> health-care expenditure that is largely out of pocket, and limited research and development (R and D) by the local pharmaceutical industry.<sup>[8]</sup>

An evaluation of drug lag (both relative and absolute) in a country would help identify the extent of the problem and potentially offer insights as to how to address it. The present study was thus carried out with the primary objective of evaluating the drug lag for new drugs approved in India relative to drugs approved in three mature markets – the US, EU, and Japan over a 15-year period.

## METHODS

### Ethics

As the data for the study were available in the public domain, our institutional ethics committee exempted the study (EC-OA-155–2017) from review.

### Time frame and choice of the regulator

New drug approvals by the four regulators – The Indian regulator, CDSCO from a low and middle-income country was compared with regulators from three mature markets – the US (US FDA), Pharmaceuticals and Medical Devices Agency (PMDA), Japan, and European Medicines Agency (EMA) over the time period 2004–2018.

### Definition of a new drug

A new drug was defined as one having an active ingredient containing no active moiety that has been previously approved in India, US, EU, and PMDA. This could be a new chemical entity or new molecular entity or a biologic.<sup>[9–11]</sup>

### Data sources

International nonproprietary name (INN) was used to identify new drugs approved in the four regions using the following databases:

- 1 India – CDSCO website (list of approved new drugs) ([https://cdsco.gov.in/opencms/opencms/en/Approval\\_new/Approved-New-Drugs/](https://cdsco.gov.in/opencms/opencms/en/Approval_new/Approved-New-Drugs/))<sup>[12]</sup>
- 2 US – drugs@FDA and CenterWatch – [https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products](https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products;https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products)<sup>[13,14]</sup>
- 3 EU – EMA website (the European Public Assessment Report) – [https://www.ema.europa.eu/en/documents/scientific-guideline/draft-reflection-paper-chemical-structure-properties-criteria-be-considered-evaluation-new-active\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/draft-reflection-paper-chemical-structure-properties-criteria-be-considered-evaluation-new-active_en.pdf)<sup>[15]</sup>
- 4 Japan – PMDA website (list of Approved products) – [http://www.jpma.or.jp/english/parj/pdf/2017\\_ch03.pdf](http://www.jpma.or.jp/english/parj/pdf/2017_ch03.pdf)<sup>[16]</sup>

Information collected from these databases was INN, date of marketing authorization, and the therapeutic area. If there were multiple indications for the same INN, the therapeutic area was selected based on the indication for which the drug was approved for the first time. The therapeutic areas were then classified into cardiovascular, oncology, pulmonology, gastrointestinal, endocrinology, neurology, hematology, urogenital, immunology/dermatology, and miscellaneous (ophthalmology, radiodiagnosis, radiation therapy, diagnostic agents, and genetic drugs). For drugs which were not available in the PMDA database, the date of approval was retrieved from scientific journals. The date of approval was taken as January 1 if only the year of approval was mentioned, to maintain uniformity.

## Eligibility criteria

### Inclusions

All new drugs approved by any regulator were included. For fixed dose combinations, the drug/drugs which are new as per the above listed definition were included in the analysis.

### Exclusions

Vaccines, vitamins, plant products, and new formulations of drugs (approved before 2004) for the same indication were excluded from the analysis.

### Outcome measures

These included (a) total number of drug approvals in the 15-year period by all regulators, (b) total number of drugs during the study period which received approval from individual regulators, (c) Total number of drug approvals per year per regulator (absolute drug lag), (d) relative drug lag (in months) for individual drugs by the Indian regulator relative to other regulators, (e) therapeutic area of approval of all new drugs, and (f) analysis of the first regulator that approved any new drug.

We also evaluated if drugs approved by any regulator before 2004 had received approval from another regulator after 2004.

## Statistical analysis

Descriptive statistics were used to analyze the data. The new drug approvals in the 15-year period were totaled, and approvals by individual regulators were expressed as proportions as also the therapeutic area of approval. Absolute drug lag was expressed as median (range) as also a difference in the number of approvals per country. Relative drug lag was expressed in months as median (range). Microsoft Excel Version 16.0 was used for data analysis.

