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### Impact of India's formulation and bulk drug registrations with U.S. FDA on its exports: A stochastic analysis

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#### ABSTRACT

*Indian pharmaceutical industry has become one of the world leaders in affordable and quality production of generic medicine. India is strategically well positioned to emerge as 'Health Keeper' of the world with its diverse advantages and continuous development of the pharma sector. In view of the growing importance of the Indian pharma research front, we have conducted a stochastic analysis/research and this article attempts to answer whether India would continue to play an important role in global pharmaceutical trade and what are the necessary policy interventions required for its future sustainability and growth.*

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#### INTRODUCTION

In the recent past Indian Pharmaceutical sector has emerged not only as an undisputed champion among Indian industries but also as a major global player challenging leading pharmaceutical manufacturing countries in the area of generics. Statistics available from Ministry of Statistics and Programme Implementation (MOSPI), Government of India and balance sheets of major Indian pharmaceutical companies reveal that these companies contributed 11.77% [1] of India's manufacturing sector GDP (at factor cost, current prices) in the year 2008-09 [2] or 1.86% of the country's GDP. Indian pharmaceutical exports have risen sharply in the recent years not only to the regulated markets such as USA and European Union (EU) [3] but also to developing countries and Least Developed Countries (LDCs). [4] India currently produces 20% of global

generics [5]. India's exports of Drugs, pharmaceuticals & fine chemicals stood at US\$8-61bn. during the year 2008-09 growing at a compounded annual growth rate (CAGR) of 21.98% during the five year period of 2004 to 2009 [6].

Indian Pharmaceutical industry has evolved from nonexistent to become one of the world leaders in affordable and quality generic medicine [7]. It is estimated that 70% of the patients belonging to 87 developing countries received medicine procured from India by the major procuring agencies like United Nations Children's Emergency Fund (UNICEF), International Dispensary Association (IDA), the Global Fund and the Clinton Foundation [8]. Indian antiretrovirals (ARVs) resulted in cost-savings of up to 90%, to 91% of the generic ARVs procured by US President's Emergency Plan for AIDS Relief (PEPFAR). Medicine Sans Frontiers (MSF) also purchases 80% of its ARVs, for its projects in over 30 countries from India [9]

India with its significant advantage of low cost innovation, low capital requirements and lower costs in running facilities, well established manufacturing processes, R&D infrastructure, compliance & chemistry capabilities, etc., is strategically well positioned to emerge as 'Health Keeper' of the world [10]. India's regulatory compliance capabilities are clearly demonstrated from the fact the country has highest number of U.S. FDA approved facilities outside USA [11]

In view of the growing importance of the Indian Pharmaceutical industry both for domestic market and the world, the present article attempts to answer whether the country would continue to play an important role in global pharmaceutical trade and what are the necessary policy interventions required for its future sustainability and growth. Towards this analysis of the latest trends in the country's registrations in various important pharmaceutical markets, bilateral trade, challenges facing the industry, etc., were undertaken.

## MATERIALS AND METHODS

The pharmaceutical market size of USA is estimated at US\$300bn [12] in the year 2009 which is 37.13% of global market estimated at US\$808bn during that year. Due to its dominant share, analysis of U.S. FDA was comprehensively carried out both for Drug Master Files (DMFs) and ANDAs. To analyze India's drug registrations, company-wise, country-wise, therapeutic category-wise, dosage form wise, analysis of type-II Active Drug Master Files (DMFs) filed with U.S. FDA and Abbreviated New Drug Approvals (ANDAs) granted by U.S. FDA were performed.

DMF is a submission of technical documentation containing chemistry, manufacturing and control of an Active Pharmaceutical Ingredient (API) to the U.S. FDA. A DMF is considered as active if it is acceptable for filing with U.S. FDA administratively and is up to date. Acting as a master document, the DMF is important in maintaining current supplier agreements as well as in developing new business relationships. U.S. FDA maintains following 5-types of DMFs,

Type I: Manufacturing Site, Facilities, Operating Procedures and Personnel

Type II: Drug Substance, drug substance intermediate and material used in their preparation, or drug product

Type III: Packaging Material

Type IV: Excipients, colorants, flavors, essence, or materials used in their preparation

Type V: FDA accepted reference information

Inspections of drug substance manufacturers are usually triggered when there is an application under review that references a DMF for the manufacture of that drug substance [13].

An Abbreviated New Drug Application (ANDA) on the other hand contains data that, when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product [14].

Examination of India's drug registrations in various other important developed and developing countries viz., UK, South Africa, Tanzania, Ethiopia, etc., was also carried out. Certificates of Suitability (CEPs) are granted by European Directorate of Quality Medicine (EDQM) for APIs through a centralized procedure and are valid in 37 convention countries. CEPs approval was also carried out to establish India's position in bulk drugs in EU.

While examining the India's official basket of the of HS codes (ITC Harmonised System of Nomenclature Rev.4 of India) at 8 digit level used for arriving at exports & imports figures under Drugs, pharmaceuticals & fine chemicals by Government of India it was found that the basket has not only formulations and bulk drugs, but also, intermediates, fine chemicals, a few herbals, products under Alternate Medicinal Systems (formulations of Ayurveda, Siddha, Unani and Homeopathy), excipients, medical & diagnostic equipment, surgicals & dressings, medical devices and diagnostic reagents. Examination revealed that the HS codes used in the official basket however, does not comprehensively cover all the HS codes available under each of the categories (Table 1). The official trade estimates therefore, it was found, does not reflect true picture. Further, it must be noted that, in internationally separate baskets are used for pharmaceutical formulations, herbals and medical equipment. In order to establish accurate picture of Pharmaceutical exports of India, authors carried out an extensive research on India's HS Codes, examining them to identify pharmaceutical related HS codes.

To ensure accuracy, verification of the commodity description was carried out with Merck Index and various pharmacopoeias. HS codes pertaining to herbals were identified into the basket, if over 50% of the commodity under the HS code is utilized in pharmaceuticals based on the judgmental approach. In case of fine chemicals as separate classification for 'medicinal grade' fine chemicals was not available in the Indian HS classification, all the fine chemical HS codes were included. Currently many countries have HS Codes identifying medicinal grade fine chemicals and HS codes at 10 digit levels while India does not have the same. The research yielded 1,150 HS codes under 10 categories whose break-up is given Table 2. Based on the HS codes thus identified, analysis was carried out to find India's exports & imports statistics, trade balance, country-wise & region-wise exports.

