POTENTIAL CHALLENGES FOR INDIA IN PRODUCT REGISTRATIONS WITH SPECIAL FOCUS ON THERAPEUTIC CATEGORY WITH U.S. - FDA – A PERSPECTIVE ANALYSIS

Uma Vasireddy[1, 2]*, G. Krishna Mohan[3], M.Lakshmi Narasu[4], P.V. Appaji[5]

[1]Research Scholar, Jawaharlal Nehru Technological University, Hyderabad, Andhra Pradesh, India; [2]Teegala Ram Reddy College of Pharmacy, Meerpet, Hyderabad, Andhra Pradesh, India; [3]Centre for Pharmaceutical Sciences, Institute of Science & Technology, Jawaharlal Nehru Technological University, Hyderabad, Andhra Pradesh, India; [4]Institute of Science & Technology, Jawaharlal Nehru Technological University, Hyderabad, Andhra Pradesh, India; [5]Pharmaceuticals Export Promotion Council, Hyderabad, Andhra Pradesh, India

[*]**Author for correspondence:** uma_vasireddy@yahoo.com; pharmaumavasireddy@gmail.com

Summary

Rapidly growing filing of Drug Master Files (DMFs) by foreign MNCs on Indian facilities, rising imports of DMF material from regulated markets and increasing registrations and exports to developing countries indicate emergence of India as manufacturing hub of the world. Growing dependence on developed countries for bulk drug imports, weak biotechnology sector and recent acquisitions of major domestic players by foreign multinationals are posing threat to the sustainability of the industry. In view of the growing importance of the Indian pharma contribution in this scenario, we have conducted a perspective analysis/research to establish if India can sustain its prominence as a major supplier of quality generics in the world. The country needs to strengthen itself in fine chemicals and medical devices to consolidate its positive trade balance. India can potentially capture the emerging opportunity available from the expiry of the top 50 block bluster molecules having huge sales in US pharmaceutical market in the next five years. Data available from the past 14 years reveals that India has received very few warning letters (ten in number) in spite being a top filer in US relative to its number of approvals compared with other countries indicating strong compliance capability of the country. In summary, India would continue to be active role in its exports in the coming years, product innovation, biogenerics, alternate regulatory pathways such as 505(b)(2), complex chemistry, clinical trials, contract research, etc., hold the key for future.

Keywords: Drug Master Files; Food and Drug Administration; Active Pharmaceutical Ingredients; Abbreviated New Drug Applications; Over the Counter Drugs; Regulatory Authority

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 in the area of generics. Indian pharmaceutical exports have risen sharply in the recent years not only to the highly regulated markets such as United States and European Union [1] but also to the developing countries and the Least Developed Countries [2]. 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 from 2004-05 to 2008-09 [3]. It must be noted that Indian Pharmaceutical industry has evolved from nonexistent to become one of the world leading suppliers of affordable and quality generic medicine [4]. The country currently produces 20% of global generics [5] and 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 [6]. Medicine Sans Frontiers (MSF) also purchases 80% of its Anti Retrovirals (ARVs), for its projects in over 30 countries are from India [7]. Indian supplies 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). Further, India's regulatory compliance capabilities are clearly demonstrated from the fact that the country has highest number of United States - Food and Drug Administration (US- FDA) approved facilities outside of the United States [8]. Therefore, 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 [9].

In view of the importance of India's pharmaceutical industry at global front, the present research aimed to establish if India can sustain its prominence as a major supplier of quality generics in the world through analysis of its (i) Trends in generic product approvals & Active Pharmaceutical Ingredients (APIs) registrations and (ii) Trends in India's bilateral trade in pharmaceuticals. Hence the main objective of the research is to Study India's strengths in formulation product approvals by molecules, therapies, segments, company and country competition, year-wise growth rates. Conclusions were then drawn on progress achieved and challenges being faced by the country which may assist in policy formulation of both regulators and commercial enterprises.

Methods

In view of overwhelming importance of US in global pharmaceutical markets, the emergence of India's pharmaceutical industry as flag-ship industry as also an industry of strategic importance for India and in view of large share of US in India's exports of pharmaceutical products, this study

aimed to study the key areas of therapeutic products. To identify India's generic product approval status, the following were studied.

1. Abbreviated New Drug Applications (ANDAs) for prescription and Over the Counter (OTC) formulation products granted by U.S. FDA. [Products which have been discontinued or tentatively approved were not considered for the analysis]
2. Company-wise and country-wise Type II Active Drug Master Files (Shaw, 2007) (DMFs) filed with U.S. FDA and Certificates of Suitability of European Pharmacopoeia monographs (CEPs) granted by EDQM
3. Country-wise, region-wise and category-wise exports and imports of Indian pharmaceuticals sector

As USA has a huge share of 37·13% (valued at US$300bn of the world market estimated at US$808bn. in the year 2009) (Doug L, 2009) in global pharmaceutical markets, analysis of U.S. FDA was comprehensively carried out both for prescription ANDAs and DMFs. Market Authorisations for generic drugs are granted by U.S. FDA through ANDAs. Under the Hatch-Waxman Act (U.S. FDA, 2010), an ANDA can be approved without having to submit studies establishing the safety and efficacy of the drug (U.S. FDA, 2010) upon submission of evidence that the active ingredient of the generic drug is ''bioequivalent'' of a drug previously approved by the U.S. FDA.

A Type II DMF on the other hand is filed with U.S. FDA for drug substances, drug intermediates and materials used in their preparation. It contains technical documentation on chemistry, manufacturing and control. A DMF is considered as active if it is acceptable for filing with U.S. FDA administratively and is up to date.

CEPs are granted by EDQM (EDQM, 2010) to manufacturers or suppliers of the pharmaceutical substance (APIs), when they have demonstrated compliance with the monographs of the European Pharmacopoeia. The CEPs are granted through a centralize procedure by EDQM and are valid in 36 European Pharmacopoeia countries besides several other non-EU countries such as Canada, Australia, New Zealand, Morocco, Tunisia , etc. (Wierer & Pouget, 2007) Analysis of CEP approvals was therefore carried out to establish India's position in bulk drugs in EU.

During the author's research on India's pharmaceutical exports using official basket for Drugs, pharmaceuticals & fine chemicals, at 8 digit HS codes it was noticed that the basket, besides formulations and bulk drugs, consists several intermediates, fine chemicals, excipients, medical & diagnostic equipment, surgicals, medical devices, diagnostic reagents, a few herbals and products under Alternate Systems of Medicine (medicine and medicaments of Ayurveda, Siddha, Unani and Homeopathy are commonly referred to as AYUSH products). However, the official basket is

not an exhaustive one and does not comprehensively cover under each of the categories all the HS codes available at eight digit level (refer table 1A at Annexure I). An attempt was therefore made to exhaustively identify all the available HS codes falling under different categories under Pharmaceutical sector. 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. Currently though many countries have HS Codes identifying medicinal grade fine chemicals and HS codes at 10 digit levels, India does not have such separate classification. Therefore, all the HS codes pertaining to fine chemicals used for pharmaceutical purposes were included based on their description. Using these HS codes analysis Country-wise, region-wise and category-wise exports and imports of Indian pharmaceuticals sector 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. The study therefore analyses India's strengths in US markets to study various therapeutic categories, their market shares, growth rates over years, high value segments, country and company competition, etc.

