Pharmaceutical Innovation and Contribution of In-house R&D of Domestic Firms after TRIPS in India

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Post-TRIPS Contribution of Domestic Firms to Pharmaceutical Innovation in India: An Assessment

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Post-TRIPS Contribution of Domestic Firms to Pharmaceutical Innovation in India: An Assessment

Dinesh Abrol [*] ***and Nidhi Singh*** [**]

[***Abstract***: *In this article we analyze the results obtained from the implementation of processes of learning, competence building and innovation making by domestic firms under the influence of the selected pathway of global integration of industry and healthcare for upgrading of pharmaceutical innovation system in the post-TRIPS era in India. Analysis is made of the claims of those who thought the gains that could accrue from the pathway of enhanced reliance on FDI, technology transfer and R&D investment from overseas would allow the Indian pharmaceutical industry and government to upgrade the pharmaceutical innovation system in a better way in the post-TRIPS era. Investigations made into the development of pharmaceutical innovation system focus on the achievements and limitations of the post-TRIPS innovation policy. Results indicate that the link between domestic firms and public sector research organisations is the weakest link of national sectoral pharmaceutical innovation system in India. It suggests that the government needs to rethink the pathway to get domestic firms to contribute to the system building activities at home. The emerging pharmaceutical innovation activity landscape needs a disruptive change and creative destruction of existing relationships to foster indigenous innovation. Investment into the building of relationships and cooperation for the upgrading of processes of learning and competence building should be collectively prioritised by the government, industry, clinicians and public research system to achieve better results with the upgrading of pharmaceutical innovation system.*]

Introduction

Catching-up requires the Indian pharmaceutical industry to catch up in the creation of knowledge for drug discovery and process innovations (Lei *et al.*, 2016). In the post-TRIPS (Trade Related Intellectual Property Rights) era, the "catching-up" country will have to devise government policies that can help establish relationships between industry-research institute-university-hospital as well as strengthen fundamental research in public sector for the benefit of drug discovery and development at home. Further, the catching-up countries in the post-TRIPS era face the challenge of preventing the system of knowledge creation for pharmaceutical manufacturing and innovation from becoming dependent on foreign firms originating from the US and Europe for maintenance of their learning and competence

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building structures. Therefore, it is important to retain strategic control over the structures of knowledge creation for pharmaceutical innovation making at home by encouraging domestic firms to build a path wherein selective delinking of emerging relationships between industry-research institute-university-hospital will be assured through development of R&D and innovation for priority diseases of catching-up countries by their respective governments.

This article examines the contribution of domestic pharmaceutical firms to the emerging pattern of pharmaceutical innovation after the implementation of TRIPS Agreement in India. Contribution focuses on the impact of the approach adopted by governments for the formulation of post-TRIPS innovation policy to address complementarities vis-à-vis the steering and coordination of policies for upgrading in-house R&D, publicly funded R&D, intellectual property, domestic industry and health system. Analysis focuses on the contribution of in-house R&D activities of domestic pharmaceutical firms, foreign technology transfer through alliance making, and collaboration and overseas R&D (ORD) undertaken in India. Results indicate that the link between domestic firms and public sector research organisations is the weakest in respect of national sectoral pharmaceutical innovation system in India. In the post-TRIPS era, the Indian pharmaceutical firms were put on the pathway of global integration of the processes of learning and competence building. They continue to pursue their innovation making strategies in line with their own thinking that their limited in-house R&D efforts when combined with contribution from strategic alliances and collaborations with foreign firms will ultimately enable them to catch-up with firms originating from the US and Europe.

Analysis suggests that the contribution of domestic firms to product, process and manufacturing innovation is embedded in the concept of learning, competence building and innovation making, which is "heroic" in terms of knowledge creation for new drug development and is "dependent" on foreign firms for competence building in terms of capacity creation for drug discovery, development, manufacturing and regulation. Consequently, at home, their current innovation strategies do not place sufficient emphasis on building industry-research institute-university-hospital relationships and on cooperation for learning and competence building within India. The contribution of domestic firms to pharmaceutical innovation activity landscape requires indigenous innovation to be prioritised by the government, industry, clinicians and public research system. The authors suggest that the government needs to reconstruct its policy of innovation making related incentives and disincentives and accordingly devise industrial and health policies to encourage domestic firms to contribute to swift organisational innovation system.

Section 1
TRIPS, Domestic Policymaking and Pharmaceutical Innovation

Argument put forth for the early implementation of TRIPS Agreement by the advocates of neoliberal economic reforms was that India needs high quality Foreign Direct Investment (FDI), Foreign Technology Transfer (FTT), overseas R&D that domestic firms need to be incentivised for new drug development through stronger patent system. Advocates of TRIPS Agreement argued that the patent policy should be consciously designed not to discourage foreign firms from investing and also entering into strategic alliances and collaborations with domestic firms in the post-TRIPS era. In the pro-neoliberal economic reforms policymaking circle, the view taken was that domestic firms should be encouraged to pursue the path of strategic alliances and collaboration agreements to inset themselves into global value chains. In many ways, this view was expressed in the writings of Watal (2016) and Ganesan (2016). Such views found their way ultimately into the official policy framework largely when the NDA government led by Atal Bihari Vajapayee took over and announced the National Pharmaceutical Policy, 2002, which the UPA government continued with and strengthened in the same direction of neoliberal path of global integration of domestic pharmaceutical production and innovation activities.

The vision and direction changed from the year 2000 for all complementary policy measures under implementation for perusal of pharmaceutical innovation and industrial development in India. Since then the political and bureaucratic apparatus has been upbeat about the contribution of the path of strategic alliances and collaborations being pursued by domestic firms with foreign pharmaceutical firms to advance the activities of pharmaceutical innovation in India. Domestic firms have been encouraged to pursue the strategy of pursuing learning, competence building and innovation making, largely through strategic alliances and collaborations. The Government of India devised a policy in support of separate R&D companies and gave liberal tax concessions. When the National Pharmaceutical Policy, 2002, was formulated, India was in the process of implementing the second amendment to the Indian Patent Act, 1970.

It was also a time when several important academic contributions explicitly favoured the argument of stronger intellectual property rights regime in their writings. Lall and Albaladejo (2002) assessed the case of uniform and strong IPRs for developing countries as a whole by classifying them using various measures of domestic innovation and technology imports. It was assessed that it is possible to argue that India has reached a stage in pharmaceutical production where stronger IPRs will induce greater innovation by local firms, though the benefits will have to be set off against the closure of other firms. Keely (2000), too, came to a similar conclusion: 'as long as the TRIPs Agreement is in place most developing countries will almost always continue to suffer a decrease in social welfare. The result gets qualified only in the case where the developing countries as a whole have a large share in the markets that are innovation intensive.' Conclusions rested on the understanding that India's industrial strength in respect of production of generics

from the basic stage and the ability to harness its scientific and technological potential for development of new drugs were robust enough to take advantage of the spillover, demonstration and competition effects of FDI and related technology transfer and overseas R&D activities.

Granville and Leonard (2003) made a case for upgrading the national innovation system through the route of trade and investment liberalisation[1]. Their argument was built around the model of knowledge diffusion occurring automatically via strong IPRs when combined with the process of liberalisation and the entry of international pharmaceutical firms. Argument favoured a strong IPR compatible FDI policy approach to industrial upgrading of pharmaceutical industry. This policy model was built on the basis that it is possible to achieve synergy between the emerging characteristics of automatic knowledge diffusion of pharmaceutical production, process development and marketing strategies and the existence of essential condition of a strong education foundation and past practice of spending in health sector. This model did not focus on the need to strike a balance between exploring fundamental science and applying existing knowledge. It did not ask the government to create favourable conditions for investment to be directed towards fundamental research, industry-research institutes-university-hospital relationships and cooperation.

Contrary voices were raised from within the Indian academia, the civil society, and the local pharmaceutical industry. These voices argued in favour of the position that not only does India need to fully exploit the transition period making use of exemptions obtained through negotiations, but also the policy of "selective delinking," strengthening of public sector and its positive discrimination in favour of private sector companies practicing indigenous innovation and new product development for the benefit of Indian priority diseases should be followed[2]. Although the challenge of TRIPS was tackled by policymakers in part in India through the pathway of delayed external liberalisation (by holding back the freedom to establish subsidiaries to foreign pharmaceutical firms and postponing the implementation of product patent until 2005), the domestic innovation policy was shaped on a significantly different understanding that stronger IPRs and

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[1] Some scholars explicitly expressed that 'neither trade liberalization nor TRIPs requirements are likely to suppress the spread of research and innovation and of generics production, which are a result of knowledge distribution and spillovers as well as property rights protection. Learning by doing is a self-sustaining process that leads naturally not only in imitative and generic production in pharmaceuticals, but also in innovation, for which incentives build up. Even limited R&D and pharmaceutical production, as taking place now through the expansion of pharmaceutical production and sales in transition and emerging economies, is knowledge intensive and has some impact. The multi-layered impact of cooperation will make it possible for these economies to access learning. Both, generics as well as patented products tap into learning, and they are both increasingly responsible for expanding markets in the pharmaceutical sector' (Granville and Leonard, 2003).

[2] See Abrol (2004), Chaudhuri (2005), and, Dhar and Gopakumar (2006).

strategic alliances with foreign firms are necessary to promote product innovation in pharmaceutical industry.

Many scholars voiced their concern about the early implementation of TRIPS, saying that they did not agree with the rosy picture being painted in respect of FDI inflows for upgrading pharmaceutical manufacturing or for transferring new technologies from R&D stage to their successful introduction into practice. They were in favour of strengthening domestic demand and gearing the public sector component of the national innovation system so as to undertake innovation making activities in priority diseases which cover both communicable and non-communicable diseases as well as address the challenge of indigenous industrial development through process manufacturing innovation (Abrol, 2004; Chaudhuri, 2005). In Section 2 we undertake an assessment of the effects of pharmaceutical innovation system resulting from the adoption of this pathway of catching-up on the pharmaceutical industry in India.

Section 2
Patents, Domestic Firms and Innovation

An assessment of the resulting efforts for the catching-up process in the post-2000 phase of pharmaceutical innovation making indicates that while the full legal effects of the Agreement were suspended during the transition period, its effects on India were nonetheless substantial, because of its impact on the behaviour and thinking of the industry and the government. With a looming deadline for TRIPS implementation and the fear of losing ground in the local market, Indian firms began to look for new markets. This led them in two directions—towards exports and towards research and development (R&D)—targeted at developed country markets. India was able to achieve a positive trade balance in pharmaceuticals in the late 1980s. Domestic firms were then increasing their focus on exports to unregulated markets in developing countries. Although the developed world has the most lucrative markets for generic drugs, extensive regulation restricts entry.

Domestic firms had to develop the necessary organisational and technological capabilities through acquisition of foreign firms as well as strategic alliances and collaborations for learning, competence building and innovation making using the opportunities available in the global pharmaceutical industry. Although the domestic firms took some time to develop in-house competence for the export of off-patent generics to regulated markets, they have mainly continued to steadily invest in the inventive activity required to be carried out for the success of this path. It is because domestic firms, until then, had chosen to rely on the capabilities of public sector industry and R&D institutions—a discontinuity which some characterize as a sign of rising star is nothing more than a sign of locking-in of domestic firms into a dependent pathway of industrial development.

Analysis of the industry-wide patenting activity indicates that innovation making activities continue to focus on the development of capabilities, innovations and technological know-how for off-patent generics that the industry is interested in exporting to regulated markets

of Europe and the US. The number of patents filed on New Chemical Entities (NCEs) is still small. Analysis of the different types (in terms of numbers) of patents in *Table 1* suggests that the economic opportunity created by the Hatch-Waxman Act of 1984 remained an important stimulus for domestic pharmaceutical firms to invest in the processes of learning, competence building, and innovation making during the post-2000 period. See *Table 1* for the historical timeline of capability development profile mapped by the authors on the basis of patents filed by the Indian pharmaceutical industry with the United States Patent and Trade Mark Office (USPTO).