Further analysis of acquisitions of Indian pharmaceutical companies based on various media reports during the last three years was carried out. During the research, several validation and data checking steps were undertaken while collecting and post collection of data to ensure its accuracy. Data were analyzed using spreadsheets. Results were then cross-checked and a data validation was performed.

**Table 1. Sample list of HS codes and their descriptions which are not included in India's official basket of HS codes for Drugs, Pharmaceuticals & Fine Chemicals**

S. No.	Commodity Code	Commodity Name	Category	Merck Index Code	Application
1	29182200	0-acetylsalicylic acid its salts and esters	API	851	Analgesic
2	29333300	Alfentanil, anileridine, propiram & trimeperidine, etc., salts	API	236	Analgesic
3	29335300	Allobarbital and other barbital compounds and its salts	API	263	Sedative ,Hypnotic
4	29339100	Alprazolam, camazepam & other compounds of zepam, salts	API	312	Anxiolytic
5	29223100	Amfepranone(inn), methdone & mormethadone salts	API	3127	Anorexic
6	29349100	Aminorex, brotizolam and other like compounds, salts thereof	API	476	Anxiolytic
7	29337200	Clobazam (inn)	API	--	Sedative & Hypnotics
8	29389020	Digitalis Glycoside	API		Cardiotonics
9	29225024	Domperidone	API	3418	Antiemetic
10	29362400	D-or dl-pantothenic acid (vitamin B3 or vitamin B5) and its derivatives	API	--	Vitamins
11	29396210	Ergotamine Tartarate	API		Anti migraine
12	29280010	Isoniazide	API	5186	Antitubercular
13	28369100	Lithium carbonates	API	--	Antimanic
14	29335500	Loprazolam, mecloqualone, methaqualone, salts thereof	API	5579	Anxiolytics, Anticonvulsants
15	29241100	Meprobamate (inn)	API	5862	Anxiolytic
16	30042097	Polymyxin b and colistin	Formulation	--	Antibiotics
17	29394200	Pseudo ephedrine (inn) and its salts	API	7916	Nasal Decongestant
18	28372050	Sodium nitropruside (sodium nitroferricyanide)	API		Vasodialators
19	29124930	Thiacetazone	API	9290	Antitubercular
20	29362940	Vitamin D	API	--	Vitamins

*Source: Authors' research based on ITC HS codes, Export Policy Schedule 2, Director General of Foreign Trade, Government of India*

**Table 2. Comparison of identified HS Codes with existing official basket of India**

S. N	Category	Codes Identified	Existing Codes
1	Formulations	164	148
2	Bulk Drugs & Intermediates	211	175
3	Biologicals	63	52
4	Excipients	34	29
5	Herbals	106	28
6	Fine Chemicals	464	6
7	Medical & Diagnostic Equipment	62	2
8	Surgical & dressings	32	14
9	Medical Devices	9	--
10	Diagnostic Reagents	5	3
Total		1,150	457

*Source: Author's research on ITC HS codes Export Policy Schedule 2, Director General of Foreign Trade, Government of India and Drugs, Pharmaceuticals & fine chemicals HS Code basket, Govt. of India*

**Table 3. Approvals received by Indian pharma companies from various regulatory agencies of the world**

Country	Regulatory compliance	No. from India Vs ROW	Rank of India	Data as on
USA	Type II active DMFs filed with U.S. FDA	2,234/7,121	First	23-Jun-10
	Companies filed Type II active DMFs with U.S. FDA	340/1,082	First	23-Jun-10
	Molecules filed for which DMFs have been filed	608/2,276	First	23-Jun-10
	Formulation companies having prescription authorisations	31/704*	Second <sup>‡</sup>	11-May-10
EDQM (Europe)	Companies having EDQM (European Directorate of Quality Medicine) CEP approvals.	139/776	First	22-Jun-10
	Valid CEPs	687/2,858	First	22-Jun-10
	Molecules for which CEPs have been granted	255/800	First	22-Jun-10
UK	Companies having formulation approvals from Medicines Healthcare Regulatory Agency (MHRA), UK	15	N.A.	22-Jun-10
Ethiopia	Companies having approved marketing Authorizations from Drug Administration and Control Authority, (DACA), Ethiopia.	51/238	First	25-Aug-09
Tanzania	Companies having approved marketing Authorizations from Tanzania Food and Drugs Authority (TFDA)	74/ 258	First	26-Mar-10
India	GMP Certified Plants (as per Central Drug Standard Control Organization)	814	First	1-Jan-10

\* 93 companies entire products are discontinued as well as company website is not available  
<sup>‡</sup>USA ranks first with a total number of 474 companies