Results and Discussion

India has grown from strength to strength in US generic markets as well as Bulk drug markets. It has been rapidly emerging as pharmaceutical manufacturing hub of the world as evidenced by the growing number of DMFs filed by foreign companies on Indian facilities especially in the last 10 years (2004-2009) and DMF material imports from USA. India thus emerged as global destination for contract manufacturing in bulk drugs.

This high number of filings not only creates a competitive situation, as formulation product manufacturers can 'shop' around in India but also would act as an encouraging factor to start formulation facilities as DMF material would be readily available.

Analysis of Generic Prescription and OTC Product Approvals

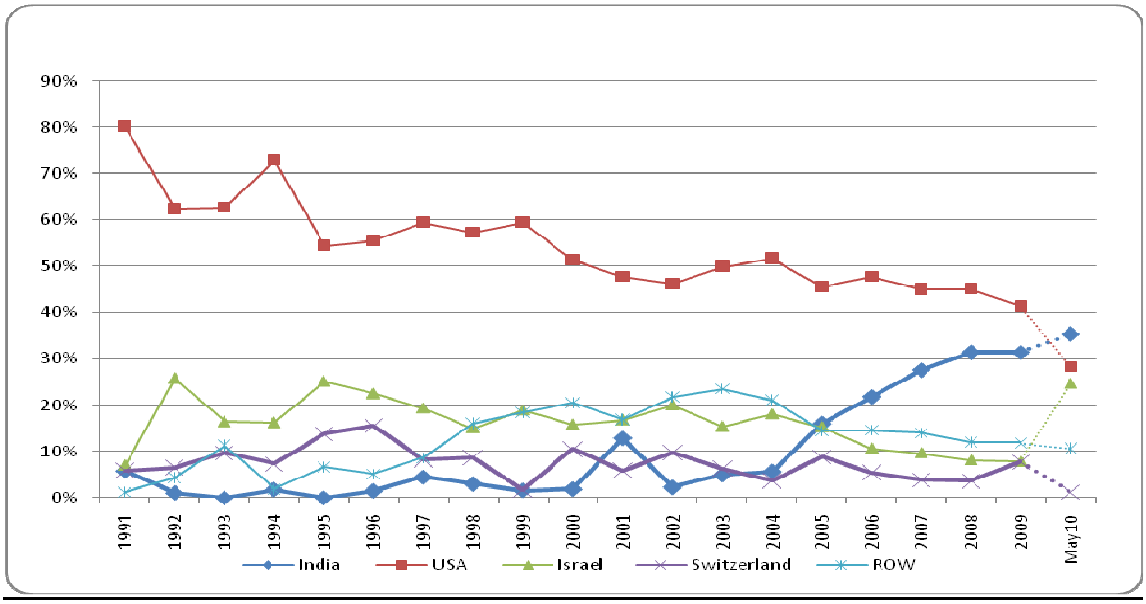
Analysis of drug registrations with U.S. FDA reveals that India is currently among the top countries in number of regulatory approvals granted. The country's generic drug approvals experienced a sudden spurt during the last five years. Currently, India accounts for 14% of the prescription and OTC generic products placing it only second to USA (Table 1). However, these approvals were granted to only 27 Indian companies as compared with 211 companies of USA.

India's number of approvals for generic prescription products (ANDA approvals excluding biologicals, OTC, discontinued and tentative approvals) with U.S. FDA during the five years from 2005 to 2009 have grown tremendously (Figure 1). The country received a total 1,077 product 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 by U.S. FDA making the country the second largest after USA (4,741). Israel (1,189), Switzerland (620) and Canada (370) occupy 3rd, 4th and 5th positions, respectively.

Table 1. India's Status in Approval-Wise Top 10 Prescription Generic Molecules

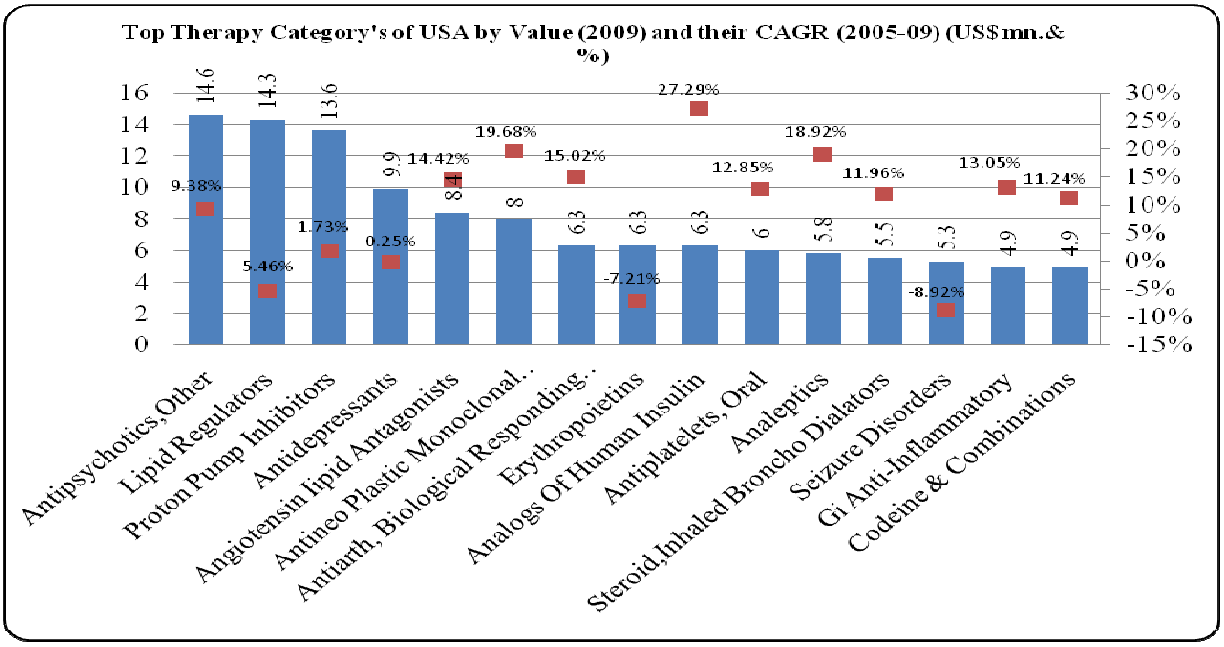
Rank	Active Ingredient	Broad Therapeutic	USA	India	Israel
1	Risperidone	CNS	38	46	7
2	Metformin Hydrochloride	Anti Diabetic	43	24	19
3	Acetaminophen; Hydrocodone Bitartrate	CNS	62	10	
4	Lisinopril	Cardiovascular	24	18	6
5	Fluconazole	Anti infective	27	17	24
6	Alprazolam	CNS	41	4	8
7	Amlodipine Besylate	Cardiovascular	33	27	3
8	Lamotrigine	CNS	21	36	12
9	Levetiracetam	CNS	27	27	9
10	Topiramate	CNS	28	29	6