Table 1: Pharmaceutical Patenting in United States from the Indian Pharmaceutical Industry, 1992–2013

SNo	*Nature of patent*	*1992–1995*	*1996–1999*	*2000–2003*	*2004–2007*	*2008–2013*	*Total*
1	Process patent		11	51	133	176	371
2	NDDS patent			18	23	10	51
3	NCE patent		3	6	10	-	19
4	Method of treatment, Dosage, Formulation Composition, Combination & Product Patent	14	26	102	261	202	403
5	New forms of substances		6	63	156	250	475
Grand total		**14**	**46**	**240**	**583**	**638**	**1521**

Source: Patents granted to top 20 domestic pharmaceutical companies by USPTO.

Chemistry driven research process leading to non-infringing processes for active pharmaceutical ingredients (APIs), identification and characterisation of impurity profiling pertaining to APIs, reduction of impurity levels, acceptable dosage forms and formulations have come to be pursued by the domestic firms as their main priority in the sphere of pharmaceutical innovation during the post-TRIPS period. Bedi and Bedi (2015), using databases like Ekaswa (TIFAC) and official websites of the European Patent Office and Indian Patent Office, also confirm that majority of the applications for top 11 large pharmaceutical companies up to 2010 were related to inventions in the field of new or improved processes for products than for the products themselves. Their analysis also confirms that product related applications are concerned with intermediates and formulations with maximum contribution in modified dosage forms.

While Bedi and Bedi (2015) indicate that there has been a small increase in the number of product patent applications filed by the top 11 large pharmaceutical companies, especially after 2005, our own analysis which covers a longer period shows that this type of inventive activity has neither been sustained nor has led to a significant increase in NCE patenting. In fact, *Table 1* shows that the NCE activity does not even figure in the trends list after 2010. Further, we would like to highlight that foreign firms dominate the process patent scene as well; there are very few patents granted to domestic firms for NCEs.

See *Figures 1 & 2* for information on patents directions given to both domestic and foreign firms by the Indian Patent Office (IPO). The number of product patents granted to foreign firms by the IPO is much higher than of domestic firms. Further, dosage and formulation and process patents account for close to 99 per cent of patents filed at the IPO.

Figure 1: Nature of Patent Granted to Domestic and Foreign Firms in IPO (2005 to March 2013)

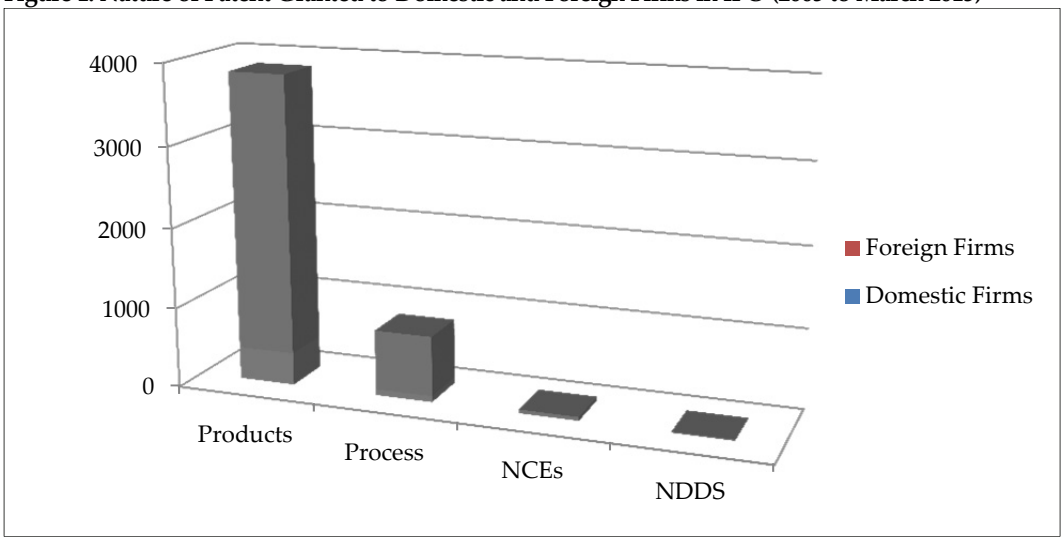
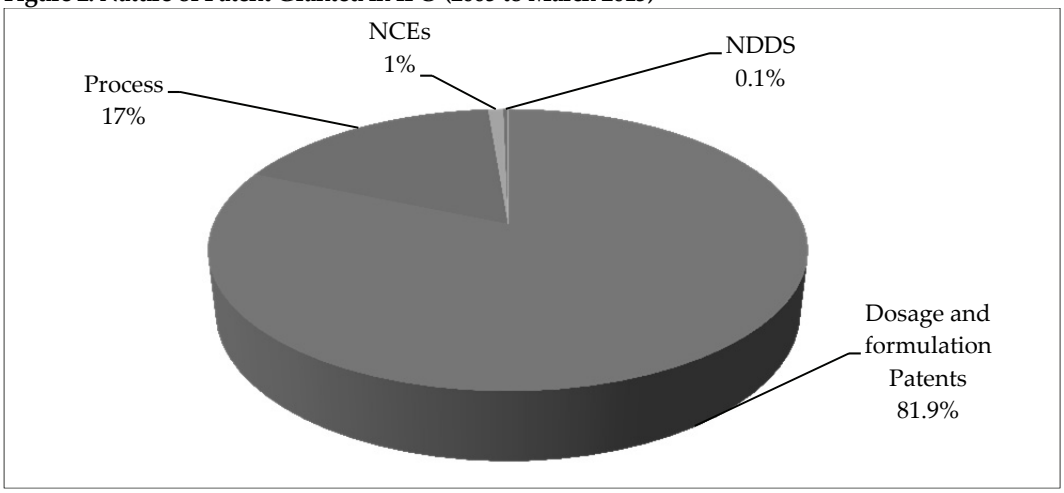


Figure 2: Nature of Patent Granted in IPO (2005 to March 2013)



Analysis of the patterns of innovation being carried out to compete in the domestic market shows that domestic firms rely on combination products, many of which are irrational, if not harmful, to build monopolies. See *Table 2* for a comparison of the innovation making conduct of the top 15 domestic pharmaceutical firms as in 2013–14. In *Table 3*, we also bring out that while both Indian companies and MNCs rely on product differentiation and

irrational combinations based product innovation activity to build product monopolies, this kind of innovation making strategy is most often employed by domestic pharmaceutical firms.

Table 2: Single Product Monopolies and Combination Product Monopolies of the Top 15 Domestic Firms in the Indian Retail Market, 2013–14

Domestic Companies	*Single product monopolies*	*Combination product monopolies*	*Patents filed in IPO*
Cipla Ltd.	14	17	15
Sun Pharmaceuticals Industries Ltd.	-	14	19
Emcure Pharmaceuticals Ltd	11	8	1
Dr. Reddys Laboratories Ltd	5	7	21
Lupin Ltd	7	5	5
Torrent Pharmaceuticals Ltd.	4	4	6
USV Ltd	3	3	5
Cadila Pharmaceuticals Ltd		2	-
Indoco Remedies Ltd	3	2	-
Natco Pharma Ltd		2	13
Biocon Ltd		1	2
Glenmark Pharmaceuticals Ltd.		1	2
Hetero Healthcare Ltd		1	1
IPCA Laboratories Pvt Ltd.		1	10
JB Chemicals	1	1	5
Total	**48**	**69**	**105**

Source: Dataset prepared on the basis of information available on the patents from IPO and market sales of individual companies and position in the market from AIOCD.

Table 3: Therapeutic Area-wise Single and Combination Product Monopolies by Indian Companies and MNCs, 2013–14

Therapeutic Groups	*Single Monopolies*		*Combinations Monopolies*	
	Indian	*MNC*	*Indian*	*MNC*
Diabetes	2	13	10	3
Malaria	2	-	2	-
Infections	17	5	28	3
Neoplasm (Tumor)	19	14	-	-
Cardiovascular diseases	27	14	39	8
Neuro/Brain disorders	19	7	7	-
Respiratory Diseases	1	7	35	5
Pain/Analgesics	23	8	61	1
Blood related disorders	12	5	2	0

Therapeutic Groups	*Single Monopolies*		*Combinations Monopolies*	
	Indian	*MNC*	*Indian*	*MNC*
Gastro intestinal infections	16	4	48	4
Skin diseases	12	8	40	11
Hormones	3	6	1	0
Opthal/Eye disease	22	4	14	5
Erectile Disinfections	1	-	2	1
Stomatologicals	1	-	1	-
Vitamins/minerals/nutrients	3	-	0	2
Gynaecologicals	5	5	3	1
Vaccines	5	1	-	2
Others	14	2	2	0
Total	**204**	**103**	**295**	**46**

Source: Dataset prepared on the basis of information available on market sales of individual companies and position in the market from AIOCD, 2015.

New product related inventive activity is certainly not known to play a role in the creation of competitive advantages for domestic pharmaceutical firms in the domestic market or export market. *Tables 2 & 3* clearly shows that product differentiation and brands still form the basis of market power for domestic companies. In export markets of the US, EU, Australia and Japan, domestic firms have had to use patenting activity, filing of Abbreviated New Drug Applications (ANDAs) and Drug Master Files (DMFs) to break into the regulated markets through exports.

See *Tables 4 & 5* for an assessment of the key competency areas of domestic pharmaceutical firms as reflected in the pattern of registration of DMFs and ANDAs prior to registering products (generics) in the US, EU and other developing countries. In case of the Indian pharmaceutical industry, the New Drug Applications (NDAs) filed with the United States Federal Drug Regulation Authority, i.e. the United States Food and Drug Administration or USFDA, are few and far between (nine in 2012). Further, we would like to note that some of the domestic companies are known to increase their investment in R&D and the filing of patents, ANDAs and DMFs to become valuable for acquisition rather than becoming competitive in the global or domestic market pharmaceutical landscape.

Fresinus Kabi and Matrix are two such examples which come to mind in respect of such behaviour in competence building and innovation making. There are also companies like Ranabaxy whose investment behaviour relating to innovation making to foray into the regulated markets for quick profits has landed them and the Indian pharmaceutical industry into serious trouble. When the promoters of Ranabaxy realised their folly they tried selling their assets to a Japanese MNC (Daichi Sankhyo) which, however, bought the company without due diligence. Resultantly, the Japanese company had to retrace its steps; Ranabaxy is now a part of Sun Pharmaceutical Industries Ltd.

Table 4: DMFs Obtained by Domestic Pharmaceutical Companies, 2008–2013

Company name	*Type I*	*Type II*	*Type III*	*Type IV*	*TYPE V*
AARTI INDUSTRIES LTD	-	**10**	**13**	**4**	**-**
ALEMBIC PHARMACEUTICALS	-	**37**	**1**	**15**	**-**
APOTEX PHARMACHEM INC	-	**45**	**1**	**15**	**-**
AUROBINDO PHARMA LTD	-	**45**	**16**	**2**	**1**
BIOCON	-	**10**	**1**	**2**	**-**
CADILA HEALTHCARE LTD	-	**45**	**23**	**5**	**1**
DR REDDYS LABORATORIES LTD	-	**60**	**21**	**9**	**2**
FRESENIUS KABI	-	**21**	**2**	**1**	**1**
GLAXOSMITHKLINE LLC	-	**9**	**-**	**-**	**-**
GLENMARK GENERICS LTD	-	**20**	**11**	**1**	**1**
HETERO DRUGS LTD	-	**102**	**8**	**5**	**-**
HIKAL LTD	-	**2**	**1**	**-**	**-**
IND SWIFT LABORATORIES LTD	-	**8**	**4**	**1**	**-**
LUPIN LTD	-	**56**	**11**	**13**	**2**
MATRIX PHARMA	-	**2**	**1**	**-**	**-**
MICRO LABS LTD	-	**8**	**-**	**-**	**-**
NOVARTIS PHARMACEUTICALS CORP	-	**3**	**1**	**1**	**-**
PIRAMAL HEALTHCARE UK LTD	-	**3**	**-**	**1**	**-**
RANBAXY LABORATORIES LTD	-	**17**	**7**	**1**	**-**
TORRENT PHARMACEUTICALS LTD	-	**9**	**6**	**4**	**-**
WOCKHARDT BIO AG	-	**6**	**10**	**6**	**-**
SUN PHARMA	-	**35**	**14**	**8**	**2**
TOTAL		**553**	**152**	**94**	**10**

Source: No. of DMF Data from http://www.betterchem.com (Drug master file database) and no. of Abbreviated New Drug Application (ANDA) from individual company website, data analysed up to 2013–14.