## RESULTS

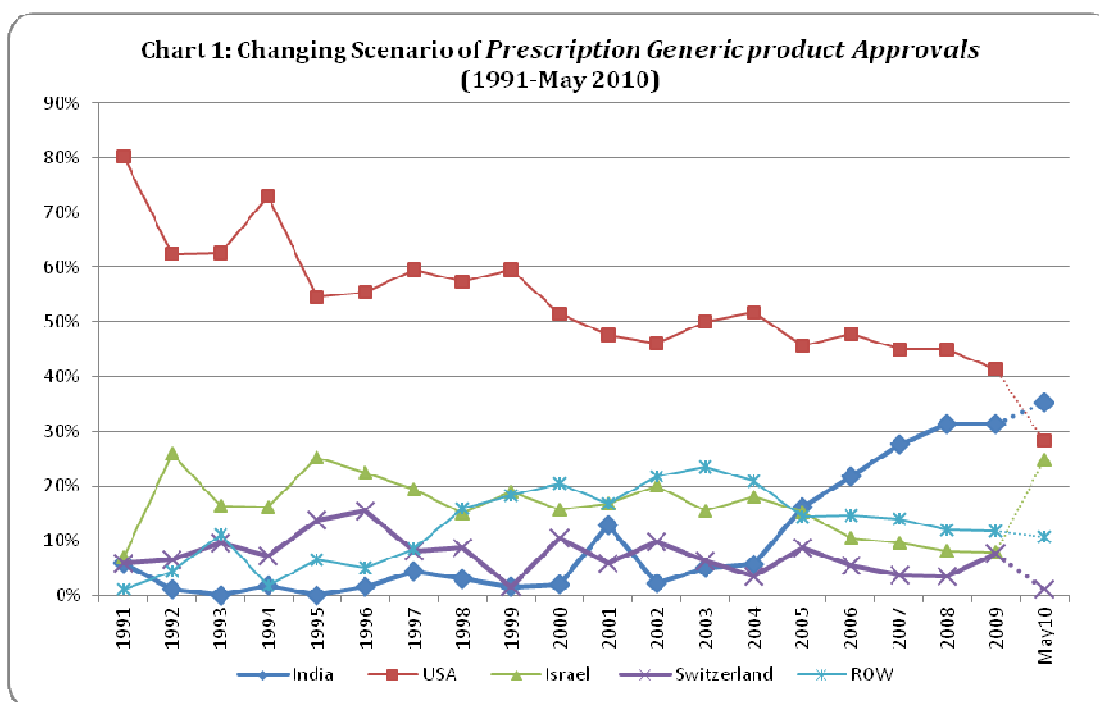
### Analysis of Regulatory Status of India

Analysis of India's drug registrations with U.S. FDA reveals that the country has emerged among the top countries in its regulatory approvals. It leads in approvals from U.S. FDA both in APIs and formulations in terms molecules, companies and number of filings/approvals (Table 3). It also leads in several African and Asian countries. It has high number of approvals in EDQM. The country has majority of qualifications granted by major global procuring agencies such as WHO, PEPFAR, etc. In U.S. FDA India ranks first in Type-II active DMFs (APIs) with a share

of 31.37% of all the filings, 31.42% of all companies are from India which account for 26.71% of molecules filed with U.S. FDA.

India is currently experience a boom in generic drug registrations. For example, the number of approvals for prescription products (ANDA approvals excluding biologicals, OTC, discontinued and tentative approvals) with U.S. FDA during five years from 2005 to 2009 have grown tremendously.

The country received a total 1,077 approvals during this five year period compared with meager 171 approvals the country has prior to it. The country has total 1,278 prescription generics product approvals out of 9,079 total granted making the country the second largest after USA (4,741). Israel (1,189), Switzerland (620) occupy 3<sup>rd</sup> and 4<sup>th</sup> positions respectively. The country's share in year-wise approvals granted has been growing exponentially during the last five years (Chart 1).



Out of total companies that have been granted approvals in generics (prescription and OTC) belonging to 27 countries, India has second largest number of companies (27) though a poor second to USA (211) (Table 4). The top 5 companies among them are very aggressive. A few other top Indian generic companies in domestic market and in exports have not yet entered into US markets. Besides, several foreign companies hold ANDA approvals on Indian facilities both for innovator as well as generics [15] which are taken into consideration. The above, it must be noted, does not include 265 prescription & OTC generic products belonging to erstwhile Indian companies of Ranbaxy, Matrix, Dabur Oncology and Minrad (subsidiary of Piramal Healthcare) which now belong to foreign acquirer companies but include 90 approvals held by Indian subsidiaries abroad. Currently there is only one Indian company out of the top 10 generic companies of the world, though most of them have their manufacturing units in India. This

clearly demonstrates India's strengths in generic formulations and there are good chances more companies from India would be among top 10 generic companies of the world.

**Table 4. Country-wise share companies<sup>^</sup> and average number of product approvals with U.S. FDA (As on 23 Jun. 10)**

S.N	Originator Country	% Share in generic companies	% share in total Prescription & OTC Generic Drugs approvals <sup>+</sup>	Avg. no. of products per applicant
1.	USA	211	4,926	23.35
2.	India	27	1,321	48.93
3.	Israel	9	1,208	134.22
4.	Switzerland	11	635	57.73
5.	Canada	8	382	47.75
ROW (22 countries)		15.29%	9.75%	19.06
<b>Grand Total</b>		100.00%	100.00%	29.89

*Source: Authors' research based on U.S. FDA; <sup>^</sup> Includes only companies that are active as on the date of analysis.; <sup>+</sup> Excluding BLAs, discontinued & tentative Products*

### **Analysis of India' Bilateral Trade in Pharmaceutical Products**

Analysis of sector-wise statistics available from DGCIS reveal that during that year, the total pharmaceutical sector exports of the country are more than automobile exports, equal to nearly half of all agricultural exports and a third of India's IT & BPO exports which is estimated at US\$60bn [16] by Nosscom. Pharmaceuticals was consistently fifth largest exported principal commodity of the country for the last over five years [17].

In terms of trade balance, it is the only Indian sector after apparels having positive trade balance consistently for the last five years. The same feat was not achieved by India's other leading principal commodity exports of Gems & jewellery, Telecommunications, Machinery, Electronic goods, metals & minerals or Chemicals (Table 5). However, authors' research on India's HS Code reveals a more the industry is actually much bigger than the figures presently being offered by official sources in India. The total exports of India of Drugs, Pharmaceutical and fine chemicals in the year 2008-09 stood at approx. US\$13,233.12mn and including medical equipment and surgical the figure stands at US\$13,831.28mn much higher than the officially estimated figure of US\$8,802.64mn. The imports are approx. at US\$10,778.33bn during the same period including imports of medical devices and surgicals which are valued at US\$787.39mn. The country thus had a positive trade balance of US\$3,052.95mn in this sector. The sector grew a Compounded Annual Growth Rate (CAGR) of 22.51% during the five year period 2004-05 to 2008-09.

Formulations exports including biologicals occupy approx. 35.9% of the country's exports followed by bulk drugs, intermediates & excipients with a share of 27.62%, fine chemicals 25.35% and AYUSH products and Herbals at 6.8%. Alternate systems of Indian medicine viz., Ayurveda, Unani, Siddha, Yunani and Homeopathy are commonly referred to as AYUSH products. Medical & diagnostic equipment, surgical and Diagnostic reagents are estimated at 4.32% (Chart 2). Majority of the imports of India are fine chemicals with a share of 54.73% followed by bulk drugs, intermediates & excipients at 19.75%, Medical & diagnostic equipment, surgical and Diagnostic reagents at 15.56%, formulations along with biological at 8.3% and

Herbal and Ayush products at 1.64% (Chart 3). India exported to some 209 countries/territories of the world and imported from 139 countries/territories during 2008-09.