Figure 1. Changing Scenario of Prescription Generic Product Approvals (1991-May 2010)



It may be noted that the top therapy categories are not necessarily have top market shares. The market value is determined by sales value of number of block buster innovator molecules in the category. In US, CNS is top therapy by value also with anti-psychotics and anti-depressants occupying 14.6% and 9.9% of the market, respectively (Figure 2). However, Human insulin, monoclonal antibodies and anti-epileptics are top growing therapies.

Figure 2. Top Therapy Category's of US by Value (2009) and their CAGR (2005-09) (US$ mn. & %)



In prescription generics Teva is the leader with 623 products followed by Mylan and Watson. The top 15 companies account for more than 50% of the approvals among which two companies viz., Aurobindo (9th position) and Dr. Reddy's (11th position) are from India. Among the total 60 companies that have product approvals in OTC sector, Perrigo with a share of 21·75% is the leader followed by Watson Labs and Dr. Reddy's. The top 15 companies account for over 72% of the total prescription generic product approvals. Out of total 753 molecules having prescription ANDAs, India is present only in 29% of the molecules. Further, analysis indicates that in nine molecules such as Cefixime, Desloratadine, Amifostine, Lithium Carbonate, Piperacillin Sodium; Tazobactam Sodium, etc. only India has prescription ANDAs. At the same time it has more than 50% share in product approvals of several Anti Retrovirals and antibiotics such as Zidovudine, Rivastigmine, Stavudine, Didanosine, Cefotaxime, Ciprofloxacin, Cefepime, etc.

It is observed that, in several other molecules having more than 20 prescription approvals such as Diltiazem HCL, Gentamicin Sulfate, Amitriptyline HCL, Lorazepam, Clonazepam, Diazepam, Acyclovir, Fentanyl, Benazepril HCL & Hydrochlorothiazide combination, Morphine,

Theophyline, Meperidine HCL, India does not have any approvals. Several of these molecules pertain to corticosteroids, controlled substances and fermentation based products (Table 2).

Table 2. Approvals-wise Top Generic Prescription Products in which India is Absent*

Rank in all molecules	Active Ingredient	Broad Therapeutic	USA	India	Israel	Grand Total (All countries)
12	Diltiazem Hydrochloride	Cardiovascular	44	0	6	71
22	Gentamicin Sulfate	Anti infective (Fermentation based product)	37	0	2	54
28	Acetaminophen; Oxycodone Hydrochloride	CNS (controlled substance)	39	0	1	49
33	Lorazepam	CNS (controlled substance)	34	0	3	46
40	Sotalol Hydrochloride	Cardiovascular	26	0	7	44
50	Doxazosin Mesylate	Cardiovascular	20	0	8	40
56	Hydrocortisone	Corticosteroid	26	0	6	38
59	Clonazepam	CNS (controlled substance)	20	0	8	37
61	Amitriptyline Hydrochloride	Cardiovascular	29	0		35
71	Meperidine Hydrochloride	CNS (controlled substance)	26	0	2	33
75	Doxycycline	Anti infective (fermentation based product)	20	0	1	32
79	Cimetidine	GI Tract	15	0	8	31
91	Morphine Sulfate	CNS (controlled substance)	23	0		28
93	Acyclovir	Anti Viral	11	0	6	27
96	Epirubicin Hydrochloride	Anti Cancer	17	0	2	26
97	Amphetamine Aspartate; Amphetamine Sulfate; Dextroamphetamine Saccharate; Dextroamphetamine Sulfate	CNS (controlled substance)	4	0	11	26
99	Phentermine Hydrochloride	CNS	11	0	5	26
102	Fentanyl	Analgesic & Anti-Inflammatory (controlled substance)	9	0	4	25
104	Diazepam	CNS (controlled substance)	16	0	6	25
107	Theophylline	Respiratory (NTI)	20	0		24

** 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 product approvals held by Indian subsidiaries abroad.*

From the table 2, 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 product approvals held by Indian subsidiaries abroad. In spite of India's regulatory strengths in various markets, currently there is only one Indian company which appears in the list of top 10 generic companies (Fierce Pharma, 2010) of the world in 2010.

India's Status in API Registrations

Currently out of 58 countries having Type II DMFs with U.S. FDA, India is the leader in terms number of filings and number of companies filing on Indian facilities. It is only second to USA in number of molecules. The country has a share of 31·37% of all the DMF filings and approximately 26·71% of molecules. Over 31% of the companies both from India and foreign countries have DMFs on Indian facilities. During the research it was observed that the foreign companies account for nearly 38% of all the companies having DMFs on Indian facilities and particularly during 2009 there were large number of filings by foreign companies. This signifies the emergence of India as manufacturing hub for pharmaceuticals.

Eight of the top 10 filers, after 'Teva Group', are from India. Among Indian companies, Dr. Reddy's ranks first followed by Aurobindo and Cipla. Out of total 608 molecules filed by India, there are four or more DMFs in 193 molecules (31·74%) and therefore has high internal competition. For example for Atorvastatin, out of the total 30 DMFs filed with U.S. FDA by all countries, India alone accounts for 21 DMFs. Similarly, over 80% of the DMFs in several top molecules such as Clopidogrel, Lamivudine, Sertraline, Ramipril, Sildenafil, Zidovudine, Fluvastatin, Tadalafil, Citalopram, etc., are filed from Indian facilities. For 137 molecules like Esomeprazole, Escitalopram, Celecoxib, Lopinavir, Naratriptan, Salmeterol, Tenofovir, etc., only India has filed DMFs.

The country is absent mostly in fermentation products, controlled substances and steroids. For example, India does not have any DMFs for several important fermentation products such as Penicillin G, Clavulanate, Fludarabine, Heparin, Acarbose, etc., controlled substances like Morphine, Fentanyl, Amphetamine, Propoxyphene, Codeine, Dronabinol, Hydromorphone, etc. and corticosteroids like Cortisone, Hydrocortisone, Fludrocortisone, Predinisone, Methylphrednisolone, etc.