## RESULTS

### Demographics

The total number of new drug approvals by any regulator was  $n = 953$ . The largest number of new drug approvals was by the US FDA ( $n = 473$ ), followed by PMDA Japan ( $n = 472$ ), the CDSCO ( $n = 453$ ), and EU ( $n = 424$ ). The year-wise distribution of new drugs approved by the four regulators is given in Table 1. Only  $n = 221/953$  (23.2%) drugs were approved by ALL regulators. A total of  $n = 263$  drugs that were approved by any regulator after 2004 had received approval from another regulator before 2004.

### Absolute drug lag

The number of drugs (median [range]) approved

per year per regulator was 27 (18–59), 31 (14–42), 32 (16–55), and 32 (9–47) for US FDA, EMA, PMDA, and CDSCO, respectively. The absolute drug lag identified for CDSCO relative to US FDA (taken because of the largest number of drug approvals by any regulator) was 19 new drugs. However, of  $n = 473$  new drugs approved by the US FDA during this period, only  $n = 193/473$  (40.8%) drugs were approved by CDSCO. Similarly, the number of drugs approved by CDSCO was  $n = 207/424$  (48.8%) and  $n = 276/472$  (58.5%) with respect to EMA ( $n = 424$ ) and PMDA ( $n = 472$ ) during the study period.

### Relative drug lag

The relative drug lag for the CDSCO *vis-a-vis*, the US FDA, EMA, and PMDA was 43.2 (2.1–1287.8), 25.6 (0.03–1310.5), and 30.3 (1.2–1242) months, respectively. However, it was also seen that some drugs were approved by CDSCO ahead of all other regulators [Table 2]. The relative drug lag of US FDA, EMA, and PMDA compared to CDSCO was 21 (0.8–149.4), 6.6 (0.2–65.1), and 27.3 (0.1–152.9) months, respectively.

**Table 1: New drugs approved by FDA, EMA, PMDA and CDSCO between 2004-2018**

Year of Approval	CDSCO	FDA	EMA	PMDA
2004	24	36	23	16
2005	38	18	14	17
2006	34	22	19	22
2007	47	18	36	30
2008	37	23	23	33
2009	41	26	31	23
2010	42	21	16	32
2011	27	30	26	33
2012	21	39	23	39
2013	9	27	32	30
2014	21	41	33	55
2015	20	45	42	34
2016	33	22	31	50
2017	32	46	37	24
2018	27	59	38	34
Total	453	473	424	472

**Table 2: Relative Drug Lag (in months) viz CDSCO vs Other regulators based on therapeutic areas**

Therapeutic Areas	FDA	EMA	PMDA
Oncology	20.1[3.7-376.2]	21.2[0.2-1310.5]	13.3[2.7-117]
Neurology	65.9[3-752.4]	38.3[3.7-195.5]	65[8.3-1224]
Infectious disease	34.6[4.8-177.4]	25.7[4.2-134.8]	34.6[2.6-215.2]
Endocrinology	72[2.9-675.8]	20.9[0.8-200]	18.6[5.7-297.4]
Immunology/ Dermatology	73.4[4.9-1284]	44.2[5.1-134.5]	45.8[5.8-78.4]
Haematology	24.5[2.1-249.1]	15.3[0.8-256]	8.3[1.2-108.2]
Cardiology	75.8[3.2-690]	42.5[7.9-182.8]	85.7[10.8-1242]
Pulmonology	45.4[12.8-305.5]	28.2[0.03-86.5]	48.5[10.1-198.2]
Gastroenterology	43.1[23-1287.8]	25.6[18-91.2]	120[14.7-162.4]
Uro-Nephrology	42.5 [9.3-165.8]	60.4[17-140.1]	31.5[2.6-84.2]
Miscellaneous	76.9[13.9-375.6]	60.1[0.2-200.4]	47.2[3.4-445]

### Therapeutic area of approvals

The largest number of approvals ( $n = 357$ ), uniformly, across all regulatory agencies was in the area of oncology. This was followed by the therapeutic areas of neurology ( $n = 254$ ) and infectious diseases ( $n = 240$ ). The CDSCO had the highest number of approvals for neurology ( $n = 84$ ), followed by oncology ( $n = 61$ ) and then infectious diseases and endocrinology ( $n = 56$  and  $n = 45$ , respectively). Details of approvals in individual therapeutic areas according to individual regulators are given in Figure 1.