Asia is the largest export destination followed by Europe and North America (Charts 4 & 5) while Asia is the largest sourcing region for imports followed by Europe and North America.

European Union is most important destination for bulk drugs & intermediates with exports over US\$1bn and a share of 52.36% in the exports to the region (Table 6 & 7). European Union is among the important destinations for India's formulations also with a share of 44.38% in the exports to the region. It is followed by North America which is important destination for formulations, biologicals as well as bulk drugs & intermediates. Africa is by far the most important destination for India's formulations exports with nearly US\$1bn exports and five year CAGR of 30.92%. Exports of bulk drugs & intermediates, biologicals and excipients are also growing at very high CAGRs to this region. The country Marjory exports formulations to CIS region. In Asia Middle East, China, S. Korea, Japan, and Taiwan are major importers of bulk drugs & intermediates. Nearly two thirds of the exports to LAC region are also bulk drugs & intermediates. India's exports to Oceania largely remained untapped.

India imports over US\$1,991.83mn worth bulk drugs & intermediates during 2008-09 with China contributing nearly 2/3<sup>rd</sup> of this valued at US\$1,252.77mn. Imports from China grew at a CAGR of 33.11% over the five year period from 2004-05 to 2008-09. European Union and North America are also among most important source regions for India's bulk drug & intermediate imports. USA with a share of 5.24% followed by Germany (3.36%), Italy (3.01%) and Japan (2.67%) are the other major supplier countries of bulk drugs & intermediates. Barring China and USA the top 10 source countries for bulk drugs & intermediates are European countries which only indicate that complex DMF material for the export purposes being imported. Formulation imports from North America and Switzerland have been growing at a very high rate during the period under consideration. Imports of Biologicals from North America and China are growing at a very high rate.

The country also is very weak in fine chemicals as evident from its nearly US\$5,899.06mn imports of which China alone contributed US\$1,214.76mn even if most of it is not medicinal grade. Imports of fine chemicals from China grew at a CAGR of 17.99% during the five year from 2008-09. Singapore, Saudi Arabia, USA, and Iran are the other top suppliers of fine chemicals to India. Further, with its strong roots in bulk drugs, intermediates and fine chemicals is thus poised to become a major threat to India in formulations in developing markets as well as India.



Table 5. India's Principal Commodity Exports (2008-09) (US\$ bn. & %)

Rank	Commodity Code (at 2 digit level)	Commodity Name	2008-09 (Exports)	2008-09 (Imports)	2008-09 (Trade Balance)	CAGR (%) (Exports)	CAGR (%) (Imports)
1	62	Articles of apparel and clothing accessories, not knitted or crocheted.	5,907.14	87.41	5,819.73	31.32%	-23.96%
2	61	Articles of apparel and clothing accessories, knitted or crocheted.	5,066.23	51.46	5,014.77	33.34%	-19.17%
3	30	Pharmaceutical products.	5,091.32	928.18	4,163.14	21.28%	-13.90%
4	10	Cereals.	3,285.38	10.02	3,275.36	347.53%	-22.32%
5	99	Miscellaneous goods.	4,678.59	1,554.81	3,123.78	33.89%	5.98%
India's Total Exports			183,091.31	299,310.96	-116,219.65	19.22%	-16.43%