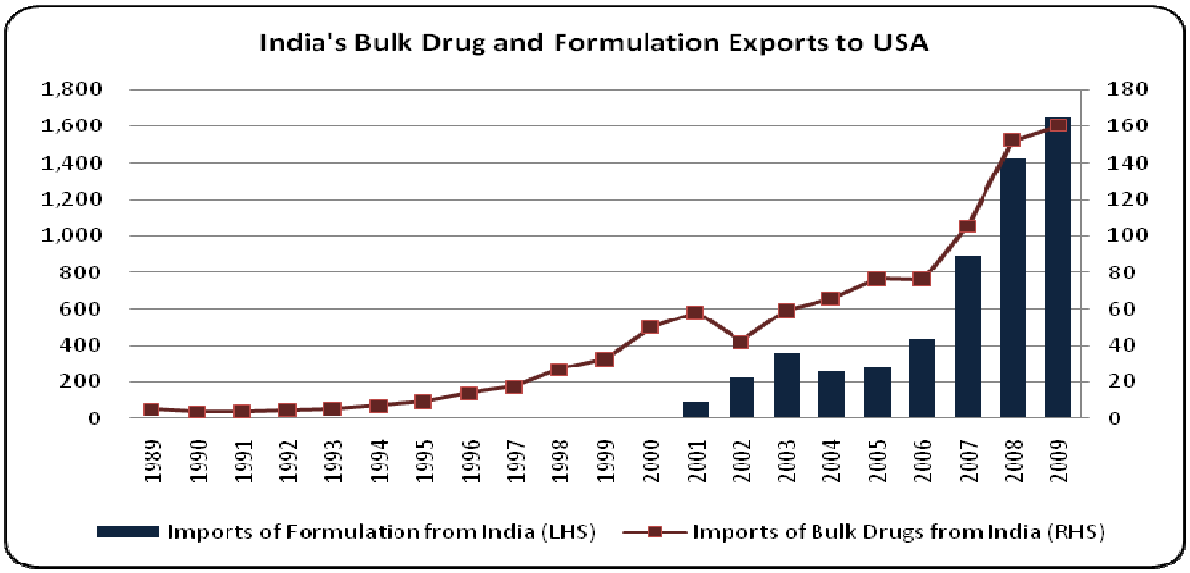
India is the leader in number of CEPs granted by EDQM. Currently it accounts for 24% of CEPs, slightly over 18% of the companies are from India which account for nearly 31·86% of the molecules with EDQM. The country leads in top categories of Antimicrobials, CNS, CVS, Analgesics and GI tract. Significantly the country is absent in biological, anti-cancer and corticosteroids.

Analysis of India' Bilateral Trade in Pharmaceutical Products

Analysis of Exports

Research on India's HS Codes reveals that the country's trade in pharmaceuticals sector is actually higher than the current understanding. India's total exports of drugs, pharmaceutical and fine chemicals in the year 2008-09 stood at approx. US$13,233·12mn. (Figure 3) 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 sector grew a compounded annual growth rate (CAGR) of 22·51% during the five year period from 2004-05 to 2008-09. The imports are approx. at US$10,778·33mn 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.

Figure 3. India's Bulk Drug and Formulation Exports to United States



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%. Medical & diagnostic equipment, surgical and diagnostic reagents are estimated at 4·32% (Figure 4). 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% (Figure 5). Currently India exports to some 209 countries/territories of the world and imported from 139 countries/territories during 2008-09.

Figure 4. Composition of India's Pharmaceutical Sector Exports (2008-09)

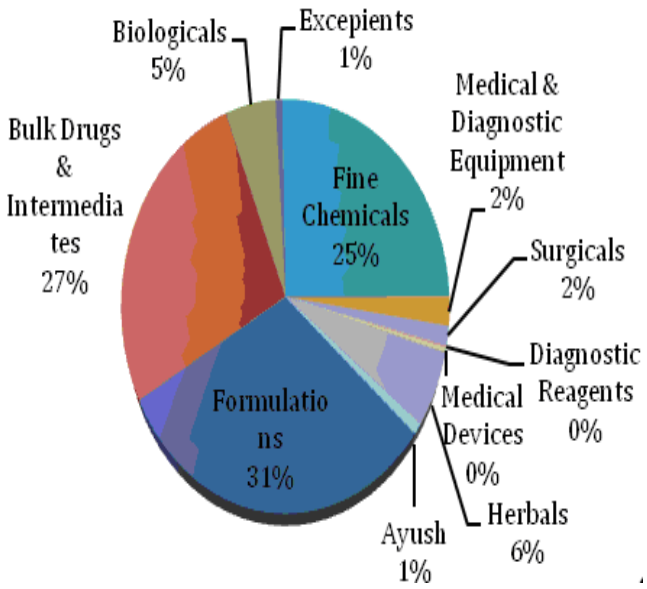
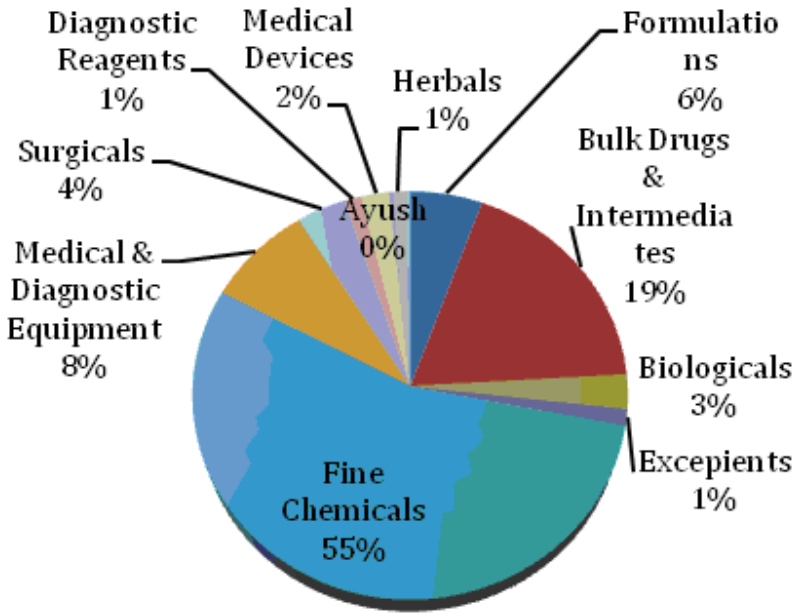


Figure 5. Composition of India's Pharmaceutical Sector Imports (2008-09)



Asia is the largest export destination of India's pharmaceuticals (excluding Medical devices and fine chemicals) followed by Europe and North America while Asia is the largest sourcing region for imports followed by Europe and North America (Figures 6 & 7).