Table 5: ANDAs of Domestic Pharmaceutical Companies, 2008–2013

Company Name	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*
DR Reddy's labs	1	4	6	5	6	5
Ranbaxy	1	3	1	1	-	-
Glenmark	-	1	3	3	2	5
Aurobindo Pharmaceuticals	3	3	-	2	8	-
Sun Pharma	2	5	2	4	5	5
Alembic ltd	-	-	1	-	-	-
Lupin	1	-	2	2	3	2
Orchid	-	2	1	-	1	-
Torrent	-	1	1	2	5	-
Wockhardt	-	1-	-	1	3	-
Cipla	-	1	-	-	1	-
Fresenius Kabi Oncology	-	1	3	-	-	-
Matrics	1	-	-	-	-	-
Strides	-	-	-	-	2	-
TOTAL	**9**	**22**	**20**	**20**	**36**	**17**

Source: ANDAs granted to domestic pharmaceutical companies by USFDA, data analysed up to 2013–14.

Domestic Firms and R&D for New Product Development

While the face of the Indian pharmaceutical industry has gradually changed owing to an R&D based domestic industrial segment which is competent to participate in the processes of learning, competence building and innovation making for the supply of off-patent generics to regulated markets, in the field of product development the bulk of its "innovative outputs" still belong to the areas of dosage/formulation/composition of matter related R&D work. This point needs emphasis because scholars studying industrial dynamics tend to become overly optimistic in their conclusions regarding the progress made by the domestic segment of the Indian pharmaceutical industry.

Our own analysis is that we need to take a long-term view because catching-up involves complex relationships between scientific research and industrial innovation, for which the industry will have to undertake lasting measures. Evidence building undertaken on new product development from the information made available by companies on their websites indicates that, initially, only 10 or 12 Indian pharmaceutical companies had earnestly started working on the development of new drugs. An estimated 60 new compounds came under the radar of domestic firms and these compounds were worked upon up till various phases of development and testing by these 10 or 12 domestic firms. But, there has been a decline in the growth of investment in new product development.

The problem of weak in-house capabilities in respect of discovery and development of new drugs in case of domestic pharmaceutical industry continues to be a major handicap for the "national innovation system" in India. Assessment indicates that the current level of activity of compound development and testing by domestic companies is still small compared to world standards. At this early stage of drug discovery, India is still weak. Many Indian companies are now pursuing a strategy that will lower their costs and risk factors. The plan is to find a new drug within an existing family that has been discovered, that is, to find a compound that is analogous to a discovered compound.

Take, for example, the case of Giltazones—one of the compounds of DRL where originally Sankhyo was doing work. This strategy cuts down on the risk. The other strategy is out-licensing where the Indian company takes some leads to pre-clinical stage. In this case, DRL's strategy was to collaborate with a foreign company to jointly pursue clinical development[3]. If all tests are cleared, the company can strike a deal with an MNC that has the right to market the compound in a particular market. The Indian company gets milestone payments for each stage of clinical trial cleared by the compound.

DRL is still one of the most determined domestic companies working on the national scene in the area of drug discovery and development. All big companies, namely Ranbaxy, DRL and Glenmark follow the out-licensing route to develop new drugs. DRL has entered into a

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[3] A company can reduce some of the uncertainties of new drug research though this may not produce a drug as big as a blockbuster.

deal with Novratis for further work on an anti-diabetic compound DRF 4158. Ranbaxy entered into a deal with Bayer for Cipro NDDS (Novel Drug Delivery System) and RBx 2258 (Benign Prostatic Hyperplasia or BPH). Glenmark has entered into a deal with Forest of North America and Tejin of Japan to experiment with compounds that could provide treatment for asthma. However, the level of success obtained by these companies through routes currently under perusal has not yet yielded the desired results in respect of new product development.

Table 6 provides details on disease focus of drugs under development in India and their current status. R&D capabilities for new drug discovery and development within the Indian firms have a global market favouring R&D orientation. Under the emerging conditions of competition in the "global" pharmaceutical industry, locally bred firms of developing countries are likely to be lured by multinational corporations to work for western markets. The result is that many Indian companies have realised that drug discovery investment is a different but risky game for which neither their capabilities nor the system of innovation are yet ready. Realising that easy success will not come like this in the near future, their strategy has changed and their investment in drug discovery is no more on a roller-coaster ride. Abandoning of molecules or resorting to contract work in drug discovery and development and contract research route can be attributed to this realisation; firms are now investing more in contract research route.

Table 6: New Chemical Entities (NCEs) Based Drug Discovery Pipeline

SN	*Companies*	*NCE Pipeline*	*Status*
1	Lupin Ltd	LLL2011 Anti-migraine, herbal (Amigra)	Phase III
		LL4218 Anti-Psoraisis (Desoside-P)	Phase II
		LL3858 Anti-TB (Sudoterb)	Phase II
		LLL3348 Anti-Psoraisis,Herbal (Desoris)	Phase II
		TypeII Diabetes	Preclinical
		Rheumatoid arthritis	Preclinical
2	Dr Reddy's Laboratories	DRF 10945 (Dyslipidemia)	Phase I
		DRF 11605 (Diabetes & Dyslipidemia)	Pre-clinical
		DRF 1042 Cancer	Phase II
		DRF 1644 Cancer	Phase I
		DRF 5265 Cancer	Pre-clinical
		RUS 3108 Cardiovascular	Pre-clinical
		DRF 13792 Bacterial infection	Pre-clinical
		DRF 2593(Metabolic Disorder)	Phase II
		DRL 16805(Atherosclerosis)	Pre-clinical
		DRL 15925(Rheumatoid Arthritis)	Pre-clinical
		DRL 12424(Mixed Dislipidemia)	Pre-clinical
		DRL 16536(Diabetes)	Pre-clinical
3	Wockhardt Ltd	W CK 771(anti- infective)	Phase II
		WCK1152(Respiratory tract infections)	phase I
		WCK 1457 (Activity against vancomycin resistant enterococci)	Pre-clinical

SN	Companies	NCE Pipeline	Status
		WCK 2370(Anti-infective)	Pre-clinical
		WCK 2664(Anti-infective)	Pre-clinical
		WCK 1734(Dermatology)	Pre-clinical
4	Lupin Ltd	LL 4858 (Anti-TB)	Phase I
		LL 4218 (Anti-psoriasis)	Phase I
		LL 3348 (Anti-psoriasis)	Phase I
		Amigra(Anti-Migraine)	Phase-III
5	Glenmark Pharmaceuticals	GRC 3886 (Asthma/chronic obstructive pulmonary completed disorder)	Phase I
		GRC 1087 (Obesity/diabetes)	Pre-clinical
		GRC 8200(Diabetes)	Pre-clinical
		PDE -4(CNS)	Pre-clinical
6	Torrent Pharmaceuticals	Anti-arrhythmic agent	Phase II
		AGE breakers(diabetes; heart diseases)	Pre-clinical
7	Orchid Pharmaceuticals	BLX 1002 (Diabetes)	Phase I
8	ZydusCadila	ZYH1 (Dyslipidemia)	Pre-clinical
		ZYH2 (Diabetes)	Pre-clinical
		ZYH3 (Dyslipidemia and diabetes)	Pre-clinical
		ZY1400 (Inflammation and pain)	Pre-clinical
		ZYO1 (Obesity)	Pre-clinical
		ZYI1 (Inflammation and pain)	Phase-I
9	Piramal Healthcare	P276 (Oncology)	Phase I/II
		Herbal (Anti-Fungal)	Phase II
10	Alembic Ltd	Pramipexole (Anti Parkinson)	Final
		Ropinirole (Anti Parkinson)	Final
		Telithromycin (Ketolide/Antimicrobial)	Initial
		Aripripazole (Antipsychotic)	Initial
11	Biocon Ltd	IN-105 Diabetes (oral insulin)	Phase II
		T1h Oncology inflammation	Phase II
12	Sun Pharmaceutical Industries	SUN 1334H (Anti-allergy)	Phase II
13	Ranbaxy Laboratories	RBx 7796 (Respiratory tract infections)	Phase II
		RBx 6198 (Urology)	Early discovery
		RBx 9001 (Urology)	Pre-clinical
		RBx 9841 Urology	Pre-clinical
		RBx 8700 (Bacterial infection)	Pre-clinical
		RBx 7644 (Bacterial infection)	Phase I
		OZ222/RBx11160(Malaria)	Phase I
		RBx 11160(Malaria)	Phase II
14	GSK Pharmaceuticals	Rotarix (Anti Diarrhoea)	Final
		Cervarix (Anti-Cancer)	Final
		Arixta (Anti-coagulant)	Final

Source: Company annual reports and websites, 2012.

The latest data on the progress made shows that close to 120 NCEs are currently progressing in the Indian preclinical and clinical R&D pipeline. This statement is in line with our own analysis which affirms that only a handful of firms continue to increase their R&D investments in new product development. R&D expenditure of the top 15 Indian pharmaceutical firms is nowhere close to the costs being incurred by generic companies of Israel and Europe. Dabur, Nicholas Piramal, Wockhardt and Shanta Biotech have had to divest important parts of their pharmaceutical business to foreign companies. In many cases these divestures have also involved R&D based segments. While it is true that DRL, Cipla, Glenmark, Lupin, Cadila, Wockhardt, Sun Pharma and Torrent are still around as integrated Indian pharmaceutical companies which have built substantial foreign sales, an analysis of the current status of new drug development indicates that most molecules have not progressed very far and many of them have been completely abandoned by the firms.

While there are certainly a few positive outcomes to report in respect of drug discovery, the number of success stories is undoubtedly small and not yet significant in terms of contribution. In June 2013, Zydus Cadila launched Saroglitazar, the first drug discovered and developed by an Indian pharmaceutical company and the first glitazar in the world to be approved for the treatment of diabetic dyslipidemia or hypertriglyceridemia in patients with type 2 diabetes.[2&3] In April 2012, Ranbaxy launched India's first domestically developed drug, Synriam, a combination of arterolane maleate and piperaquine phosphate, for the treatment of Plasmodium falciparum malaria. Although arterolane was not discovered in India, but by a collaborative drug discovery project funded by the Medicines for Malaria Venture (MMV), Ranbaxy partnered in 2003 to carry out development work for which it was granted a worldwide license.

Glenmark and US partner Salix Pharmaceuticals gained approval by the US Food and Drug Administration (FDA) in December 2012 for crofelemer, licensed from Napo Pharmaceuticals, for treatment of non-infectious diarrhoea in patients undergoing antiretroviral therapy for HIV/AIDS. Crofelemer, a purified oligomericproanthocyanidin (Mr up to 9 kDa) isolated from the latex of the South American Sangre de Grado tree (Croton lechleri), has a new mechanism of action: it blocks two structurally unrelated chloride channels in the gut, thereby decreasing the excretion of water and reducing the duration of diarrhea.[5]

Discussions about where hopes lie in respect of new drug development has led some to suggest that India's first innovative drug could come from a new generation of pharmaceutical companies. In recent years, ambitious new startup discovery firms backed by private equity investors such as Pune-based NovaLead and Indus Biotech have come up. They gained success where Indian pharma goliaths wandered into and faltered (*Businessworld*, November 08, 2014). Not surprisingly, the *Businessworld* article questioned if this was the end or the beginning of the story? Whether the dream can be revived for the Indian domestic pharmaceutical firms is in need of rigorous analysis if the policy design is to be worked out appropriately. See *Tables 7, 8, 9 & 10* to determine the current status of NCE based drug discovery and development work. Analysis of the pipeline of

pharmaceutical firms and the disease focus of product development work is described in *Table 8*. *Table 9* provides an analysis of the disease focus of clinical development work being undertaken by domestic pharmaceutical firms. *Table 10* brings out the mismatch in terms of disease focus of the R&D activity of these firms with the priorities indicated by the disease burden of the country as such.