Source: CMIE Trade Database 'India Trades' Authors' Research

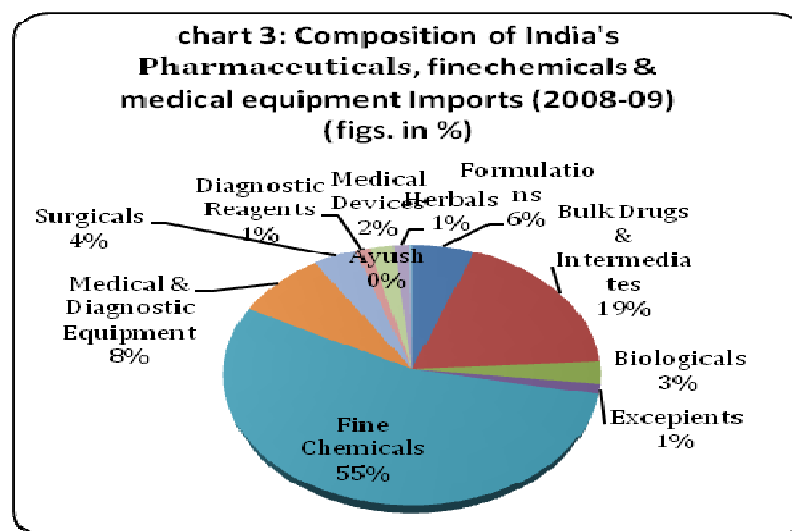
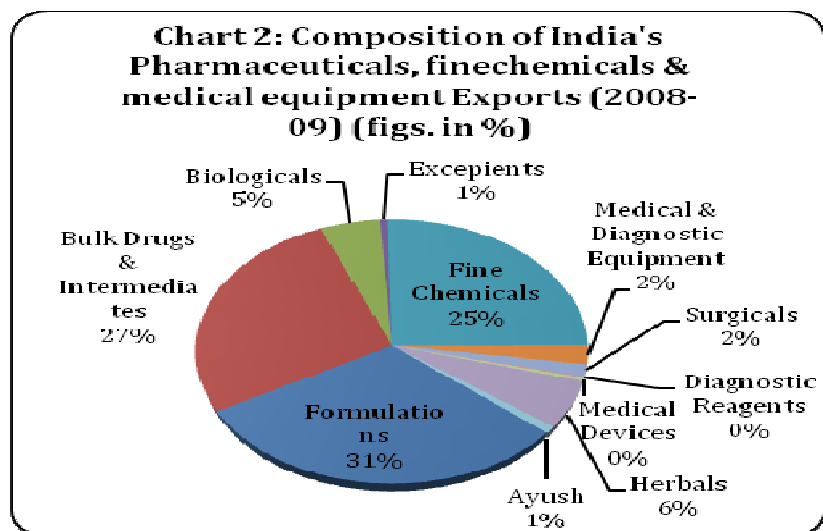
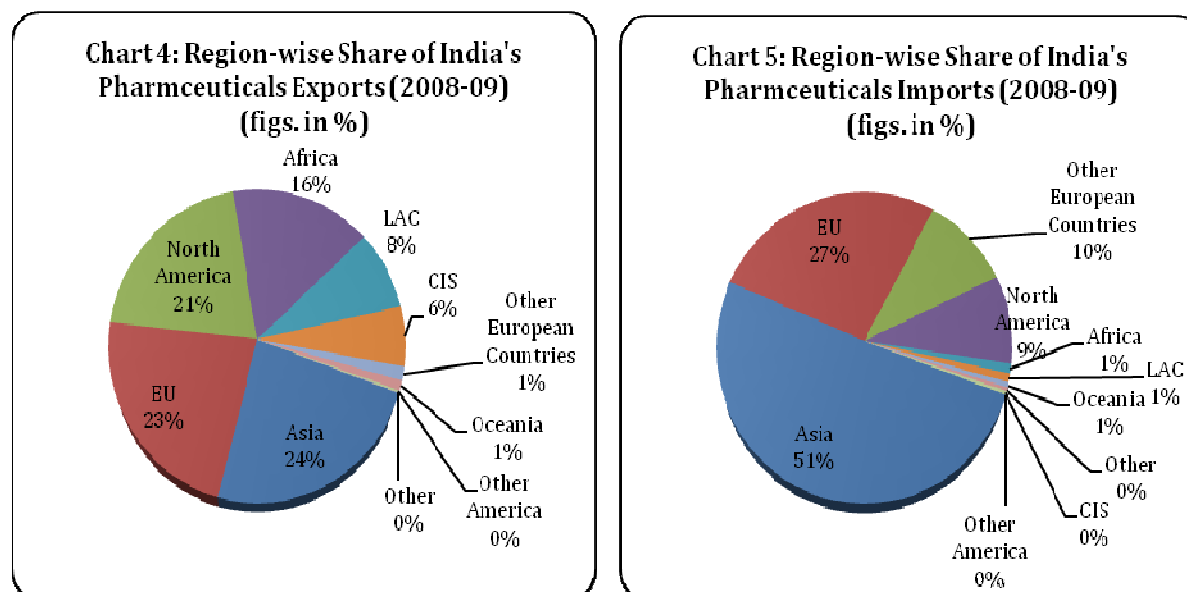


Table 6. Segment-wise &amp; region-wise analysis of India's pharmaceuticals trade exports (figs. in US\$ mn. &amp; %)

Region	Formulations				Bulk Drugs & Intermediates				Biologicals				Excipients				Total Exports	
	2008-09 US\$ mn.	CAGR (%) (2004-05 to 2008-09)	% share in Segment (2008-09)	% Share in Exports to the region (2008-09)	2008-09 US\$ mn.	CAGR (%) (2004-05 to 2008-09)	% share in Segment (2008-09)	% Share in Exports to the region (2008-09)	2008-09 US\$ mn.	CAGR (%) (2004-05 to 2008-09)	% share in Segment (2008-09)	% Share in Exports to the region (2008-09)	2008-09 US\$ mn.	CAGR (%) (2004-05 to 2008-09)	% share in Segment (2008-09)	% Share in Exports to the region (2008-09)	(2008-09) US\$ mn.	CAGR (%) (Exports 2004-05 to 2008-09)
Africa	991.86	30.92%	23.33%	70.24%	202.63	33.98%	5.43%	14.35%	204.62	48.98%	28.66%	14.49%	12.91	40.96%	14.15%	0.91%	1,412.02	33.45%
Asian	231.65	17.45%	5.45%	42.98%	259.25	9.81%	6.95%	48.10%	37.37	28.96%	5.23%	6.93%	10.76	60.54%	11.80%	2.00%	539.03	14.36%
Asia (Excluding Middle East)	86.06	3.29%	2.02%	19.01%	342.85	11.22%	9.20%	75.75%	19.59	29.25%	2.74%	4.33%	4.10	-7.99%	4.50%	0.91%	452.60	9.71%
CIS	460.90	16.90%	10.84%	84.67%	26.51	13.85%	0.71%	4.87%	55.81	20.72%	7.82%	10.25%	1.16	17.92%	1.27%	0.21%	544.38	17.10%
EU	881.33	31.35%	20.73%	44.38%	1,039.59	19.39%	27.88%	52.36%	51.43	11.52%	7.20%	2.59%	13.30	20.63%	14.58%	0.67%	1,985.65	23.73%
LAC	304.83	25.08%	7.17%	41.67%	346.98	20.42%	9.31%	47.43%	78.02	32.27%	10.93%	10.66%	1.78	38.06%	1.95%	0.24%	731.61	23.40%
Middle East	214.03	13.80%	5.03%	28.64%	473.15	28.19%	12.69%	63.31%	27.02	18.64%	3.78%	3.62%	33.10	28.24%	36.29%	4.43%	747.30	22.79%
North America	837.25	30.47%	19.69%	46.55%	778.34	21.65%	20.88%	43.28%	175.98	24.96%	24.65%	9.78%	6.93	10.02%	7.60%	0.39%	1,798.50	25.66%
Oceania	64.72	32.45%	1.52%	71.22%	21.26	11.69%	0.57%	23.40%	4.37	37.57%	0.61%	4.81%	0.52	-3.91%	0.57%	0.57%	90.87	25.60%
ROW	1.52	-7.09%	0.04%	23.24%	0.58	-28.59%	0.02%	8.87%	4.33	121.46%	0.61%	66.21%	0.11		0.12%	1.68%	6.54	10.10%
Other America	16.09	19.42%	0.38%	80.29%	0.46	-16.14%	0.01%	2.30%	3.47	19.35%	0.49%	17.32%	0.02		0.02%	0.10%	20.04	17.40%
Other European Countries	16.12	11.05%	0.38%	12.80%	107.74	21.77%	2.89%	85.58%	1.87	-1.79%	0.26%	1.49%	0.16	7.46%	0.18%	0.13%	125.89	19.50%
South Asia	145.49	12.54%	3.42%	43.97%	129.07	7.69%	3.46%	39.00%	50.00	21.85%	7.00%	15.11%	6.36	25.42%	6.97%	1.92%	330.92	11.79%
<b>Grand Total</b>	<b>4,251.85</b>	<b>24.83%</b>	<b>100.00%</b>	<b>48.40%</b>	<b>3,728.41</b>	<b>19.15%</b>	<b>100.00%</b>	<b>42.44%</b>	<b>713.88</b>	<b>28.64%</b>	<b>100.00%</b>	<b>8.13%</b>	<b>91.21</b>	<b>24.27%</b>	<b>100.00%</b>	<b>1.04%</b>	<b>8,785.35</b>	<b>22.51%</b>