Figure 6. Region wise Share of India's Pharmaceutical Exports (2008-09)

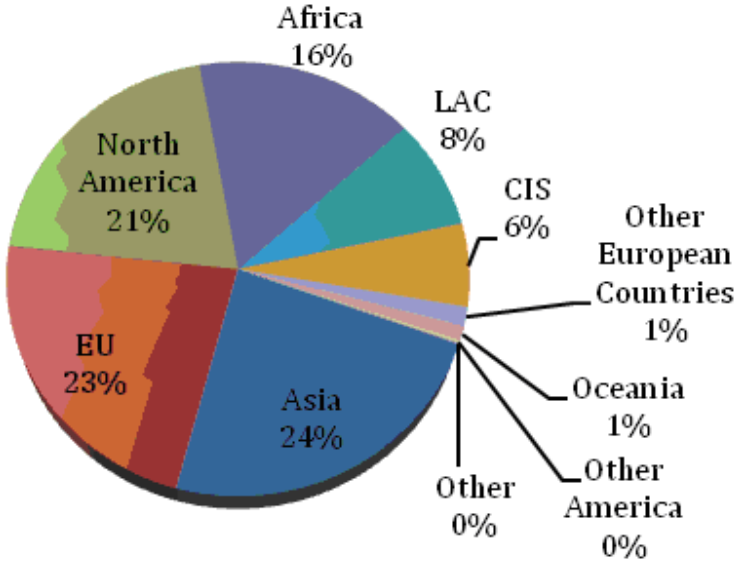
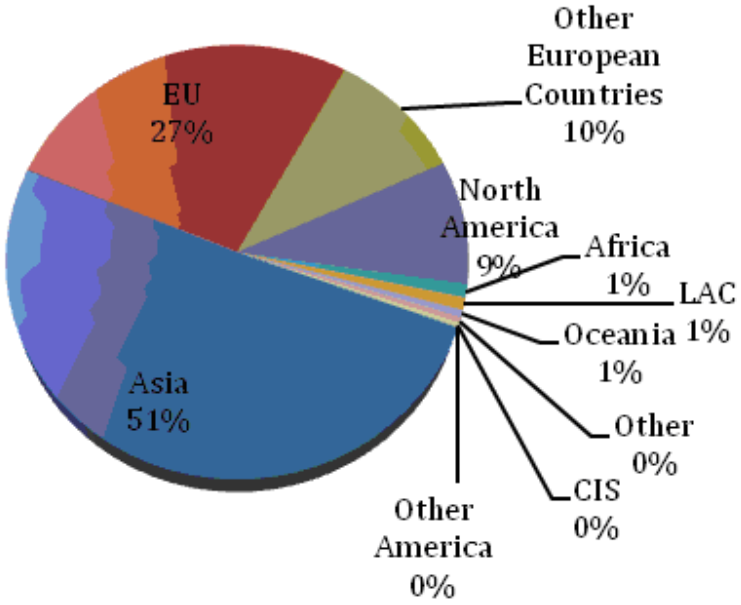


Figure 7. Region wise Share of India's Pharmaceutical Imports (2008-09)



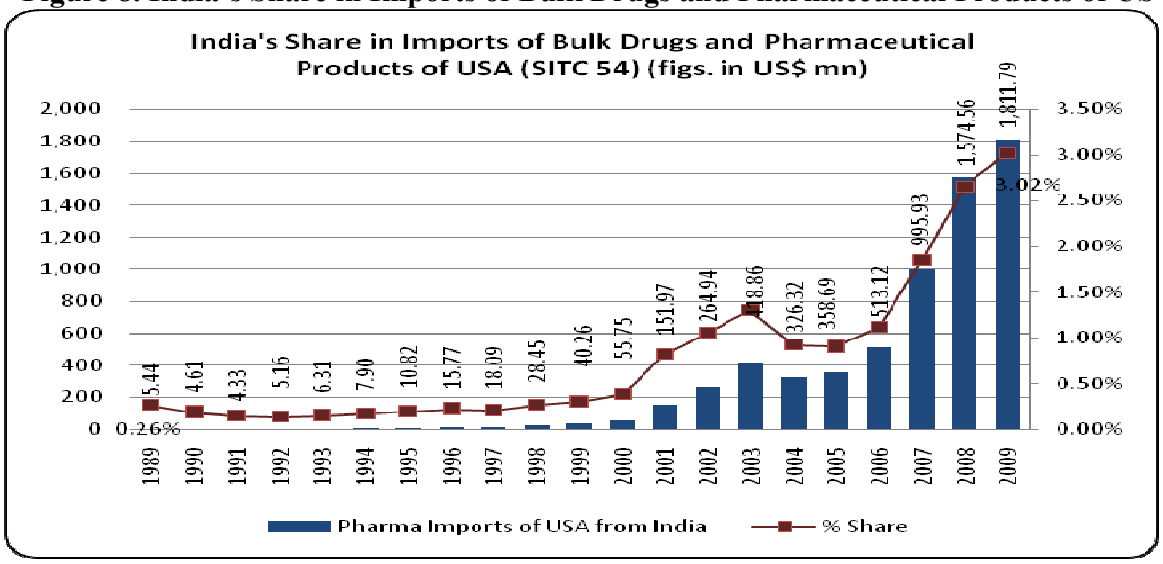
For bulk drugs & intermediates EU is the most important destination with exports over US$1bn. and the region is also among the important destinations for India's formulations. An estimated 52·36% on the exports to the region are bulk drugs & intermediates followed by formulations with a share of 44·38%. EU is followed by North America which is an important destination for

formulations, biologicals as well as bulk drugs & intermediates. Africa is by far the most important destination for India's formulation exports valued at nearly US$1bn. growing at a 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, the major importers of bulk drugs & intermediates from India are China, Israel, Turkey, S. Korea, and Thailand and nearly two thirds of the exports to LAC region are also bulk drugs & intermediates. India's exports potential to Oceania region is largely untapped as evident from the country's share compared with market size of the region.

Analysis of Imports

During 2008-09, India imported over US$1,991·83mn worth bulk drugs & intermediates with China contributing nearly 2/3rd 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. EU 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%) being the other major suppliers. Barring China and USA, the top 10 supplier countries are from Europe. Formulation imports from USA 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.