Table 7: Status of NCE Based Drug Discovery Pipeline

Name of the firm	*Disease Focus*	*Current Status*
DRL		
DRF 2593	Diabetes (PPAR)	Licensed out to Rheoscience in 2004, now in Phase III trials
DRF 1042	Oncology	Abandoned after partner Clintech couldn't raise funds for phase II
DRF 10945	Metabolic disorder (PPAR agonist)	Phase I completed – showed little progress so was abandoned
DRL 17822	Dyslipidemia ,atherosclerosis and associated cardiovascular diseases	In Phase I Studies
RUS 3108	Cardiovascular	Abandoned in Phase I
DRL 11605	Metabolic disorder (PPAR agonist)	Preclinical, Abandoned in 2007
DRL 16536	Metabolic disorder (AMPK modulator)	Preclinical, Abandoned in 2007
DRF – 4848	Anti-inflammatory	Preclinical, Abandoned in 2003
DRF – 3188	Cancer, viral infection and immune stimulation	Preclinical, Abandoned in 2003
DRF – NPPC	Insulin sensitizer	Preclinical, Abandoned in 2003
DRF – 4158	Insulin sensitizer for type 2 diabetes	Out-licensing partner Novartis suspended clinical trial in Jan 2003
DRF – 2725	Insulin sensitizer for type 2 diabetes	Bladder tumors were found in rats treated with the drug. Out-licensing partner Novonordisk suspended trial in 2002
GLENMARK		
GRC 3886 Oglemilast	Chronic obstructive pulmonary disease (COPD), asthma	Trials on COPD proved in conclusive. Tests are on for asthma
GRC 2200	Diabetes type 2	Molecules return by licensing partner Merck after it decided to get out of diabetes research. Phase II completed
GRC 6211 Melogliptis	Osteoarthritic pain , incontinence, neuropathic pain	Out-licencing partner Eli lily suspended clinical trials in early October 2008 after it was found that the drug has side effects
GRC 4039	Rheumatoid arthritis, multiple sclerosis	Phase I trials completed
GRC 10693	neuropathic pain, osteoarthritis, and other inflammatory pain	Phase I trials completed
GRC 15300	Pain	In phase I trials
GBR 500	Sclerosis, Inflammatory disorder	In phase I trials
GBR 600	Anti-platelet, adjunct to PCI/acute coronary syndrome	In phase I trials

Name of the firm	*Disease Focus*	*Current Status*
LUPIN		
LL4858	Anti-TB	Slow development now in phase II trials. No USFDA approval
Ll3348*	Anti-Psoriasis	Slow development now in phase II trials. No USFDA approval
LL4218	Anti-Psoriasis	Phase II trials. No USFDA approval
LL2011*	Anti-migraine	In Phase III trials. No USFDA approval
Unnamed	Diabetes	In preclinical development
Unnamed	Rheumatoid arthritis	In preclinical development
ORCHID		
BLX1002	Orally active anti-diabetic compound	Phase II trials in Europe over in September in 2003. No progress since.
PIRAMAL HEALTHCARE		
P276	Mantle cell lymphoma. Malignant melanoma, multiple myeloma and head and neck cancer	Received IND status from USFDA for mantle cell lymphoma and currently in Phase II clinical trials in US
P1446	Oncology	Phase I in Canada and India. Does not have IND status from USFDA
P1736	Type II Diabetes	In phase I trials in Netherlands. Does not have IND status from USFDA
NPS31807-TNF*	Rheumatoid and psoriasis	Phase II completed
NPH30907*	Dermatology	Phase II completed
NPB00105-Bcr-Abl*	Chronic myeloid leukemia	In Phase I/II
PP9706642*	Herpes	Preclinical development
P3914	Non-steroidal anti-inflammatory drug	Preclinical development
PM181184	Methicillin-resistant Staphylococcus aureus/ vancomycin- resistant enterococcus	Preclinical development
RANBAXY		
RBx11160	Malaria	In phase III. No USFDA approval. Progressing slowly
RX9841	Urinary incontinence	Phase I completed. Phase II never initiated
RBX7796 (Oral & IV)	Allergic rhinitis and asthma	Entered Phase II trial in 2003. Its development was later suspended
RBx10558	Dyslipidemia	Filed an IND with DCGI 2005. Development later suspended
RBx2258	Benign prostatic hyperplasia	Trials suspended by out-licencing partner Schwarz Pharma in Nov.2004
RBx7644	Anti-bacterial	Development suspended during Phase I trials in 2003
RBx9001	Benign prostatic hyperplasia	Development suspended during Preclinical development in 2003
RBx6198	Benign prostatic hyperplasia	Development suspended during Preclinical development in 2003
TORRENT		

Name of the firm	*Disease Focus*	*Current Status*
TRC4149	Heart disease	Licensed out to Novartis in 2004. Torrent stop development in 2005
Wockhardt		
WCK771	Antibiotics	In Phase II of clinical trials. No USFDA approvals
WCK1152	Respiratory infection	Started trials in May 2004. Hasn't progressed since. No USFDA approvals

Source: BW Online Bureau (2014), 'Death of a Dream,' Businessworld, November 08. Available at: http://businessworld.in/article/Death-Of-A-Dream/08-11-2014-65256/

Table 8: Disease Type-wise Product Specific R&D Activities of Domestic firms Active in India, 1999–2009

Domestic Companies	*1999–2001*			*2002–2004*			*2005–2007*			*2008–2009*			
	DISEASE TYPE												
	I	*II*	*III*	*I*	*II*	*III*	*I*	*II*	*III*	*I*	*II*	*III*	*Total*
Orchid Pharmaceuticals Ltd				2			6			2			10
Sun Pharmaceutical Ltd							2			7			9
Biocon Ltd				2			4			6			12
GlenmarkPharmaceuticalsLtd				1			5		1	7			14
Bharat Biotech Ltd								1	1	3		2	7
Alembic Ltd													-
Dr.Reddy's Laboratories Ltd				7			2	1		15			25
Lupin Ltd	1				1		4	4		4		1	15
Cadila Healthcare Ltd							3	1		9			13
Piramal Healthcare Ltd							7			5			12
Wockhardt Ltd							1			2			3
IPCA Laboratories Ltd										2	2		4
Aurobindo Pharmaceutical Ltd													-
Torrent Pharmaceuticals										1			1
Ajanta Pharma										7			7
NatcoPharma										2			2
Granules India Ltd										1			1
SMS Pharmaceutical										10			10
Shanta Biotech							3		2	10	1		16
Panacea Biotech												2	2
Matrix Laboratories										3			3
Grand total	**1**			**12**	**1**		**37**	**7**	**4**	**96**	**3**	**5**	**166**

Notes: Disease type: Type-I, Type-II, Type-III; Type-I – Diabetes, Cancer, Metabolic Diseases, Hepatitis, Influenza, Cardiovascular, Infectious Diseases, Inflammatory Diseases, Allergy, Respiratory Diseases; Type-II – HIV/AIDS, Tuberculosis, Malaria; Type-III – Leishmaniasis, Trypanosomiasis, Lymphatic filariasis, Leprosy, Diarrhoea (Neglected diseases of the poor in developing world).

Source: Data collected from individual website & latest annual report of individual pharmaceutical companies and CTRI Clinical trial registry India

Table 9: Clinical Phases of Compound for Various Diseases by Foreign and Domestic Pharmaceutical Firms, 2007–2009

Company	*Disease Type*			*Status of trial/Phases*			
Domestic Firms	Type-I	Type-II	Type-III	Phase-I	Phase-II	Phase-III	Phase-IV
(16 Companies)	65	3	2	5	20	35	9
Foreign Firms	Type-I	Type-II	Type-III	Phase-I	Phase-II	Phase-III	Phase-IV
(9 Companies)	110	3	3	12	23	12	9

Notes: Disease type: Type-I, Type-II, Type-III; Type-I – Diabetes, Cancer, Metabolic Diseases, Hepatitis, Influenza, Cardiovascular, Infectious Diseases, Inflammatory Diseases, Allergy, Respiratory Diseases; Type-II – HIV/AIDS, Tuberculosis, Malaria; Type-III – Leishmaniasis, Trypanosomiasis, Lymphatic filariasis, Leprosy, Diarrhoea; Status of involvement of domestic and foreign firms in the trials (Phase-I, Phase-II, Phase-III, Phase-IV)

Source: Clinical Trial Registry Analysis (CTRI) 2007–2009.

Table 10: Therapeutic Area-wise Estimation of Pharmaceutical Projects and Patents and the Pattern of Matches with the National Burden of Disease, 1992–2007

SN	*Major therapeutic areas/Disease/Health conditions*	*Share in the total burden of disease (%)*	*Domestic Pharmaceutical project (%)*	*Foreign Pharmaceutical project (%)*	*Domestic Cos. Pharmaceutical Patents Percentage (%) of Total Domestic Patents*	*Domestic Cos. Pharmaceutical Patents Percentage (%) of Total Patents*	*Foreign Cos pharmaceutical Patents Percentage (%) of Total Foreign Patents*	*Foreign Cos pharmaceutical Patents Percentage (%) of Total Patents*
1	Diabetes	0.7	17.15	16.36	5.94	5.91	20	0.084
2	Cancer	3.4	10.05	8.81	5.6	5.57		
3	Tuberculosis	2.8	1.18		0.50	0.50		
4	Malaria	1.6	2.36		0.93	0.92		
5	Metabolic disease	-	7.36	0.9	6.79	6.76	20	0.084
6	HIV/Aids	2.1	0.59	0.23	0.84	0.84		
7	Inflammatory diseases		3.55	0.67	5.6	5.57		
8	Infectious diseases/Injuries	16.1	8.28	4.54	38.96	38.79		
9	Respiratory diseases	1.5	4.73	5.61	1.1	1.09		
10	Arthritis	-						
11	Bone disease	-	4.73	6.63	1.27	1.26		
12	Brain disorders	8.5		0.56	10.18	10.14	40	0.16
13	Ulcer	-			0.5	0.50		
14	Psoriasis	-			0.33	0.33		
15	Cardiovascular	10.0	0.59		2.63	2.78	20	0.084
16	Maternal & prenatal problems	11.6	1.34		0.25	0.25		
17	Diarrhoea	8.2	1.77		0.08	0.084		
18	Heart Disease	-			0.93	0.92		
19	Depression	-			3.56	3.55		

SN	Major therapeutic areas/Disease/Health conditions	Share in the total burden of disease (%)	Domestic Pharmaceutical project (%)	Foreign Pharmaceutical project (%)	Domestic Cos. Pharmaceutical Patents Percentage (%) of Total Domestic Patents	Domestic Cos. Pharmaceutical Patents Percentage (%) of Total Patents	Foreign Cos pharmaceutical Patents Percentage (%) of Total Foreign Patents	Foreign Cos pharmaceutical Patents Percentage (%) of Total Patents
20	Hypertension	-		10.12	4.49	4.48		
21	Allergy	-			1.78	1.77		
22	Hepatitis	-		1.81	0.16	0.16		
	Leprosy	0.1						
23	Childhood disease	5.4						
24	Otitis Media	0.1						
25	Blindness	1.4						
26	Oral diseases	0.5						
27	Prosthetic hyperplasia	-			1.01	1.014		
28	Others	25.4	30.17	18.18	6.45	6.42		

Source: USPTO from1992–2007, Company websites and data available on the Burden of Disease from GOI.

An analysis of the disease focus based on tables provided above makes clear the current status of domestic firms' R&D and innovation behaviour. It confirms that the Indian companies consider the domestic market to be of small size and not attractive enough to take up development work on new products in the drugs and pharmaceutical sector. See *Table 11* for company-wise figures of investigational new drugs (INDs) registered by domestic companies.

Table 11: Investigational New Drugs (INDs), 2008–2013

Company Name	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*
DR Reddy's labs		2	2	2	4	3
Ranbaxy	1	7	5	6		
Aurobindo					1	1
Wockhardt		2		2		
Glenmark		8	14	16	9	8
Piramal Healthcare		1			3	3
Sun Pharma	1	9	18	8	10	5
Lupin		4				
Cipla		9	4	11	4	
Cadila	2	14	21	11	12	7
Glaxosmithkline (foreign)		7	1			
Novartis (foreign)		1	3			
AstraZeneca (foreign)	2	9	12	8	10	1
TOTAL	**6**	**73**	**80**	**64**	**53**	**25**

Source: Compiled by the authors.

Again, this table confirms a declining trend for the submission of INDs from 2010 onward. New product development is certainly not an important outcome of the global integration of domestic pharmaceutical firms. It would not be wrong to suggest that the TRIPS based patent reform system—which favours stronger patents—is not the way to incentivize domestic pharmaceutical firms to invest in new product development in a sustained way. The government needs to intensify its search for alternatives to patents to stimulate drug discovery and development activity of domestic firms.

