

Intellectual Property: Research, Innovation and Access and Affordability of Medicines in Developing Countries (A Case Study of India)

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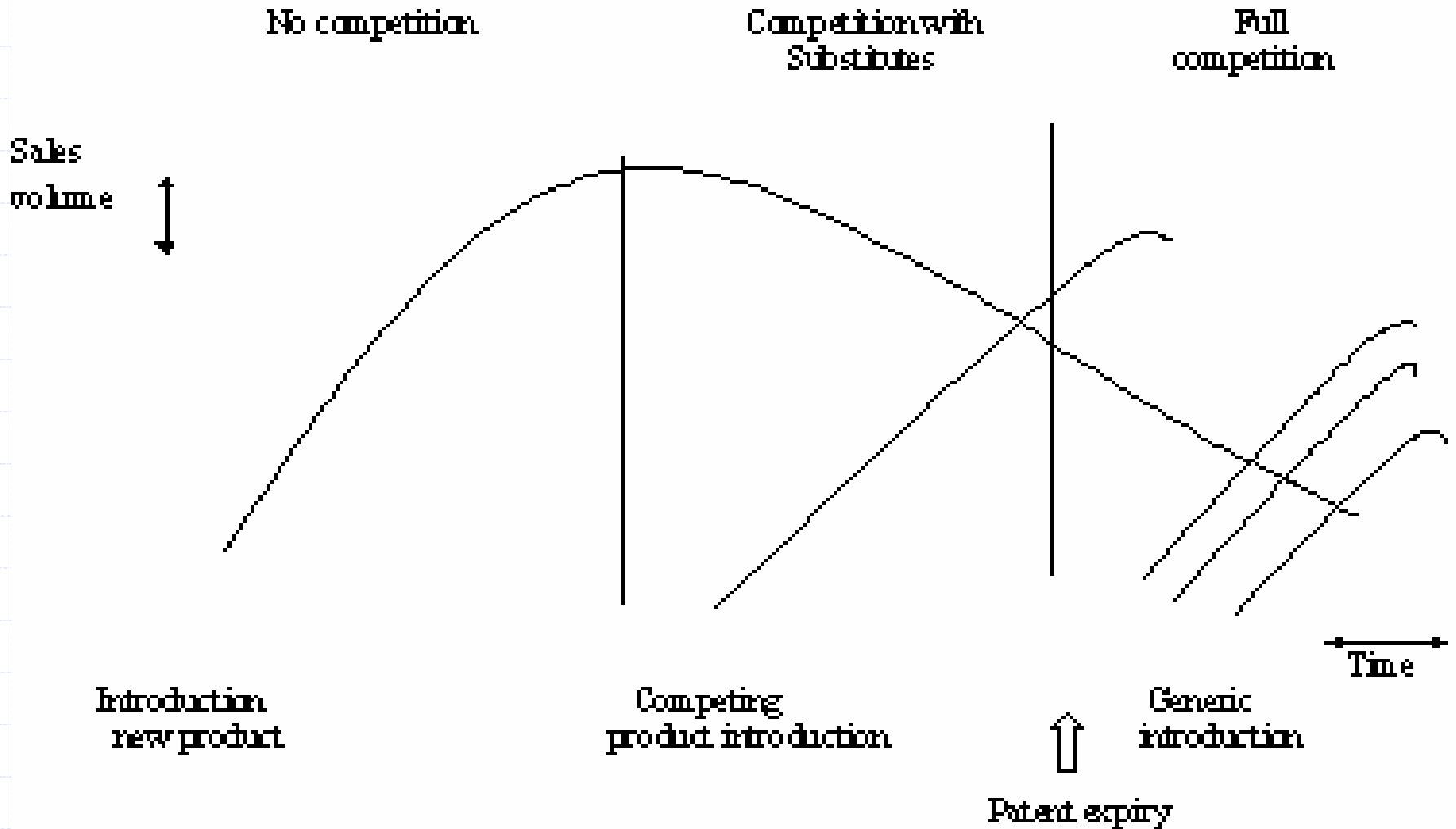
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BACKGROUND