Table 7. Segment-wise &amp; region-wise analysis of India's pharmaceuticals trade imports (figs. in US\$ mn. &amp; %)

Region	Formulations				Bulk Drugs & Intermediates				Biologicals				Excipients				Total Imports	
	2008-09 US\$ mn.	CAGR (%) (2004-05 to 2008-09)	% share in Segment (2008-09)	% Share in Exports to the region (2008-09)	2008-09 US\$ mn.	CAGR (%) (2004-05 to 2008-09)	% share in Segment (2008-09)	% Share in Exports to the region (2008-09)	2008-09 US\$ mn.	CAGR (%) (2004-05 to 2008-09)	% share in Segment (2008-09)	% Share in Exports to the region (2008-09)	2008-09 US\$ mn.	CAGR (%) (2004-05 to 2008-09)	% share in Segment (2008-09)	% Share in Exports to the region (2008-09)	(2008-09) US\$ mn.	CAGR (%) (Exports 2004-05 to 2008-09)
Africa	24.17	432.77%	4.01%	78.32%	4.51	3.70%	0.23%	14.61%	1.70	43.58%	0.58%	5.51%	0.48	163.21%	0.35%	1.56%	30.86	63.30%
Asian	8.55	37.10%	1.42%	12.47%	40.89	12.08%	2.05%	59.63%	10.58	37.97%	3.60%	15.43%	8.55	10.91%	6.22%	12.47%	68.57	16.76%
Asia (Excluding Middle East)	27.57	23.77%	4.57%	1.90%	1,345.78	28.11%	67.57%	92.76%	37.23	47.62%	12.67%	2.57%	40.17	27.73%	29.23%	2.77%	1,450.75	28.36%
CIS	0.30	31.61%	0.05%	2.68%	9.75	30.32%	0.49%	87.21%	0.91	16.74%	0.31%	8.14%	0.22	-6.67%	0.16%	1.97%	11.18	27.28%
EU	203.23	29.21%	33.70%	25.12%	398.08	11.01%	19.99%	49.21%	149.01	25.69%	50.73%	18.42%	58.64	19.91%	42.68%	7.25%	808.96	17.59%
LAC	5.75	39.69%	0.95%	20.80%	19.85	-8.84%	1.00%	71.82%	0.85	0.29%	3.08%	1.19	111.03%	0.87%	4.31%	27.64	-2.29%	
Middle East	4.58	104.87%	0.76%	29.19%	6.22	-2.98%	0.31%	39.64%	4.16	41.42%	1.42%	26.51%	0.73	0.00%	0.53%	4.65%	15.69	14.75%
North America	81.84	45.74%	13.57%	29.43%	109.39	13.65%	5.49%	39.34%	63.57	55.30%	21.64%	22.86%	23.24	15.92%	16.91%	8.36%	278.04	26.81%
Oceania	2.04	20.42%	0.34%	12.73%	10.31	52.23%	0.52%	64.36%	0.67	-28.26%	0.23%	4.18%	3.00	7.58%	2.18%	18.73%	16.02	20.26%
ROW	1.89	15.83%	0.31%	15.90%	9.05	26.90%	0.45%	76.11%	0.55	18.39%	0.19%	4.63%	0.40	111.47%	0.29%	3.36%	11.89	25.19%
Other America	0.04		0.01%	50.00%	0.04		0.00%	50.00%			0.00%	0.00%			0.00%	0.00%	0.08	
Other European Countries	243.09	33.36%	40.31%	79.44%	37.88	-2.73%	1.90%	12.38%	24.53	81.51%	8.35%	8.02%	0.50	14.59%	0.36%	0.16%	306.00	25.92%
South Asia	0.04	-44.11%	0.01%	9.76%	0.08	-44.61%	0.00%	19.51%	0.00	-100.00%	0.00%	0.00%	0.29	0.00%	0.21%	70.73%	0.41	-29.18%
<b>Grand Total</b>	<b>603.09</b>	<b>34.12%</b>	<b>100.00%</b>	<b>19.93%</b>	<b>1,991.83</b>	<b>20.49%</b>	<b>100.00%</b>	<b>65.82%</b>	<b>293.76</b>	<b>34.99%</b>	<b>100.00%</b>	<b>9.71%</b>	<b>137.41</b>	<b>20.17%</b>	<b>100.00%</b>	<b>4.54%</b>	<b>3,026.09</b>	<b>23.86%</b>



The country sources Medical & diagnostic equipment/surgicals from EU, North America and Asia, Medical devices/diagnostic reagents from North America and EU and in Ayush and herbal sector it has a healthy positive trade balance.

While India on the whole has a positive trade balance in formulations, bulk drugs and intermediates, biological and excipients valued at US\$5.76bn., it has negative trade balance of US\$2,329.19mn in fine chemicals and US\$1,078.62mn. in Medical & diagnostic equipment, devices and surgicals (Table 8). USA, Germany, China, UK and Indonesia are the largest export destinations for India's pharmaceutical exports while, China, USA, Germany, Singapore and Saudi Arabia are largest source countries. Among the top 25 trading partners, India's Exports to South Africa, Belgium and Saudi Arabia are growing at very high pace while imports from China, Iran and Taiwan are growing rapidly (Table 9).