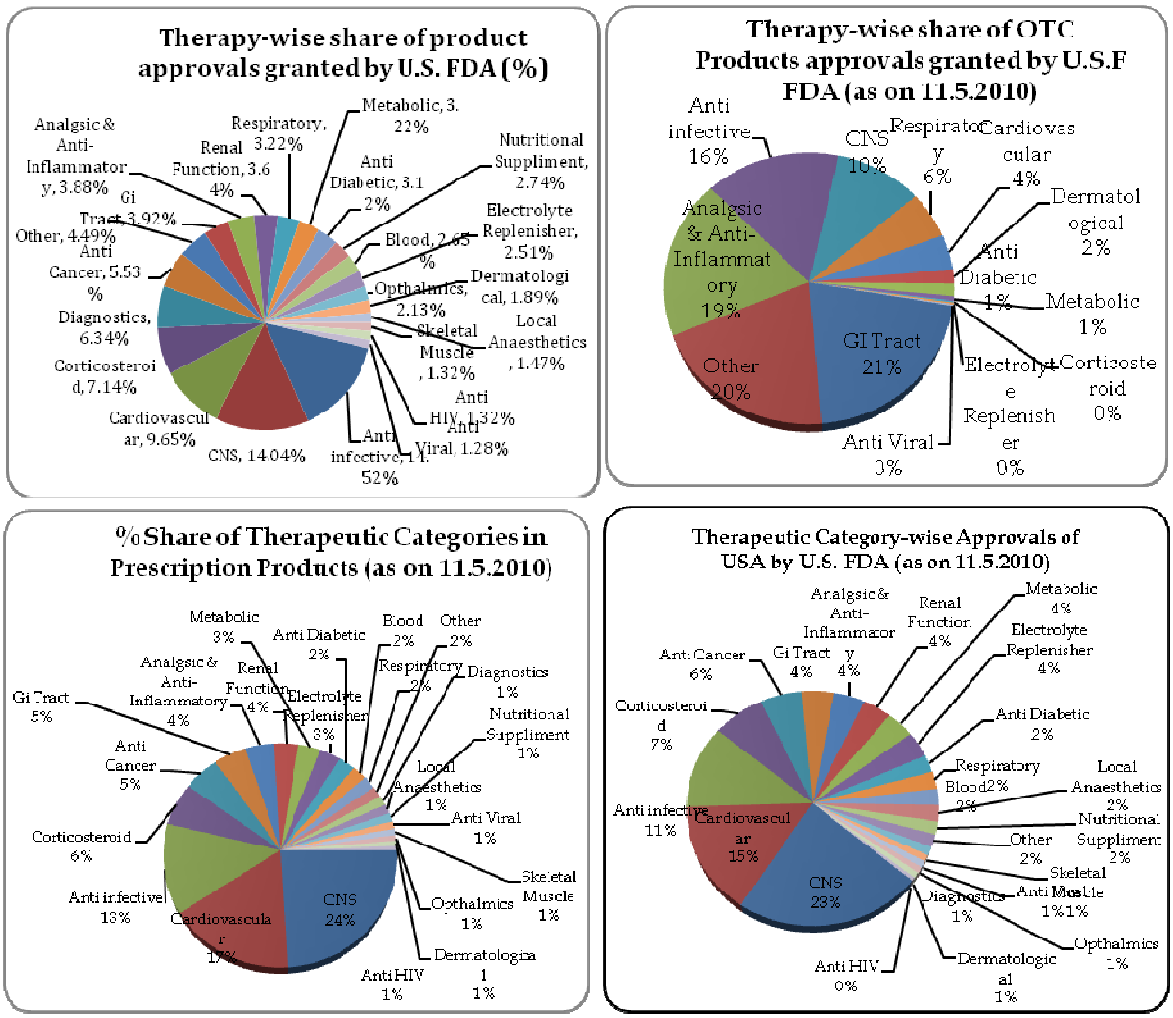
Figure 8. India's Share in Imports of Bulk Drugs and Pharmaceutical Products of US



India 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. 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. India's growing dependency on China for bulk drugs and fine chemicals indicates erosion of country's competitiveness in the segment. While India on the whole has a positive trade balance in formulations, bulk drugs & intermediates, biologicals and excipients, it has increasing negative trade balance of US$2,329·19mn and US$1,078·62mn in fine chemicals and Medical & diagnostic equipment, devices and surgicals, respectively.

Figure 9. Representation of Pharma Products Approvals and Sharing by Therapy Wise



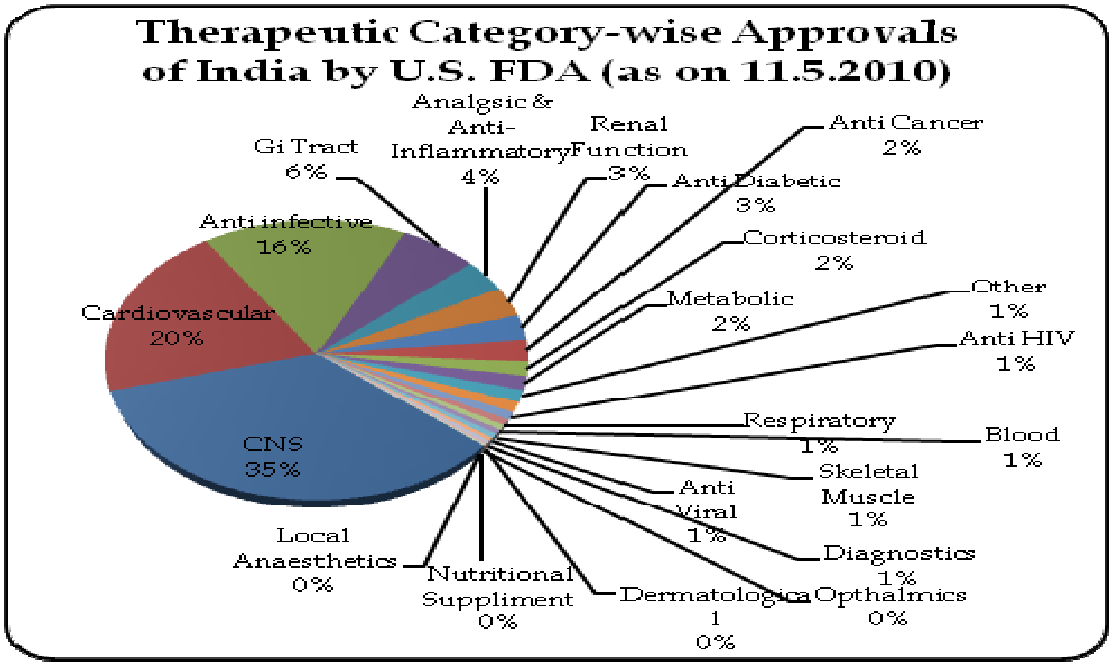
Analysis of India's Status in various Therapeutic Categories

Highest number of generic product approvals by U.S. FDA was granted in the Anti-infectives category which has share of 14.52%. It is followed by CNS, cardiovascular, corticosteroids and

diagnostics (Figure 9 & 10). Most of GI Tract and Analgesic approvals are OTC products. However, most number of prescription approvals is for CNS and CVS. Analgesics stand third followed by corticosteroids.