Domestic Pharmaceutical Firms and Contract Research Route

There is now more investment from domestic pharmaceutical firms towards broadening of activities and services as well as for deepening of the skills required for contract research route. From, initially, custom chemistry services based on the country's long tradition in chemical manufacturing, many of the major Indian Contract Research Organisations (CROs) have evolved toward higher value-added activities such medicinal chemistry, biology, ADME (absorption, distribution, metabolism, and excretion), animal pharmacology and safety studies, and integrated drug discovery capabilities. The terms of recent deals have evolved from Fee-for-service (FFS) and Full-time Equivalent (FTE) agreements to collaborative research agreements, partly shared risk collaborations, with milestone payments and eventually royalty payments in addition to research fee.

This evolution, to a large extent, has been driven by the need of western pharmaceutical companies to address the declining productivity of drug discovery. Outsourcing and partnering with companies in emerging, low-cost countries remains an option for western companies to address rising costs. Most of the major western pharmaceutical and biotech companies have been building on the valuable resources in India for a number of years through strategic collaborative partnerships and alliances to fuel their in-house discovery and development pipeline. Pharmaceutical companies have been outsourcing non-IP (Intellectual Property) sensitive chemistry activities to India since the late 1990s, when only a limited number of CROs were offering such services.

Several contract research companies capable of pursuing drug discovery collaborations have emerged (Advinus, Aurigene, Jubilant, Syngene), and many others are closely following (e.g., GVK Bio, Orchid, TCG Lifesciences, Torrent, Zydus Cadila). These collaborations have produced 71 patent applications and publications. Close to 25 collaborations have been entered into, which illustrates the extent to which major pharmaceutical companies have initiated research activities in India. All the different approaches taken by them in their collaborations with Indian CROs and biotech companies reveal some interesting results in respect of the intellectual property scenario. At least seven out of the top 20 pharmaceutical companies have filed patent applications on the basis of these collaborations. Far less intellectual property is, in contrast, generated in India by pharma companies in the top 21–100. According to Differding (2014), out of the 80 companies studied only five had applied for patents.

So far, several of these alliances have been quite productive for western companies. This is evidenced not only by the significant number of patent applications and publications, but also by the rising number of disclosed preclinical and clinical development candidates that have been injected into R&D pipeline projects of western pharmaceutical companies. Differding (2014) opines that despite progress, very little has appeared in press on the process and progress of drug discovery itself (such as targets or modes of action involved), on scientific output, and on NCEs coming out of India through research collaborations.

More undisclosed compounds are currently under progress in preclinical and clinical development. The vast majority of pharma companies are opting for multiple partners, with the advantages of distributing the inherent risk of drug discovery in general, and of being potentially more competitive in particular as it allows them to select best-in-class partners for each project, such as Endo, Forest, Janssen, Merck Serono, Merck Sharpe and Dohme, and Novartis. Others prefer a strategic collaboration with one carefully selected key partner, thereby decreasing complexity and internal management and communication needs.

Differding (2014) suggests that western pharmaceutical companies have been on a learning curve in their alliances with Indian companies, and many of them have already learned how to successfully generate IP with Indian inventors. It is not unreasonable to speculate that other pharmaceutical and biotech companies will follow. According to a 2011 Boston Consulting Group (BCG) survey of 40 global biopharma companies, more than 70 per cent of executives were satisfied with their Indian R&D alliances, and three out of four expected to increase their R&D activities in India. This survey reveals how the R&D game is being played, and how India will gain from this game is certainly a matter of further investigation and assessment.

Technology Acquisition by Domestic Firms

Again the claimed benefit of increased technology transfer to domestic firms through contract, alliances and joint ventures is also not evident in the case of India. Foreign technical collaborations have not been important for export; therefore, only small- and medium-scale firms have entered into such collaborations, mostly to cater to the domestic market. Expectations from the route of contract manufacturing are also not clear with regard to technology acquisition in the case of India. Exploiting contract manufacturing will not improve the prospects of technology transfer by itself because there are no new technologies being transferred. Production capabilities can certainly get better on account of the enforcement of Good Manufacturing Practice (GMP) in the case of some firms. Analysis indicates that though players like Matrix Laboratories, Divi or Shasun Chemicals or Cadilla have made much use of this opportunity to grow, their technological capabilities have not been upgraded despite provision of contract manufacturing services. Apart from Ranbaxy and Cipla, which were earlier warned by the USFDA, Matrix was the third drug

company working from India for the US market to get a warning from the regulatory authorities of United States[4].

There is evidence that as far as the terms and conditions of contract manufacturing of bulk drugs are concerned, the deals being entered into by Indian firms in the post-TRIPS era are far from being equal. Ranbaxy Laboratories and Lupin Laboratories were among the first Indian companies to bag manufacturing contracts from multinational companies—Ranbaxy from Eli Lilly and Lupin from Cynamid. In the pre-TRIPS period, manufacturing contracts came through when Ranbaxy developed an alternative process for manufacturing Eli Lilly's patented drug, Cefaclor, because the American Company sensed that it would lose its markets to Ranbaxy's low cost substitute in countries that did not recognize product patents. Eli Lilly offered a manufacturing contract to Ranbaxy for producing 7 ACCA, an intermediate for Cefaclor, to make the best of a bad situation.

Today, the situation has changed due to the implementation of TRIPS Agreement. Take, for example, the case of Nicholas Piramal. It entered into a joint venture (49:51) with Allergan Incorporated, USA to earn business for the manufacture of bulk drugs. The same is true for its negotiations with UK based Baker Norton to earn business in the form of contract manufacturing. It seems that the growth in contract manufacturing will come about due to the efforts of companies such as Divi, Sashun and Nicholas Piramal India (now taken over by Abbot Laboratories, USA), which have been willing to accept even "subordinate relationships" in their collaborations. See *Table 12* for a glimpse into the pattern of CRAMS (Contract Research and Manufacturing Services) activities being undertaken by large domestic pharmaceutical firms since the adoption of TRIPS Agreement in India.

Table 12: Pharmaceutical Companies in CRAMS Activities in India

Companies in Contract Research (excluding Clinical Trials)	*Clinical Trials*
Nicholas Piramal	Clingene (Biocon)
Aurigene (DR. Reddy's)	Jubilant Clinsys (Jubilant Organosys)
Syngene (Biocon)	WellQuest (Nicholas Piramal
GVK Biosciences	Synchron
Jubilant Organosys	Vimta Labs
Divi's Laboratories	Lambada
SuvenLifesciences	SiroClinpharm
Dr Reddy's Laboratories	Relience Life Sciences
Vimta Labs	Asian Clinical Trials (Suven Life Sciences)

Source: Annual Report and IDMA news 2007 (International Disease Management Alliance).

[4] When it comes to manufacturing, India ranks only second to the US in the number of global Drug Master Filings (DMF) every year. DMF is essentially permission to enter the US bulk actives market with the objective of either supplying to a large US generics player or captive consumption. DMFs by Indian companies rose to 19 per cent of the world filings in 2003 compared to 2.4 per cent in 1991. For the April-June Quarter 2003, India accounted for 34 per cent of the world's filings.

It needs to be stressed that not all modes of collaboration lead to enhanced competencies. In-licensing and out-licensing of compounds for further development are primarily market penetration strategies targeted towards increased time and cost efficiency.

Capability Building, Exports to Regulated Markets and Domestic firms

The export of generics to regulated markets of the US and Europe is no longer considered an option for upgrading the capabilities of domestic firms. Domestic companies are currently investing a lot of money into generic market with the intention of making the maximum profit when market competition is less and the margins high. As such things are possible only in the beginning when drugs become off-patent, they file four to five ANDAs every year to be first in the market and exploit the period of exclusivity available under the US drug regulation laws. Experience, however, indicates that the road ahead for export of generics to regulated US market is likely to be tedious and full of hurdles.

To be specific, in the US, under the Hatch-Waxman Act, the government has a system of patent term "restoration" which can extend the monopoly of the original patentee for a maximum of five years, in addition to the initial patent term. In EU, too, there exists a scheme for Supplementary Protection Certificate (SPC). In the US, no ANDA can be submitted until five years after the referenced brand name product gets its first FDA approval if the originator product was the first drug product to contain that active ingredient to obtain approval. Similarly, an ANDA cannot be submitted for three years if an originator's new drug application or supplementary application is supported by new clinical investigations conducted by the applicant and essential for approval (normally for a new indication). As of 1997, the US now allows for an additional six months of exclusivity as a reward for studying drugs in children. In the US, the first version of an orphan drug is entitled to seven years of exclusivity, preventing approval of an ANDA. The US also allows, as a reward, 180 days exclusivity to the first generic manufacturer to file a successful paragraph IV certification alleging that a listed patent is invalid or not infringed. Thus, as far as the question of export of generics is concerned it faces important IPR related hurdles today in the markets of EU and US.

It is clear that Indian pharmaceutical firms cannot expect that the opportunity for developing traditional pharmaceutical generics will automatically fall in their lap. As evidence shows, even in the area of biogenerics a tough fight is in waiting for the Indian pharmaceutical industry. The recombinant products market has been led so far by imports of established global brands and marketing of the products either by local subsidiaries (SmithKline Beecham, Novo) or through marketing arrangements as in the case of Nicholas Piramal and Roche. Though changes have come in due to the recent introduction of local firms such as Shanta, Bharat, Panacea and Wockhardt in the Indian market for products like Hepatitis B Vaccine, Interferon-alpha, insulin and EPO, the situation will change radically after January 01, 2005. As discussed in the earlier section, Indian policymakers should expect litigations to grow in the case of biogenerics. The Indian industry is getting a

taste of this at an early stage. Of late, almost all export oriented Indian firms have faced this challenge in the US.

Studies differ in their degree of optimism in respect of the positive effects of stronger patents on product development by local firms based on disclosed foreign patents and on additional R&D efforts. Looking at the domestic sector today, only a handful of firms have been able to increase their R&D investments. Some of these have earlier demonstrated that they can, with the help of public sector research, hone their expertise in creation of new processes for patented products. Dr. Reddy's Group was the first domestic company to file the first two product patent applications for anti-cancer and anti-diabetes substances in the US. However, it is clear that Dr. Reddy's Group does not want to engage autonomously in new drug development. It has been selling its rights to foreign partners because it does not have the capacity to invest further. In fact, it has stopped working after the drug discovery phase. Examples of Wockhardt joining hands with Rhein Biotech GmbH, Germany, Ranbaxy shaking hands with Eli Lilly for development work, and Cipla undertaking custom synthesis and collaborations with Japanese and Swiss firms, indicate the limitations of and opportunities available to Indian firms.

Based on her investigative interviews with executives of domestic firms, Sophia Ackerhans (2016) suggests that the 22 firms and industry experts considered the political framework and government incentives aimed to facilitate R&D collaboration to be of lowest importance in respect of policy and other motives of research and development. Within this category, the aim to access public funding of the host/home government was evaluated with the lowest dispersion, followed by the desire to support the regulatory framework and adapt to the market or regulatory environment.

India does not seem to figure much in the increased strategic R&D alliance activity of the global biopharmaceutical and biotechnology firms. Federica (2014) reveals that a gap exists between R&D deals and manufacturing/marketing deals despite some progress. This study also shows that 60 companies out of the isolated 123 did not report any alliance during the period of observation. There is a simple explanation for this: in biopharmaceutical research the distribution of capabilities is the major determinant of the partner and the mode of alliance. The dynamic of biotechnology in India is also dependent on the overall movement of internationalisation of R&D. Outsourcing markets in clinical trials, R&D, and production are becoming accessible to the locally bred firms of countries like India. Because of many short-term benefits, it is obviously tempting to direct the industry totally or mainly for these markets.

The examples of DRL and Biocon are especially useful for discussion on the conditions for gains to accrue from the contract work being undertaken by these two companies. Both these companies have created several entities, each of them corresponding to a different strategy. DRL is involved in the development of recombinant DNA-based products and has an internal programme of BT-based (biotechnology-based) drug targets discovery. It has also set up a company named Molecular Connections Pvt Ltd, and a contract research

company named Aurigene, involved in chemical and biological research for drug discovery. Similarly, Bicon, too, whose core activity is manufacture of industrial enzymes, has set up a contract research subsidiary named Syngene, and a clinical Research Organisation named Clinigene.