## DISCUSSION

While major pharmaceutical manufacturers in India are vertically integrated and manufacture their APIs as well, majority of the other API manufacturing facilities under take contract manufacturing for top 100 companies which account for approx. 50% of the India's production. Biotechnology is emerging segment in healthcare industry. The segment is growing rapidly. For example global biotech sales increased by 12.5% while pharmaceutical sales increased by 6.4% [18]. Several of the most successful and pioneering drugs of this decade are biologics [19]. Biopharmaceuticals comprise recombinant therapeutic proteins, monoclonal antibody and nucleic acid based-products used for medical purposes. Examples include Granulocyte-Colony Stimulating Factor, Interferons, Recombinant Human Insulin, Erythropoietin, Human Growth Hormones, etc.

**Table 8. Segment-wise and Region-wise Trade Balance of India's Pharmaceuticals, Fine chemicals & medical equipment sector**

Region	Formulations	Bulk Drugs & Intermediates	Biologicals	Excipients	Total	Fine Chemicals	Diagnostic Reagents	Surgicals	Medical & Diagnostic Equipment	Medical Devices	Total
Africa	967.69	198.12	202.92	12.43	1,381.16	7.85	1.64	23.70	9.37	7.86	42.57
Asian	223.10	218.36	26.79	2.21	470.46	-387.67	-3.98	6.94	-2.07	-10.66	-9.77
Asia (Excluding Middle East)	58.49	-1,002.93	-17.64	-36.07	-998.15	-1,362.18	-15.42	-62.91	-130.46	-14.46	-223.25
CIS	460.60	16.76	54.90	0.94	533.20	-72.69	1.05	2.39	2.00	0.79	6.23
EU	678.10	641.51	-97.58	-45.34	1,176.69	-6.10	-51.49	-71.17	-299.40	-60.42	-482.48
LAC	299.08	327.13	77.17	0.59	703.97	58.87	0.91	-50.09	10.85	1.98	-36.35
Middle East	209.45	466.93	22.86	32.37	731.61	-810.72	3.91	17.05	6.19	12.11	39.26
North America	755.41	668.95	112.41	-16.31	1,520.46	-102.98	-55.31	-76.40	-149.68	-104.46	-385.85
Oceania	62.68	10.95	3.70	-2.48	74.85	13.27	-1.22	-5.60	-1.94	0.11	-8.65
Other	-0.37	-8.47	3.78	-0.29	-5.35	-17.98	-0.30	-0.31	-7.06	-0.57	-8.24
Other America	16.05	0.42	3.47	0.02	19.96	-0.81	0.07	0.30	0.00	0.06	0.43
Other European Countries	-226.97	69.86	-22.66	-0.34	-180.11	-9.96	-2.54	-7.00	-22.95	-12.80	-45.29
South Asia	145.45	128.99	50.00	6.07	330.51	298.91	2.18	18.90	7.74	3.95	32.77
<b>Grand Total</b>	3,648.76	1,736.58	420.12	-46.20	5,759.26	-2,392.19	-120.50	-204.20	-577.41	-176.51	-1,078.62

*Source: Authors' research based on DGCIS data*

Table 9. India's Top 10 Export and Import partners for Indian Pharmaceutical Sector^ (figs. in US\$ mn.)

Rank	Exports					Imports				
	Country	2008-09	CAGR	% Share	Cumulative % Share	Country	2008-09	CAGR	% Share	Cumulative % Share
1	USA	2,349.90	23.64%	16.99%	16.99%	China	2,650.95	34.91%	24.60%	24.60%
2	Germany	628.10	14.58%	4.54%	21.53%	USA	1,227.26	17.53%	11.39%	35.98%
3	China	504.94	4.54%	3.65%	25.18%	Germany	814.02	19.74%	7.55%	43.53%
4	UK	399.38	17.62%	2.89%	28.07%	Singapore	733.92	17.08%	6.81%	50.34%
5	Indonesia	379.11	5.73%	2.74%	30.81%	Saudi Arabia	562.60	11.14%	5.22%	55.56%
6	Pakistan	366.87	13.99%	2.65%	33.46%	Switzerland	421.53	23.77%	3.91%	59.47%
7	Russia	361.99	18.78%	2.62%	36.08%	Japan	388.18	11.27%	3.60%	63.08%
8	Netherlands	358.07	24.87%	2.59%	38.67%	Korea Republic (South)	350.84	29.56%	3.26%	66.33%
9	Brazil	341.90	25.13%	2.47%	41.14%	Iran	336.43	42.71%	3.12%	69.45%
10	Austria	312.63	150.42%	2.26%	43.40%	Malaysia	311.41	7.95%	2.89%	72.34%

Source: Authors' research based on DGCIS data

^ Includes fine chemicals, herbal & Alternate systems of Medicine

Table 10. Impact of foreign acquisitions on top listed Indian pharmaceutical companies

Rank	Company	Cumulative % Share in Sales	Cumulative % Share in Exports	Current MNCs activities
1	Cipla Ltd.	6.69%	9.26%	Indian company
2	Dr. Reddy's Laboratories Ltd.	12.49%	19.02%	Marketing agreement with GSK of UK; Dr Reddy's may sell stake in domestic formulations biz to GSK
3	Ranbaxy Laboratories Ltd.	17.51%	28.07%	Acquired by Daiichi Sankyo of Japan
4	Lupin Ltd.	21.38%	33.51%	Indian company
5	Aurobindo Pharma Ltd.	25.03%	39.41%	Marketing agreement with Pfizer of USA
6	Sun Pharmaceutical Industries Ltd.	28.61%	42.15%	Indian company
7	Piramal Healthcare Ltd.	31.82%	44.07%	Acquired by Abbott Laboratories of US in May, 2010
8	Cadila Healthcare Ltd.	34.53%	46.24%	Indian company
9	Glaxosmithkline Pharmaceuticals Ltd.	36.84%	46.44%	Foreign Multinational
10	Glenmark Pharmaceuticals Ltd.	38.96%	47.14%	Indian company
11	Matrix Laboratories Ltd.	40.93%	51.38%	Acquired by Mylan of USA
12	Wockhardt Ltd.	42.77%	53.15%	Wockhardt (nutrition business) acquired by Abbott Laboratories, USA and Animal care subsidiary acquired by Vetogquinol SA (US\$ 130mn. & US\$ 31.2mn resp.)
13	IPCA Laboratories Ltd.	44.46%	55.37%	Indian company
14	Divi's Laboratories Ltd.	45.98%	59.09%	Contract Manufacturer/Custom synthesis
15	Orchid Chemicals & Pharmaceuticals Ltd.	47.50%	62.24%	Generic injectable finished-dosage form pharmaceuticals business of Orchid has been acquired by Hospira for US\$400mn.