India's approvals are broadly in synchrony with the approval therapy-wise approval trends in U.S. FDA. The country also has highest number of approvals in U.S. FDA in CNS category, Cardiovascular, Anti-infectives and GI tract. It is comparatively stronger in number of approvals in Antiretrovirals, Antimicrobials, CVS, anti-diabetics, CNS and dermatologicals. However, it is poor in corticosteriods, Anti-cancer and diagnostics. Further examination reveals the country is weak in Biotechnology products including fermentation products, complex chemistry, advanced dosage formulations and specialty formulations.

Figure 10. Therapeutic Category-wise Approvals of India by US-FDA (as on 11-15-2010)



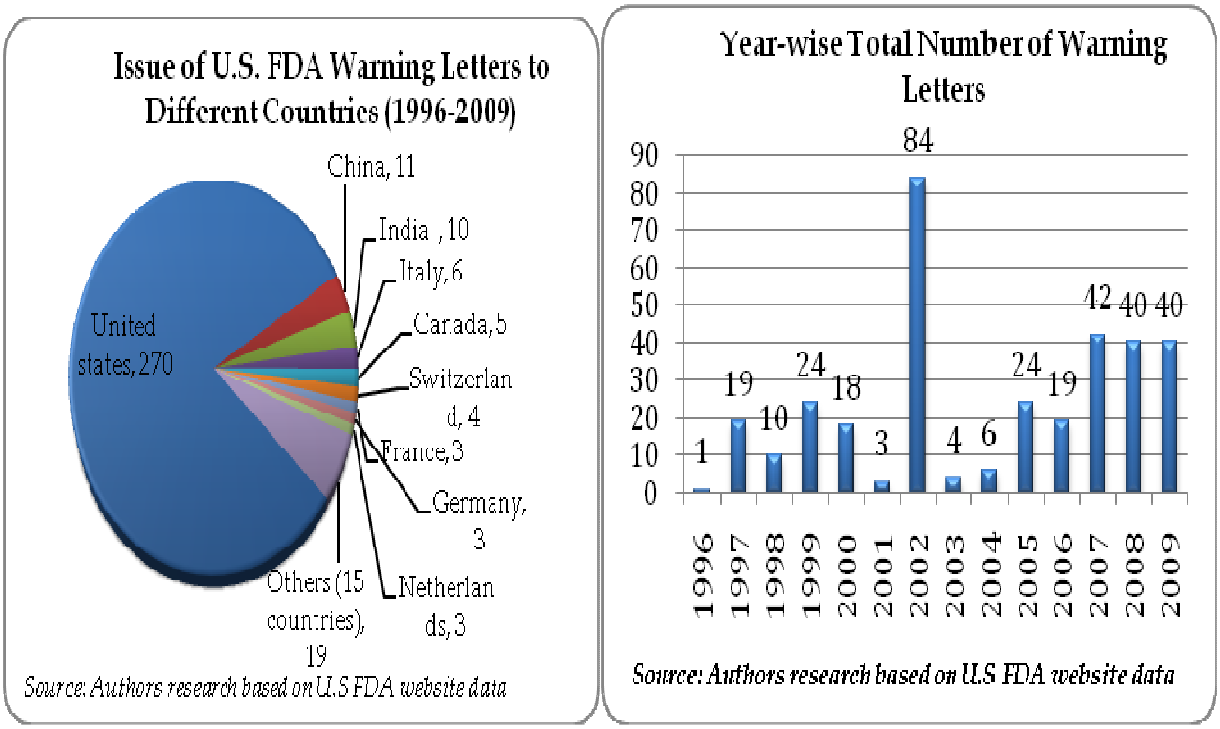
Emerging Opportunity for India in US Pharmaceutical Market

From the patent expiries of top 50 innovator molecules by sales, it is observed that patents of several block buster molecules whose sales are between US$723mn. to US$4.98bn are expiring in the five years between 2011 to 2015. Montelukast Sodium, Esomeprazole Magnesium, Olanzapine, etc. are among the top molecules whose patents are expiring. The opportunity from these top 50 molecules alone is valued at US$63.85bn. if their sales are assumed to remain same as in 2009. Of this 80% market value will erode after patent expiry which implies the market or generics is valued at US$12.77bn. Generic companies can potentially capture 20-30% of this market estimated at US$2.55-3.83bn.

Warning Letters issued by U.S. FDA

Examination of number of warning letter issued by U.S. FDA to companies belonging to various countries during the last 14 years for which data is available indicates that India has received very few warning letter relative to its number of approvals compared with USA (Figure 11). In spite of the fact, India's only recent emergence as top filer in USA, mere 10 warning letters issued to the country compares favorably with other countries indicating strong compliance capability of the country.

Figure 11. Summary of US-FDA Warning Letters



Reasons for all warning letter issued to Indian companies are presented in Table 3. Analysis indicates that out of 10 warning letters two were issued to API companies while the rest were for formulations. Out of the 8 warning letters 6 were for CGMP deviations while two were due to according of new drug substance status.

Table 3. Total number of Warning Letters Issued to Indian Companies with the Reasons

S. No	Organisation	Year	Reason for Warning letter
1	Lupin Limited	2009	CGMP for Finished Pharmaceuticals/Deviations/Adulterated
2	Ranbaxy Laboratories, Ltd., Dewas, India	2008	CGMP/Drug/Deviations/Adulterated
3	Ranbaxy Laboratories, Ltd., Ponta Sahib, India	2008	CGMP/Drug/Deviations/Adulterated
4	Ranbaxy Laboratories Limited	2006	Current Good Manufacturing Practices for Finished Pharmaceuticals/Adulterated
5	Wockhardt Ltd	2006	Current Good Manufacturing Practices/Active Pharmaceuticals Ingredient/Adulterated
6	Ranbaxy Pharmaceuticals Inc.	2002	Certain Drugs Accord New Drug Status through Rulemaking Procedures/Guaifenesin
7	M G Acquisition LLC	2002	Certain Drugs Accorded New Drug Status through Rulemaking Procedures/Guaifenesin
8	Granules India Limited	2001	Active Pharmaceutical Ingredient Manufacturing Facility/Adulterated
9	SOL Pharmaceuticals Limited (Dr. Reddy's)	2000	Good Manufacturing Practices for Active Pharmaceutical Ingredient
10	FDC Ltd.	1999	Active Pharmaceutical Ingredient
Source: Authors research based on U.S FDA website data			

Paragraph IV challenge

Analysis of Para IV challenges filed by various companies in US during the past five years indicates that Teva continued to be by far the most prolific filer of ANDAs with patent challenges of 136 products. Mylan has stayed in second place with links to patent challenges on 65 different products, up from 61 the quarter before, with Novartis closely behind with challenges on 62 products. Four Indian companies viz., Ranbaxy, Sun, Dr. Reddy's and Lupin find place among the top 10 challengers who have collectively challenged patents of 54 molecules/products. While these companies collectively have 6 Patent challenges in settled in their favor these are only 11.11% among their total patent challenges and is among the lowest the lowest in the top 15 companies (Table 4). However, it indicates growing skills in patents domain and confidence in Indian companies.