However, as far as the contribution of these domestic firms to meet the product development challenge for neglected diseases is concerned, our analysis makes it clear that the current level of opportunities which limit Aurigene, GVK Bio, and Syngene to cloning and getting the genes to express will not allow these companies to build an industry capable of doing cutting edge biotechnology research. At the moment, the mother companies have no intention of interfering with their subsidiaries because of confidentiality agreement signed by them with partners who have outsourced the part of drug discovery or clinical research to them. This means that no technological information can circulate between the company in charge of contract research work and the parent company involved in its own research.

From the standpoint of priorities of public health protection, the moot question is: How will it benefit the country in terms of promotion of indigenous drug discovery and development efforts? As mentioned earlier, it is clear that under the existing policy environment and the emerging conditions of competition in the global pharmaceutical industry, locally bred firms of developing countries are likely to be lured by the multinational corporations to work for the western markets. The situation as it stands is that pharmaceutical research is largely directed towards the needs of the western markets. The message is clear that the industry is least concerned with undertaking of R&D for neglected diseases of the poor.

Nature of Interdependence Emerging at the Level of Industrial Networks and Science Industry Links

Assessment of relationships forged through acquisitions, alliances, collaborations and agreements while undertaking Outward Foreign Direct Investment (OFDI) indicates that for the establishment of appropriate industrial networks these firms have failed to give priority to the objective of capability building for development of new drugs. See *Tables 13 & 14* for details on the pattern of functions being served through acquisitions of foreign firms and divisions made by these 14 firms.

Analysis suggests that R&D related acquisitions are far less in number than acquisitions for marketing and production activities. In case of all 14 firms, the number of alliances, collaborations and acquisitions remained skewed in favour of the purposes relating to marketing, manufacturing and supply of R&D services. Their acquisitions were mainly for strengthening their foreign markets. Assessment also indicates that a very small number of firms are involved in asset augmentation for the purpose of manufacturing. R&D alliances and collaborations involve still fewer firms.

Compared to the acquisition of manufacturing and distribution arms abroad by each and every firm in the sample, only a small number of companies have acquired firms abroad with the motive of upgrading R&D capabilities. As far as the number of acquisitions made for the purpose of boosting drug discovery R&D is concerned, it is a small number reflecting the bias of ties and connections under establishment. See *Table 14* for details on the types of R&D being served through acquisitions made by these firms during the period under observation.

See *Table 15* for details on the types of alliances, collaborations and agreements signed by these firms with research institutions and firms, both foreign and domestic. Analysis shows that R&D acquisitions have been made mostly for the purpose of establishing research service facilities for the benefit of generic entry. Research services function seems to dominate acquisitions made with the objective of establishing facilities in the host country for preparing dossiers and undertaking laboratory work. Foreign firms account for the maximum number of alliances, collaborations and licensing agreements entered into by these firms during the period under observation.

Table 13: Type of R&D & Marketing Acquisitions Pattern of Indian Pharmaceuticals, 1999–2011

Companies	*R&D acquisitions*		*Sub total*	*Marketing/Productions acquisitions*		*Sub total*	*Total of all acquisitions*
	Firms			*Firms*			
	Domestic acquisitions	*Foreign acquisitions*		*Domestic acquisitions*	*Foreign acquisitions*		
Top 14 leading Indian Pharmaceutical	2	20	22	3	72	75	97

Source & Notes: Individual Company website Press releases, News, Archive etc, data accessed as on Nov 2011; # Top 14 leading Indian Pharmaceutical Industries are: (*Ranbaxy laboratories, Cipla ltd, Dr. Reddy's Laboratories, Cadilla healthcare, Biocon Ltd, Sun pharmaceuticals, Lupin Ltd, *Piramal healthcare, Glenmark pharmaceuticals, Torrent pharmaceuticals, Strides arcolab, *Wockhardt ltd, IPCA laboratories, *Orchid pharmaceuticals).

Table 14: Type of R&D Acquisitions with Industries, 1999–2011

Companies	*Discovery R&D*		*Sub total*	*Clinical Development*		*Sub total*	*Research Services*		*Sub total*	*Grand total*
	DO	*FO*		*DO*	*FO*		*DO*	*FO*		
Top 14 leading Indian Pharmaceutical							**2**	**20**	**20**	**22**

Source & Notes: As provided in Table13.

Table 15: Type of R&D Alliances, Collaborations and Licensing Agreements, 1999–2011

Top 14 Pharmaceutical Industry In India		*R&D alliances*			*R&D Collaborations*			*IN Licensing*			*OUT Licensing*		
		Discovery R&D	*Clinical development*	*Research Services*	*Discovery R&D*	*Clinical Trial*	*Research Services*	*Discovery R&D*	*Clinical Trial*	*Research Services*	*Discovery R&D*	*Clinical Trial*	*Research Services*
RI/AI	Domestic	2		1	5	3	1			1			
	Foreign				2	4	3						
Industry	Domestic		1		1	1				1			
	Foreign	2	2	8	12	17	19		5	6		4	5
Grand total		**4**	**3**	**9**	**20**	**25**	**23**		**5**	**8**		**4**	**5**

Source & Notes: As provided in Table 13; RI: Research Institution, AI: Academic Institution; Alliances and collaborations have been distinguished on the basis of the time horizon involved, alliances involve long-term ties.

In case of R&D related ties, research services function dominated the relationships forged with foreign companies. It is also clear that these firms did very little to use the alliances, collaborations and agreements to strengthen their drug discovery. Discovery R&D was the objective of forging a relationship with foreign firms in far fewer cases compared to research services and clinical trials. However, these firms have hardly used these relationships for strengthening of R&D function and new drug discovery and development; even in their relationships with foreign firms it is the short-term objectives which seem to have dominated.

Not only are domestic pharmaceutical firms ready to out-license clinical development of their NCEs to firms that have considerable market operations in the sector of drugs and pharmaceuticals in India, but also they are entering into in-licensing deals for undertaking bioequivalence studies in case of formulations and dosages. In-licensing arrangements are being used to build a portfolio for the purpose of growing in the domestic market. For example, Nicholas Piramal has had arrangements with Roche for launching products relating to cancer, epilepsy and AIDS. Glenmark has in-licensed Crofelemer, Napo's proprietary anti-diarrheal compound. Wockhardt has had arrangements for the in-licensing of Syrio Pharma SpA for dermatological products. Ranbaxy has had arrangements with KS Biomedix Ltd for EMRs to market Trans MID in India with an option to expand into China and other South East Asian Countries.

Foreign firms are apparently gaining financially and control far more R&D and marketing relationships than what these companies could forge through OFDI. Take the examples of out-licensing and in-licensing agreements being signed by these companies. In case of in-licensing agreements, payments to foreign firms are on a recurrent basis with guaranteed returns. Imbalance is also evident at the level of number of agreements entered into by these companies for marketing and research. Marketing as a purpose dominates the agreements. In-licensing agreements in R&D area are for bioequivalence studies. In respect of product development, the area of bioequivalence is not a gap that has to be filled through in-licensing agreements. However, this is not the case when one analyses the out-

licensing deals because the agreement pertains to clinical development of earlier phases and pre-clinical toxicology studies.

Domestic ties with research institutions and the academia have received the least attention from emerging Indian pharmaceutical multinationals. Although domestic firms are the major beneficiaries of R&D services sourced from public sector research laboratories, there are very few alliances for undertaking collaborative drug discovery and development related R&D work between domestic firms and public sector research institutions. Just two firms used the domestic R&D institutions for the purpose of R&D alliances. See *Table 16* for the pattern of ties built with domestic R&D institutions for clinical and discovery R&D by these firms during the period 1999–2011.

Table 16: Type of R&D Alliances with RI/Academia

Companies	*Clinical & Discovery R&D*		*Sub total*	*Research services*		*Sub total*	*Grand total*
	DO	*FO*		*DO*	*FO*		
IPCA laboratories	1		**1**				**1**
*Piramal healthcare	1		**1**	1		**1**	**2**
Total	2		**2**	1		**1**	**3**

Source & Notes: As provided in Table 13. Among the 14 leading Pharmaceutical companies, only IPCA and Piramal have concluded alliance style cooperation with RI/academia.

See *Table 17* for details on the strengthening of market function through new ties with foreign firms. It is evident that marketing activity related relationships dominate alliances and collaborations. Some of the Indian pharmaceutical firms prefer to rely only on marketing alliances abroad instead of setting up subsidiaries or production facilities.

Table 17: Pattern of Marketing Alliances, Collaborations and Licensing Agreements, 1999–2011

Top 14 Pharmaceutical Industry In India	*Marketing alliances*		*Marketing Collaborations*		*IN Licensing (Marketing)*		*OUT Licensing (Marketing)*	
	Domestic	*Foreign*	*Domestic*	*Foreign*	*Domestic*	*Foreign*	*Domestic*	*Foreign*
Industry	10	111	5	101		21	2	6
Grand total	10	111	5	101		21	2	6

Source & Notes: As provided in Table 13.

Further, we also note with some concern that most of these firms have chosen to enter into alliances, collaborations and agreements with foreign firms having presence in the Indian market. By forging a close relationship for the supply of contract research and manufacturing services with these foreign actors having a global presence, quite a few of these firms have made it clear that they have no plans to compete with big pharmas, either in the domestic market or the foreign market. Lupin has a marketing alliance with Cornerstone to market Suprax. DRL has an alliance with Pilva for development and marketing of oncology products in Europe; DRL and Glaxo-Smithkline have a multi-product agreement; DRL is collaborating with Pharmascience Group for development and marketing of generic products in Canada; and, Glenmark has a supply and marketing agreement with Lehigh Valley. Certainly, some of these marketing alliances reflect an

element of strategic choice. At the moment DRL, Glenmark and Lupin are, seemingly, examples of strategic elements guiding their relationships, but it is not the case with most firms whose relationships we have analysed.

Evidence of dominance of marketing function is clearly indicated in different types of relationships forged by each of the 14 firms. Cases of domestic R&D institutions being targeted for in-licensing agreements are very few. In some cases, global pharmaceutical companies are out-licensing their products to Indian firms. This relationship brings regular royalty payments at minimum investment with a wider geographical coverage for their products. Strides Acrolab Ltd has entered into a number of such deals with companies in the US, UK, Japan and Europe. Clinical outsourcing is also being treated as a lucrative strategy by some Indian firms. Cadila Healthcare has entered into alliances with Atlanta Pharma, Schering AG, and Boehringer Ingelheim. Lupin has a licensing agreement with Cornerstone Bio Pharma Inc for clinical development of NDDS for an anti-infective product.

Ranbaxy has entered into a few collaborative research programmes involving global pharmaceutical firms, e.g. with Medicines for Malaria Venture (MMV), Geneva, for an anti-malarial molecule, Rbx 11160; with GlaxoSmithKline for drug discovery and clinical development for a wide range of therapeutic areas; with University of Strathclyde, UK, in new drug delivery system (NDDS); Ranabaxy has a collaborative relationship with Eli Lily, Pfizer and Novartis in drug discovery and with Vectura (a drug delivery company) for development of platform technologies in the area of oral controlled release system. Ranabaxy, Reddy's Laboratories, Lupin, Glenmark, Torrent, Sun pharmaceutical, Cadila and Biocon figure prominently in the agreements, collaborations and alliances entered into for the purpose of R&D. But there are only a few examples of collaborative R&D programmes which follow one or another kind of risk sharing involving joint venture or collaboration with another pharmaceutical company in order to develop and commercialise a product. They are largely entering into one-way relationships, which may hardly prove advantageous in the long run.

Torrent has entered into a collaborative research programme for drug discovery in the area of treatment of hypertension with AstraZeneca. Dependent or potentially compromising relationships will not benefit the firms as much and can the affect the national system of innovation adversely when pressure is being mounted on the industry to accept TRIPS plus provisions of data exclusivity. Of course, there are some exceptions. Cipla has entered into a collaborative programme of risk sharing type with a domestic company set up by a non-resident Indian, namely Avesthagen Laboratories, to produce biogeneric drug for Arthritis, N-Bril. Although Avesthagen has an ongoing collaborative programme with Nestle, Bio Mereleux, France and other companies, Cipla's relationship with Avesthagen is unlikely to prove compromising and can be handled independently.