### First regulator that approved any new drug

The US FDA had the largest number of “first approvals” ( $n = 361/473$ ; 76.3%), followed by the EMA ( $n = 126/424$ ; 29.7%), PMDA ( $n = 102/472$ ; 21.6%), and CDSCO ( $n = 65/453$ ; 14.3%), and the US FDA had the largest “first approval” of drugs in all the therapeutic areas except in hematology and urology/nephrology where EMA had the highest “first approvals.” The details of “first approvals” are shown in Table 3.

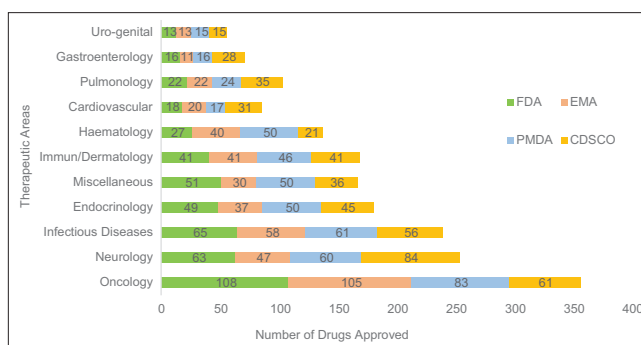
### First approval by the Indian regulator (relative to other regulators)

A total of  $n = 96$  drugs received approval first by the Indian regulator relative to the other three regulators ( $n = 26$  vs. US FDA,  $n = 23$  vs. EMA, and  $n = 67$  vs. PMDA). Representative examples of these approvals by CDSCO include apixaban (cardiology, relative to US FDA), crizotinib (oncology, relative to EMA), and sofosbuvir (infectious diseases, relative to PMDA).

## DISCUSSION

Our study evaluated drug lag over a 15-year period and analyzed the approvals by CDSCO relative to the US FDA, EMA, and PMDA and found that the Indian regulator largely lagged behind the other three regulators. With regard to absolute drug lag (total number of drugs approved over the 15-year study period), CDSCO was third behind the US FDA and PMDA and only slightly ahead of EMA. The relative drug lag for the Indian regulator was more than 2 years with regard to the EU and close to 3 and 4 years with regard to the Japanese and US regulators, respectively.

The relative drug lag seen with CDSCO was the highest for the therapeutic areas of immunology, infectious diseases, and neurology. For example, Golimumab, a highly prescribed drug for rheumatoid arthritis worldwide, was cleared by CDSCO Five years after the US FDA approval. Anti-infectives such as ceftaroline, ceftazidime/avibactam, and ceftolozane/tazobactam also took more than 3 years to be available in Indian market as compared to the other



**Figure 1:** New Drugs approved by all Regulatory agencies – classified per therapeutic area (2004-18)

**Table 3:** Number of drugs approved first by either of the regulatory agencies between 2004-2018

Therapeutic Areas	FDA	EMA	PMDA	CDSCO
Oncology	98	16	9	2
Neurology	44	23	5	19
Infectious Disease	51	12	21	7
Endocrinology	27	15	15	3
Immunology/Dermatology	28	9	10	5
Haematology	18	20	18	1
Cardiology	12	6	1	5
Pulmonology	17	3	2	8
Gastroenterology	19	3	5	7
Uro-Nephrology	2	7	5	2
Miscellaneous	45	12	12	6

three markets. Drugs such as ustekinumab (US FDA 2009) for psoriasis, boceprevir (US FDA 2011), glecaprevir/pibrentasvir (US FDA 2017), and several antihepatitis C drugs are not yet available in the Indian market. This is alarming given the heavy burden of these diseases in the Indian population.<sup>[17,18]</sup> This indicates that the pace of approval of new drugs in India falls short of regulators from mature markets and will preclude our patients from gaining timely access to new drugs.