Source: Author's Research based on CMIE database 'Prowess', Company websites

Currently there are several block buster molecules in biopharma sector. For example, Adalimumab, Bevacizumab, Etanercept, Infliximab and Rituximab have more than US\$5.5bn. in annual sales globally [20]. Biopharmaceuticals while having high developing and approvals costs offer higher profit margins, insusceptible to price fluctuations and lower competition. By the end of 2010 patents of brand biologics with \$14bn in annual sales are expiring [21] and are estimated to touch around US\$115bn. by 2015. As per author's research based on patent database 'Dialogpro', it is observed that several Biologicals such as Neupogen, Novolin, Protropin, Activase, Epogen, Nutropin, Avonex, Humulin, etc., have already expired creating space in biogenerics. It is estimated that by 2012, nearly half of all newly approved products by U.S. FDA will be biopharmaceuticals [22]. Currently there are around 150 biopharmaceutical drugs in the world. Commodity generics have low barriers of entry and low margins of profits due to competitive pricing, while specialty and super generic drugs are reformulations of off-patent drugs and have higher margins [23]. This situation can dramatically change the industry landscape through large number of technologically focused companies with customized manufacturing.

India remains very weak in biopharmaceutical products. China currently produces over 20 biopharmaceutical products. on the other hand is strategically developing in Biotechnology segment and is the only developing country participating in genomic research. The country not only has very little presence in the world markets in the segment, it depends on Chinese imports for many of the biotechnology and fermentation based products [24]. It is already identified that India is weak in advanced formulations, complex chemistry, biotechnology & fermentation. The country has just embarked on drug discovery. However, the current balance sheets of the domestic companies do not permit the investments required for drug discovery projects in any significant way. India has made a simple beginning through alternate path ways such as 505(b)(2), international acquisitions, etc.

As per data available from Department of Pharmaceuticals, Government of India, there are around 9,000 pharmaceutical manufacturing facilities for both APIs and formulations belong to some 3,000 companies [25]. As per the directory of Pharmaceuticals Exports promotion council there are approximately 1,300 active pharmaceutical exporters in India. This notwithstanding this, examination of companies registered with various regulated/non-regulated markets reveal that there are only around 175-200 Indian pharma companies that have notable presence in global markets. In spite of its obvious fragmentation, industry is also focused among a few top companies. It may be noted that the top 15 companies account for nearly half of India's Pharmaceutical industry size and these companies account for 62.24% of the country's exports (Table 10). As previously mentioned, many of the companies cater to requirements of top 100 companies. Industry therefore is quite susceptible to changes in demand of these top few companies.

However, in the recent past foreign multinationals have acquired 4 of the top 15 companies, part of another company and entered into major marketing agreements with another two companies. Of the remaining one is a foreign MNC and another is pure contract manufacturing and customs synthesis company. As per author's research, in the year 2008-09, among the listed pharmaceutical companies of India, foreign multinationals account for 17%-20% share in sales revenue as well as exports. After considering non-listed foreign MNCs present in the domestic

market, their share could be as high as 22-24%. Many of the domestic companies also undertake contract manufacturing/contract synthesis for multinationals.

Promoters of some of the Indian pharma companies like Piramal Healthcare, Ranbaxy, Santha Biotech and Dabur Pharma have already sold their controlling shares to US, Japanese and German MNCs. Many other major and minor domestic drug manufacturers are reportedly interested in similar disinvestment. These developments would result in MNCs gaining market supremacy and essential medicines are bound to become costlier.

### CONCLUSION

India is growing from strength to strength in generic drug industry. India has large number of facilities for bulk drugs to enable cost effective sourcing for generics. It has several predispositions that can make it a global leader in the next decade. It also has several challenges facing it that are threatening the country from tapping this opportunity.

The country presently has strong presence in generics, has presence in all most all developing countries and LDCs with growing populations that demand low cost generics. Due to expansion of population in developing countries, the global pharmaceutical markets are growing in volumes and the business will continue to remain focused on volumes. India is with large installed capacities is favorably suited to tap this opportunity. The patent cliff would add to the number of molecules that would be produced in the country. It would pave way for the next growth trajectory.

India has a growing dependency on imports for bulk drugs, intermediates, fine chemicals and medical devices and has a weak presence biotechnology, which are major threats. The country has to upgrade itself into next orbit through incremental research and strengthen itself in drug discovery, complex molecules, specialty generics and advanced dosage forms. The trend in imports and source countries clearly points to weak organic chemistry industry of the country which the country needs to strengthen.

The emergence of firms from developing countries and their transformation into multinationals has been one of the distinctive phenomenon in the globalization of pharmaceutical companies during the last two decades. This is an opportune time for Indian pharmaceutical firms to diversify their exports to exploit niche or specialty generics in international markets.

India has not made significant progress in the segment and the next growth opportunity lies in this segment. There is an urgent need for strengthening India's biopharmaceutical sector. While the country has large number of manufacturing facilities, international marketing & contract manufacturing, regulatory capabilities remain concentrated with top few companies and current spree of acquisitions by foreign MNCs can erode the domestic industry. So far the focus of the MNCs present in India was to capture share in domestic market. However, the current acquisition spree appears to be aimed at tapping the global compliances and low cost manufacturing capabilities. Such acquisitions may have serious consequences for India as prices in its domestic markets as well as export markets will rise and intangible assets both current &

future will be transferred to foreign acquirer. On the positive side, more chemistry capabilities, advanced formulations and technologies may be developed.

The future for India's pharmaceuticals industry lies in flexibility, speed, supply chain strengths and going global. The country has to tap its potential true innovation, clinical research, contract R&D and drug delivery systems. Neither innovation nor generics but only 'compelling total offer' would put the country among the very top.

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