Domestic companies consider the domestic market to be of small size and not sufficiently attractive for taking up development of new products in the drugs and pharmaceutical

sector. See *Table 18* for the pattern of disease orientation of compounds launched. Most of the compounds in demand belong to the category of Type I diseases. In the absence of stimulus for augmentation of home country demand, the conditions continue to favour the target of low value added products required by global markets. It is this imbalance in policy design which is reinforcing skewed research priorities in the public sector research system. From the point of view of current public health situation, this certainly does not suit the country on whose shoulders the domestic industry still depends.

Table 18: Domestic Pharmaceutical Activities of Commercialised/Launched Generic Compounds

Domestic Companies	*1999–2001*			*2002–2004*			*2005–2007*			*2008–2011*			*Total*
	DISEASE TYPE												
	I	*II*	*III*	*I*	*II*	*III*	*I*	*II*	*III*	*I*	*II*	*III*	
Top 14 leading pharmaceutical industries	5			27	4	2	52	6	4	79	20	3	202

Notes: Disease type: Type-I, Type-II, Type-III; Type-I - Diabetes, Cancer, Metabolic Diseases, Hepatitis, Influenza, Cardiovascular, Infectious Diseases, Inflammatory Diseases, Allergy, Respiratory Diseases; Type-II - HIV/AIDS, Tuberculosis, Malari; Type-III - Leishmaniasis, Trypanosomiasis, Lymphatic filariasis, Leprosy, Diarrhoea.

Source: Data collected from individual website & latest annual report of individual pharma companies and Cygnus research, data accessed as on Nov 2011;

There is evidence of a shift in R&D priorities. Analysis of the evidence processed by us shows that all important developments that we see in respect of the creation of R&D capabilities for new drug discovery and development within Indian firms have a global market favouring R&D orientation. As things stand now, it is clear that pharmaceutical research is largely directed to the needs of the regulated markets of the US and Europe. Even high burden disease areas in India have not been able to attract locally bred firms. Analysis indicates preponderance of medium burden disease areas—Cancer (3.4), Tuberculosis (2.8), HIV/Aids (2.1), Malaria (1.6), Respiratory diseases (1.5), Blindness (1.4), Diabetes (0.7)—being covered by the firms in their relationships with academic institutions and industry networks. See *Table 19* for the pattern of coverage of different types of diseases in academic alliances and collaborations.

Table 19: Pattern of Coverage of Different Types of Burden of Diseases in Academic Collaborations and Alliances, 1999–2011

Companies	*Collaborations & Alliances for Discovery & Clinical R&D with RI/Academia*					
	Domestic Institutions			*Foreign Institutions*		
	High burden disease areas	*Medium burden disease areas*	*Low burden disease areas*	*High burden disease areas*	*Medium burden disease areas*	*Low burden disease areas*
Top 13 leading pharmaceutical industries	4	15	3		1	

Source: Individual Company website Press releases, News, Archives, etc.

See *Table 20* for the pattern of coverage of diseases as focus of development of NCEs among these firms. The table shows the development of new chemical entities (NCEs) through alliances formed with foreign firms for drug discovery and clinical trials. The focus is on medium burden diseases like Cancer, Tuberculosis, HIV/Aids, Malaria, Respiratory diseases, Blindness and Diabetes, which affect both the developed and the developing countries. Diseases for which capability development is being undertaken with the help of foreign firms are those in which the developed world has more interest. The Indian scenario, in terms of high burden disease areas has garnered the least interest over the years.

Table 20: Pattern of Coverage of Different Types of Disease Burden for New Chemical Entities under Development by Indian Pharmaceutical Companies, 1999–2011

Companies	*NCE's Pipeline*		
	High Burden Disease Areas	*Medium Burden Disease Areas*	*Low Burden Disease Areas*
Top 13 leading pharmaceutical industries	17	34	32

Source & Notes: As provided in Table 11.

Impact of government R&D schemes

While the industry is complaining about the rather small size of government funding for direct benefit of R&D in industry, it is interesting to note that they are not even utilizing the existing schemes in a big way. Medium burden diseases are a major focus of the projects undertaken by the industry. This is because of the worldwide emphasis on many of those diseases at the level of R&D funding. The impact of OFDI connections on the lack of balance in R&D priorities is starkly visible in case of use of government schemes by the emerging Indian pharmaceutical multinationals. *Table 21* indicates that most of the emerging Indian pharmaceutical multinationals have not been leveraging government funding for undertaking industrial R&D.

Table 21: Pattern of Coverage of Different Types of Burden of Diseases in Industrial Collaborations and Alliances, 1999–2011

Companies	*Collaboration & Alliances for Discovery and Clinical R&D with Industry*					
	Domestic Firms			*Foreign Firms*		
	High burden disease areas	*Medium burden disease areas*	*Low burden disease areas*	*High burden disease areas*	*Medium burden disease areas*	*Low burden disease areas*
Top 14 leading pharmaceutical industries	**1**			**15**	**31**	**19**

Source: As in Table 15.

More than half of these 14 large domestic firms chose to ignore—almost completely—the schemes formulated by the government industrial research financing altogether. There

were only six firms out of the 14 that undertook government funded projects funded for creation of facilities and activities required for development of new drugs. But large domestic firms accounted for just 15 projects in the portfolio out of the 104 sanctioned by the government. See *Tables 22 & 23* for the pattern of diseases covered by domestic firms while using government funded programmes and schemes initiated for the benefit of pharmaceutical innovation.

Table 22: Pattern of Government Funding Agencies Programmes/Schemes funded Burden of Diseases by Industry, 2005–2011

Funding Agencies	*High Burden*	*Medium Burden*	*Low Burden*	*Total*
DPRP	23	30	13	66
BIPP	6	5	1	12
SBIRI	2	14	10	26
Grand Total	**31**	**49**	**24**	**104**

Source: Compiled by the authors from the information available on these schemes.

Table 23: Firm-wise Pattern of Government Funding Agencies Programmes/Schemes Funded Burden of Diseases by Industry, 2005–2011

Companies	*DPRP*			*BIPP*			*SBIRI*		
	High Burden	*Medium Burden*	*Low Burden*	*High Burden*	*Medium Burden*	*Low Burden*	*High Burden*	*Medium Burden*	*Low Burden*
Total no of Projects in different classes of disease burden	23	30	13	6	5	1	2	14	10
Torrent Pharma	-	1	4	-	-	-	-	-	-
Ranbaxy Laboratories	-	5	-	-	-	-	-	-	-
Strides Arcolab	1	-	-	-		-	-	-	-
Lupin Pharma	1	-	1	-		-	-	-	-
Cadilla Healthcare	-	3	-	-	-	-	-	-	1
Biocon Ltd	-	-	-	-	1	-	-	-	-
Total	**2**	**6**	**5**	**-**	**2**	**-**	**-**	**-**	**1**

Source: Compiled by the authors from the websites of the ministries administering these schemes.

Since domestic firms have not come forward in a big way to use government schemes for R&D and innovation of therapeutics for tackling priority diseases, it is obvious that the national links of these firms are only getting weaker instead of becoming stronger. Despite the government agreeing to cede the ownership of intellectual property rights (IPRs) to collaborating firms, there is lack of interest among emerging Indian pharmaceutical multinationals in these schemes. Some of these firms have now been sold by their

promoters to foreign firms. Certainly, OFDI connections of the strategies of the emerging Indian pharmaceutical multinationals are adversely affecting the plans of the policymakers for the development of a national system of innovation for the benefit of Indian pharmaceutical industry.

Emerging Relations of Domestic Firms with Public Sector R&D

On the issue of emerging relations of public sector R&D with industry, the main challenge is that public sector R&D institutions maintain a long-term vision and strategy directed by public health priorities where citizens have a first claim on their outcomes. See *Table 24* for the current status of matches and mismatches of R&D priorities under perusal along with the priorities of burden of disease in the public sector. It appears that there are too many mismatches to be taken care of, which reflect a clear systemic failure seemingly connected to the determination of disciplinary priorities of the Indian scientific community in the west and the decisions of the government to subject the public sector to short-term demands of private sector in the post-TRIPS period. In the absence of stimulus for augmentation of home demand, the conditions continue to favour the target of low value added products required by global markets. It is this imbalance in policy design which is reinforcing skewed research priorities in the public sector research system.

Public-Private Partnership (PPP) is the latest buzzword in the system of health research and technology development. In India, The New Millennium Indian Technology Leadership Initiative (NMITLI) of the Council of Scientific and Industrial Research (CSIR), Drugs and Pharmaceuticals Research Programme (DPRP) and Technology Development Board (TDB) of Department of Science and Technology (DST) and Small Business Innovation Research Initiative (SBIRI) of Department of Biotechnology (DBT) constitutes the main example of a public private partnership. Strong experience has been gathered through these schemes in respect of the determinants of success in implementation of PPPs. A large number of NMITLI based PPPs have preferred to catalyse health innovation as a vehicle for domestic industry, mainly to attain global leadership in selected niche areas by synergising the best competencies of publicly funded R&D institutions, academia and private industry.

Table 24: Comparison with Disease Burden of Public Sector Projects from 1992–2007

SN.	*Major therapeutic areas/Disease/Health conditions*	*Share in the total burden of disease (%)*	*IMR Projects (%)*	*EMR Projects (%)*	*Public Sector Patents as Percentage (%) of Total Patents*
1	Diabetes	0.7	2.08	8.29	5.96
2	Cancer	3.4	12.71	19.21	13.1
3	Tuberculosis	2.8	8.30	12.66	6.37
4	Malaria	1.6	10.38	5.24	9.87
5	Metabolic disease	-			4.73
6	HIV/Aids	2.1	8.43	10.26	9.85

SN.	Major therapeutic areas/Disease/Health conditions	Share in the total burden of disease (%)	IMR Projects (%)	EMR Projects (%)	Public Sector Patents as Percentage (%) of Total Patents
7	Inflammatory diseases				2.05
8	Infectious diseases/Injuries	16.1			24.27
9	Respiratory diseases	1.5		1.74	2.26
10	Bone disease	-		2.35	1.4
11	Brain disorders	8.5		4.71	2.26
12	Ulcer	-			
13	Psoriasis	-			
14	Cardiovascular	10.0	1.43	2.18	4.11
15	Maternal & prenatal problems	11.6	5.96	3.02	5.25
16	Diarrhoeal diseases	8.2	0.26	1.39	0.20
17	Heart Disease	-			
18	Depression	-			0.41
19	Hypertension	-			2.26
20	Allergy	-			
21	Hepatitis	-	3.37	5.02	2.44
22	Leprosy	0.1	4.15	3.93	2.24
23	Childhood disease	5.4	2.52	1.21	0.41
24	Otitis Media	0.1			
25	Blindness	1.4			0.2
26	Oral diseases	0.5			0.3
27	Prosthetic hyperplasia	-			
28	JE		3.11		0.61
29	Dengue		3.11	0.43	0.41
30	Leishmaniasis		9.86	4.80	3.29
31	Others	25.4	23.48		12.1

Source: Project specific database built by the authors from the public databases on R&D projects and patenting activities being undertaken by the public sector R&D organisations in India, 2009.

NMITLI was responsible for supporting 42 R&D initiatives in various fields including new targets, drug delivery systems, bioenhancers and therapeutics for psoriasis, tuberculosis, pain management in osteoarthritis, insulin sensitisation in diabetes mellitus type II and process of tamiflu, etc., with nearly 287 partners, 222 in public sector and 65 in private sector with an estimated outlay of over Rs 300 crore. Analysis of SIBRI efforts (37 cases till May 2008) shows that there is not much focus on diseases of Indian interest though a couple of cases pertain to malaria and typhoid. Similarly, in the case of DPRP, it is known that the government had to add a special grant-in-aid programme for promotion of research on neglected diseases because in the earlier years the programme was unable to attract domestic companies to work on these areas.

Conceived in 2003, the Golden Triangle partnership is also now receiving special budgetary support for an integrated technology mission focused on the development of Ayurveda and traditional medical knowledge that synthesizes modern medicine, traditional medicine, and modern science. Similarly, efforts towards traditional medicine have also picked up momentum. The CSIR and ICMR (Indian Council of Medical Research) are working with the Department of Ayurveda, Siddha, and Homeopathy to bring out safe, efficacious, and standardised classical products for identified disease conditions. New Ayurvedic and herbal products for diseases of national/global importance are also being pursued. Innovative technologies are being used to develop single and poly-herbal-mineral products, which have the potential for IP protection and commercial exploitation by national/multinational pharma companies.