Optimizing time to approval is a challenge for any regulator regardless of the country which they serve. CDSCO approved the drug pirfenidone (for idiopathic pulmonary fibrosis [IPF]) in 2010, Four years before the US FDA approved it. The current estimate of patients with IPF in India is 130,000, and the early approval of this drug by our regulator will improve access and decrease the DALYs with this difficult-to-treat disease.<sup>[19]</sup>

The R and D for new drugs worldwide primarily focuses on oncology rather than other therapeutic areas.<sup>[20]</sup> This is reflected by the fact that regulators from all three mature markets uniformly had the highest approvals in oncology. CDSCO had drug approvals in oncology as the second largest therapeutic area. This correlates with the analysis by Chaturvedi M *et al.* of the Clinical Trials Registry of India, which shows the highest number of oncology trials



conducted in India, though neoplastic diseases ranked sixth in terms of DALYs.<sup>[21]</sup>

CDSCO had a number of “first approvals” ( $n = 65$ ) to its credit. An analysis of these approvals showed that most of the drugs were developed and first approved outside India in countries, such as Korea (for example, ilaprazole [in dyspepsia and peptic ulcer disease] or gemigliptin [as antidiabetic]) and in select European countries (for example, cerebrolysin [in stroke] or udenafil [in erectile dysfunction]).<sup>[22-25]</sup> India is not well geared yet for new drug development in terms of facilities/human resources or even investment, and this is reflected in the lack of innovative drug approvals by CDSCO. India had rather few innovative approvals of medicines made within the country, for example, saroglitazar (hypertriglyceridemia), itolizumab (psoriasis), and anti-rabies monoclonal antibody (for category III animal bites).<sup>[26-28]</sup> Given that we do not have information on when the submissions (for approval) for these products were made to the CDSCO, it is difficult, if not impossible, to obtain a “time to approval” for drugs that have come from within the country. This also precludes an “apple to apple” comparison of products reviewed by the CDSCO with regulators from the mature markets. The process of approval is estimated to have a time frame of 12–18 months<sup>[29]</sup> although no specific time limit is prescribed by the regulator in the country.

The differences in drug approvals across regulators represent a complex interplay of several factors.<sup>[28]</sup> Both US-FDA and EU have a fast track approval system (priority review, accelerated approval, and conditional marketing) based on estimates of the disease burden which helps early introduction of new drugs. PMDA’s recent guidelines also facilitate expedited new drug approval. This provides the necessary impetus to the local pharmaceutical industry to invest in R and D.<sup>[30-33]</sup> Unlike regulators from mature markets where drug approvals are based on only on critical appraisal of data on innovative products, CDSCO’s drug approvals are based on a mix of analysis of data produced elsewhere and some data generated within the country by the Indian pharmaceutical industry and viewing it in the context of the country’s unmet need, benefit risk, and disease burden. However, an important issue that the CDSCO needs to address is the method of review and approval of new drugs as evidenced by the disparity in the review process in the various Subject Expert Committee (SEC) of the Government of India.<sup>[34]</sup> The New Clinical Trials Rules of 2019 address this to a certain extent by giving a 60-day period for the expert committees to submit their review.<sup>[35]</sup> In addition, the New Drugs and Clinical Trial Rules, 2019 has a newly introduced accelerated

approval process and expedited review process (albeit without timelines) with an aim to accelerate access to drugs related to rare or neglected disease or in emergency conditions. The impact of these rules on drug lag will be seen in the coming years.<sup>[35]</sup>

In mature markets, drugs discovered in the laboratories of academic institutions and universities are picked up by the pharmaceutical industry for development.<sup>[36-38]</sup> India too has various organizations such as Indian Council of Medical Research, Department of Biotechnology, and Department of Science and Technology that fund drug development research. It is important that drugs from this research are picked up by the Indian pharmaceutical industry to provide an impetus to the country’s meager R and D.

Our study is limited by the fact that we have not identified the determinants of drug lag such as the timeline to obtain certificate of pharmaceutical product, submission and review time lag between various regulators, difference in their guidelines, and financial commitment of pharmaceutical companies.<sup>[1,39]</sup> We have also not included vaccines in our analysis.

## CONCLUSION

Our study shows a significant drug lag between India and three mature markets (US, EU, and Japan). The New Drugs and Clinical Trials Rules of 2019 has brought hope for reduction in drug lag in the near future.

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Nil.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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