Table 4. Analysis of top 15 Companies by Number of Patent Challenges (Para IV filings) US

Company	Won	%	Dropped/ Settled	%	Lost	%	Total	% Success	Launched at Risk
Teva	27	25%	57	53%	24	22%	108	78%	13
Watson	6	15%	29	74%	4	10%	39	90%	0
Mylan	7	28%	9	36%	9	36%	25	64%	1
Sandoz	11	46%	10	42%	3	13%	24	88%	6
Apotex	2	10%	7	33%	12	57%	21	43%	1
Ranbaxy	2	11%	10	53%	7	37%	19	63%	0
Dr. Reddy's	2	11%	9	50%	7	39%	18	61%	0
Par	4	27%	9	60%	2	13%	15	87%	1
Impax	4	29%	8	57%	2	14%	14	86%	0
Sun	1	11%	5	56%	3	33%	9	67%	2
Lupin	1	13%	5	63%	2	25%	8	75%	0
Perrigo	1	13%	7	88%	0	0%	8	100%	1
KV Pharm	1	14%	5	71%	1	14%	7	86%	0
Actavis	2	33%	3	50%	1	17%	6	83%	1
URL Pharma	1	20%	2	40%	2	40%	5	60%	0

Conclusion

Research reveals that India has highest number of approvals in U.S. FDA in Anti-hypertensive, Anti-HIV, Anti-diabetic, GI Tract, antiviral, anti-infectives, CNS category, cardiovascular, and dermatologicals etc. However, it is poor in Corticosteriods, Anti-cancer and diagnostics, Biotechnology products including fermentation products, complex chemistry, advanced dosage formulations and specialty formulations. Out of total 753 molecules having prescription ANDAs, India is present only in 29% of the molecules and does not have any approvals in several other molecules having more than 20 prescription approvals. India therefore needs to strengthen in areas of CNS particularly anti-psychotics and anti-depressants, Lipid regulators, proton pump inhibitors, Human insulin, monoclonal antibodies and anti-epileptics having a huge market value.

As patents of several block buster molecules having huge sales in US market are expiring in the next five years of 2011 to 2015, this becomes a golden opportunity for Indian Generic companies which can potentially capture 20-30% of this market estimated at US$2.55-3.83bn. Inspite being a top filer in US market, India has received very few warning letters from the past 14 years.

The country has to overcome several challenges to reach its full potential. In formulations, the country has to upgrade itself into next orbit through incremental research like changes in dosage form, composition, route of administration, new formulation and combination of individual approved molecules [10, 11], etc. The country needs to strengthen itself complex molecules, specialty generics and advanced dosage forms (value added products) which have high barriers of entry and high margins of profits [11].

India has very little presence in the world markets in biologics and the country depends on Chinese imports for many of the biotechnology and fermentation based products. On the other hand China has been strategically developing in biotechnology segment and is well advanced in molecular biology, gene therapy, genomics and proteomics research [12]. Hence this is an opportune time for Indian pharmaceutical firms to diversify their exports to exploit niche or specialty generics in international markets. The future for India's pharmaceuticals industry lies in flexibility, speed & supply chain strengths. Neither innovation nor generics but only 'compelling total offer' would put the country among the very top.

Disclaimer

This research article is a product of professional research and presents views, opinions solely of the authors. It is not meant to represent position or opinion of Pharmexcil or those of Government of India nor official position of any of the staff members. Any errors are the fault of the authors.

Funding for the Article: None

This article has not been funded directly or indirectly by any government or non-government or commercial or any other type of organization or individuals. However, the establishment, resources and one database of Pharmaceuticals Promotion Council (Pharmexcil) were used and the article was developed during off-duty hours.

Acknowledgements

The authors are grateful to PHARMEXCIL team for their kind support during this research.

References

1. Chadha A, Product cycles, Innovation, and Exports: A study of Indian Pharmaceuticals, World Development 2009;37(9):1478-1483.
2. Chittoor R., Ray S. Internationalisation paths of Indian Pharmaceutical firms – A strategic group analysis, Journal of International Management 2007;13:338-355.

3. Exports Performance of Indian Pharmaceuticals Industry - 2008-09, Pharmaceuticals Export Promotion Council of Indian (Pharmexcil). Annual Report 2008-09, http://pharmexcil.org/index.php?option=com_content&view=article&id=864&Itemid=343 (Accessed on 22.11.2010)
4. William G. The Emergence of India's Pharmaceutical Industry and Implications for the U.S. Generic Drug Market. U.S. International Trade Commission, May 2007.
5. PricewaterhouseCoopers, 'Global Pharmaceutical Companies Need To Take An Even Closer Look At India'. http://www.pwc.com/gx/en/press-room/2010/global-pharma-cos-need-to-take-closer-look-at-India.jhtml (Accessed on 22.11.2010)
6. Ellen F.M. 't Hoen, LL.M., The Global Politics of Pharmaceutical Monopoly Power, AMB 2009. http://www.soros.org/initiatives/health/focus/access/articles_publications/publications/aem_20090312/politics_20090312.pdf (Accessed Feb. 2, 2010)
7. Nicoli Nattrass. Government Leadership and ARV Provision in Developing Countries. Centre for social science research AIDS and society research unit. Working paper no. 14. (Accessed on 22.11.2010)
8. IHS Global Insight. Increasing Demand for Indian Drugs Prompts Calls for Permanent U.S. FDA Presence in India, 18 Jun 07. http://www.ihsglobalinsight.com/SDA/SDADetail9647.htm.
9. Department of Commerce, Ministry of Commerce and Industry, Government of India. Report of the Task Force, 'Strategy for Increasing Exports of Pharmaceutical Products', December 12, 2008. http://www.commerce.nic.in/publications/Report%20Tas%20Force%20Pharma%2012th%20Dec%2008.pdf?id=16 (Accessed on 30.11.2009)
10. Jena P. Presence of Indian pharmaceutical industries in US market: An empirical analysis, Journal of Generic Medicines 2009; 6 (4), 333–344.
11. Sawant M., Opportunity for India in the World Generics Market, Frost & Sullivan, http://pharmalicensing.com/public/articles/view/1144147543_44324e57b031f/opportunity-for-india-in-the-world-generics-market (Accessed on 24.11.2010)
12. Chervenak M. China appears to be Moving towards A More Innovation–Based Pharmaceutical Industry. Drug Discovery Today 2005; 10 (17):225