Areas identified are limited to mainly rasayana (rejuvenators/immunomodulators) for healthy aging, joint disorders, memory disorders, bronchial allergy, fertility/infertility, cardiac disorders (cardio-protective and antiatherosclerotic), sleep disorders, and diabetes. Identifying the strengths and weaknesses of existing modern medical products, the strategy seeks to develop new products to address gaps; formulate an appropriate R&D strategy for standardisation, quality control, IP, and other related issues; take up toxicity/efficacy studies in government laboratories, medical colleges, and universities; prepare detailed dossiers of effective formulations; and, negotiate with an identified industry partner to begin commercialisation after clinical trials are carried out using standard protocols. This ambitious multiagency programme proposes to spend more than Rs 350 million in the next three years. Several areas have already been identified and research is underway.

Failure in Respect of Steering and Coordination

Although major steps have been identified by the government appointed expert groups with regard to national health research policy, plan and system development, most of these steps are still awaiting implementation. In order to take care of many such concerns, establishment of a national health management research forum was proposed in the health research policy document. This forum is also yet to be set up by the government. Action is also required to be undertaken to strengthen the role and place of medical colleges in the system of health R&D in India. Relatively speaking, medical colleges are still a weak component, lacking in institutionalised capacity for research. Physician-scientists are vital to the advancement of medical knowledge as they bring to medical research the unique perspective of asking scientific questions inspired by their experience of caring for patients. Physician-scientists working on rare diseases and pursuing translational research in academic institutions and medical colleges/hospitals are a rare breed in India. As there is an urgent need to fill the physician-researcher gap in India, the government needs to take an urgent look at the status of institutionalised capacity for health research in medical colleges and academic institutions.

The system of health research is lacking in both learning and reflection; the government is yet to give attention to the creation of this capacity. Mechanisms are required to be created for a systematic health research system analysis to be undertaken on a periodical basis by the Department of Health Research. Other concerns are also required to be taken care of for the promotion of R&D and S&T (Science & Technology) departments' extra mural research priorities, stability of funding, network development and access related IP management issues. Evidence collated as a part of the preliminary health research system analysis (HRSA) undertaken has confirmed, in many specialties, important gaps & mismatches, narrow research base in many areas, fragmentation of research effort, lack of coherence, development gap, competence in biology for drug discovery work being not adequate, and so on. Some examples of research imbalances are indicated here as illustrations. It appears that besides the importance of increasing research efforts on neglected diseases in India, one can talk of underdevelopment of toxicology research and drug development for treatment of arsenic and lead. There are about 1000 qualified occupational health professionals in India and only 100 qualified hygienists. The country needs close to 8000 qualified occupational health professionals and there is obviously a tremendous gap between the need and availability of qualified personnel.

India, however, has been witnessing a spurt in research investments for neglected diseases. Some of the international partners include (i) WHO Special Programme for Research and Training in Tropical Diseases (TDR), (ii) the Global Alliance for Tuberculosis Drug Development (TB Alliance), iii) the Medicines for Malaria Venture (MMV) for Malaria vaccine, iv) the International AIDS Vaccine Initiative (IAVI) for HIV/AIDS Vaccine, v) the Institute for One World Health (iOWH), vi) Drugs for Neglected Diseases Initiative (DNDi) for sleeping sickness, Chagas disease, leishmaniasis, and malaria, (vii) Programme for Applied Technology for Health (PATH) for JE vaccine, and, (viii) Concept Foundation for microbicides. The MMV is collaborating with Ranbaxy for developing anti-malarials. The Institute for OneWorld Health (IOWH) is collaborating with the ICMR in the clinical trials of paromomycin for visceral leishmaniasis.

Earlier in 2003–2004, for the segment of neglected Type III diseases, India had also taken another important initiative for development of new generation vaccines for cholera, malaria, tuberculosis, Japanese encephalitis (JE) and HIV/AIDS. Projects initiated as a part of Jai Vigyan programme of the Ministry of Science & Technology are known to be following a different route of PPPs where collaboration in technology development involves partners located in the advanced world for technology transfer. Under this initiative, the government had also signed a number of technology licensing agreements to obtain technologies required for tackling the diseases of the poor. Of the 21 technology missions for integrated R&D that will benefit rural people, the development of new generation vaccines is an important time-bound initiative. The main objective is to develop candidate vaccines for cholera, rabies, JE, tuberculosis, malaria, and HIV infections using novel strategies. These include recombinant proteins; DNA vaccines; recombinant/peptide

vaccines for cholera, malaria, tuberculosis, JE, and rabies (for animals and humans); and preventive/therapeutic DNA candidate vaccine(s) for HIV infection.

Even now there is considerable activity going on in public sector research organisations in the fields of genomics and proteomics in India. It is possible to conceive a route of public-private partnership to give momentum to the field of discovery and development research in the area of pharmaceuticals that will take care of the priorities of national public health and neglected diseases of the poor of developing world as a whole. Although at the moment the future of pharmaceutical production innovation appears to be—in a critical way—in the hands of these companies' potential partners abroad, the outcomes of public sector R&D can be leveraged to align their priorities with the public health goals if the pathways and models of innovation are redirected suitably.

From the above analysis it is clear that the leadership has also been willing to subject the priorities of public sector R&D organisations to short-term priorities of the domestic industry during the post-TRIPS period. The scientific community did not resist the pressures and inducements. Leadership of the scientific community clearly did choose to give a higher priority to the R&D work to be undertaken on the problems of ageing disorders, psoriasis, rejuvenates and so on rather than putting in money into products for neglected diseases (Type III). However, with the intervention of public sector agencies the situation can change for the better. It is essential to plan, monitor and evaluate public sector R&D institutions on the basis of public health priorities. Here, too, the results will be in favour of public health if the agency is determined to pursue the roadmap for the development of products that are required locally and have the support of public health system.

Conclusion

Contrary to expectations of policymakers, growing global integration is failing to generate the "best case conditions" predicted to be prevailing for the prospects of industrial upgrading of the pharmaceutical sector and knowledge creation for the acceleration of catching-up process and for the benefit of public health in India. Large-sized domestic firms are making far more investments in marketing activities than in competence building, interactive learning and innovation making activities. Domestic firms have failed to utilise the strategic advantage of industrial capabilities developed with the help of public investment. The primary incentive to invest in R&D, whether for NCEs, modifications or development of generics, has not arisen in a big way from the new TRIPS-compliant product patent regime in India. While in the post-TRIPS era the government has been able to accelerate the contribution of in-house R&D to the emerging pharmaceutical innovation making landscape because of the anticipated shrinkage of off-patent opportunities for domestic firms, it is also true that even in the absence of TRIPS such R&D activities would still have been possibly undertaken by quite a few domestic firms because of their decision to enter the regulated markets to take advantage of the opportunities opened for generics.

While R&D activities have diversified, no NCE has yet been developed. Domestic pharmaceutical firms are yet to prove their competence in respect of the development of new products. There have been several setbacks and the partnership model has not always worked properly. Little has changed to dispute the traditional wisdom that developing countries should not grant product patent protection (Chaudhuri, 2007)[5]. It is necessary to accelerate the processes of learning, competence building and innovation making by establishing a clear national strategy with the aim of strengthening the place of domestic pharmaceutical firms and of enhancing the systemic autonomy and coherence of national system of innovation. Policy intervention in the way of increasing the size of domestic market and rapidly expanding the knowledge base in the public sector with the aim to encourage domestic firms to undertake more technological activities directed at meeting the needs of Indian people has been suggested as a remedial step.

Coming to the beginning of the change in the composition of drivers of funding for research for health in favour of Type-III diseases and traditional medicine, in India the enabling environment to steer and coordinate, manage, appraise, articulate demand and appropriate IPRs is still missing. Markets for knowledge and technology are by no means neutral space; policy interventions for industrial upgrading have to take into account that there is an international division of labour being constituted through the route of outsourcing. Innovation systems must stay clear of the traps that this division of labour is laying down for domestic firms. As things stand today, it would not be possible for domestic firms to grow beyond a point through the selected routes of export of generics and contract work in research and manufacturing. These routes can be used to only supplement the strategy of expanding the domestic market but to mainly depend on these routes for further growth would take the domestic firms away from the real needs based innovation. It is likely that most domestic firms will ultimately settle down to accept the role of junior partners in the new game of proteomics and genomics based innovation wherein the R&D platform/tools are already monopolised via the route of strong IPRs.

Prospects for domestic R&D for neglected diseases and conditions will improve only when the constraint of market size are suitably eased for the benefit of local pharmaceutical firms. To alleviate the constraint of small market size the Indian government must also step in to improve the demand conditions. In the recent period, health expenditure has been declining across the board in India. This is a direct consequence of the implementation of neoliberal fiscal strategy. It is too much to expect from domestic pharmaceutical firms—whose revenues are insecure—to contribute to R&D investment for neglected diseases under the situation of declining public health expenditure.

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[5] Recently, Chaudhuri (2010) explored the issue of policy options in light of the experience of the Indian private sector and the public-private partnerships initiated in India for the development of new drugs and suggested the expansion of public-private partnerships to include organisations from other innovative developing countries such as Brazil and China.

Policymakers will also have to seek significant changes on the side of supply of innovation capacities if their new strategies for industrial upgrading are to obtain significant success. They need to get the private sector to coordinate with the public sector in the creation of a programme for upgrading innovation capacities in order to play a positive role in drug development for diseases of the poor in India. Policymakers will also have to target for direct support for R&D facilities for clinical trials. Domestic firms should not get incentivised for inappropriate product targets. Dependent relationships being forged through excessive reliance on low quality contract work in both manufacturing and research will have to be discouraged.

Decoupling of research costs from price of product under sales can be an important step in the appropriate direction. Rewards for R&D financing need to be redesigned to discourage inefficient and unfair innovation work. For example, the encouragement to invest in India in the case of Open Source Drug Discovery (OSDD) movement does not rely on monetary incentives. It also offers the model for emulation to achieve the goal of decoupling of R&D from the price of product. Licensing mechanisms need to be used to maximise access. Pressures on the Indian government to desist from issuing compulsory licenses (CLs) and moving away from the implementation and strengthening of Section 3(d) need to be opposed. The focus of the public sector with regard to the implementation of IPR regime should be looked into from the standpoint of where the innovation policy needs to redirect the efforts in public interest.

As far as the impact of pro-TRIPS domestic innovation policy on the contribution of domestic firms to pharmaceutical innovation is concerned, it is necessary to point out that evidence is building up to contradict the claim that the adverse effect on prices of patented medicines would be adequately compensated by the diffusion of new technological capabilities and advanced pharmaceutical knowledge[6]. Apparently, the activity of mergers and acquisitions prompted the Department of Industrial Promotion and Policy (DIPP) to express concern with regard to access to medicines in the paper issued on November 30, 2011. Control of the home market was recognised by the DIPP to be gradually moving away from the hands of domestic firms. Foreign firms are better placed to use the Indian production base, charging higher prices for medicines because of their growing market power (Chaudhuri, 2010).

Policymakers will have to try getting the domestic firms to concentrate their efforts on the real needs based innovations and strategies that will largely free the Indian firms from getting into dependent relationships with foreign firms. Experience of the worldwide practice of negative innovation emanating from the pharmaceutical sector under the

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[6] Recently, this apprehension was confirmed by the official paper of Department of Industrial Promotion and Policy (DIPP) of Government of India (DIPP, 2011). The paper has attempted to bring issues concerning the regulation of foreign direct investment (FDI) and the use of provisions of compulsory licensing to deal with the policy challenge once again on the agenda of the Government of India.

strategy of "innovation for profit," the Indian policymakers have a social responsibility to ensure that the institutions of health sciences remain geared to producing more of public goods rather than market goods. In particular, they have a duty to use the instruments of public sector R&D and governmental support for innovation to the private sector in a targeted way.

In order to accelerate the processes of knowledge creation for the benefit of acceleration of the catching-up process, the Indian pharmaceutical industry is shown to be in the urgent need of creating complementarities and linkages to establish the new pathways of growth with a view to impact the processes of learning, competence building and innovation making for the improvement of public health in India. Steps that are considered necessary to bring about a radical change in the impact of active policies under implementation are identified as challenges facing the policymakers in respect of the tasks of domestic market building, dealing with information externalities arising out of weak institutional research base, and remedying the coordination failure and various other such problems of promotion and regulation of technology development.

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