- ◆ World pharmaceutical market can be distinguished in terms of patented drugs and generics. Price of generic can be 70-90 % of the price of patented drug.
- ◆ Health care in developing countries are mainly dependent on the generic drug supply.
- ◆ TRIPs governed patent rules and regulations have considerably reduced the space for interventions (in their patenting provisions) in countries that are signatory to the WTO agreement.
- ◆ Advent of TRIPs governed regime would severely restrict the production and supply of generic drugs as countries that are main producers i.e. India, China, Brazil would have to stop production of drugs patented post 1995; being signatory to the WTO agreement.

Figure 1: The product life cycle for pharmaceuticals



Source: Adapted from Schulm³

Background (Contd.)

- ◆ Multi-lateral bodies (prime among them the WTO) and industrialized economies, argue that strengthened IPR provisions and enforcement mechanisms in developing countries would have distinct set of advantages.
- ◆ According to them:
 - Provide stimulus to the development of drugs;
 - Better medical treatments for diseases confronting the developing countries i.e. neglected diseases;
 - Compel domestic firms to undertake research activity that would have long term benefits, etc.

Study Objective

- ◆ The main objective of this study was to examine to what extent the TRIPs challenge has provided the stimulus for enhanced commitment to health research in developing countries. We restrict our study to India.
- ◆ The study has sought answers to the following research questions:
Whether there has been a significant shift of domestic firms from reverse engineering towards process of innovation?;
Are firms paying attention to development of drugs that are confronting diseases mainly prevalent in developing countries?;
Do we observe new opportunities for development/access of drugs in 'neglected' diseases (diseases confronting mainly the poor/rural population) ?.

Methodology and Scope

◆ The study addressed the objective based on multiple approaches:

(A) Analyzed the contemporary status of the Industry, and the Government Initiatives- post TRIPS period.

(B) Analyzed major MNCs and multi-lateral health agencies involvement with Indian entities.

Part (A) and (B) were based primarily on secondary sources including accessing patent databases.

(C) Examined the activities of 98 Indian pharmaceutical firms; firms covered were mid-size to bigger firms who had reported R&D investment. Along with sending direct response sheet, secondary sources were extensively used.

Analysis was undertaken under three periods: 1990-95 (pre-TRIPS), 1996-2000 (post TRIPs) and 2001-2005 (Contemporary period).



Disease Burden in India

Disease Burden in India - Estimated from Different Sources

- ◆ 17 priority health conditions have been identified by the GOI (NCMH).
Figure 2 and Figure 3
- ◆ Evidence of a large number of diseases which were considered to be lifestyle-related and affecting the rich were seen to be affecting the poor as well, and increasingly so.
- ◆ **TB is the single most important cause of death in India at present.** Nearly 40% of the Indian population of all ages has Mycobacterium Tuberculosis infection (NCMH).
- ◆ HIV/AIDS and infections such as TB and drug-resistant malaria are likely to increase (NCMH).
- ◆ Maternal, perinatal and childhood conditions account for another significant percentage of the disease burden, of particular importance for the poor.
Neonatal, infant, under-5 and maternal mortality rates, continue to be unacceptably high.
- ◆ Malaria, dengue and other vector-borne conditions were estimated to account for 1.6% of India's total disease burden (WHO 1998). However, the actual number is estimated to be much higher.
- ◆ Leishmaniasis (Kala azar) , 12 million people effected in India and killing estimated 200,000 people annually. Disease affecting poor-rural population in India

Disease Burden in India

- ◆ Prevalence rates of CVD in rural populations will remain lower than that of urban populations, they will continue to increase, reaching around 13.5% of the rural population in the age group of 60–69 years by 2015.
- ◆ Diabetes is emerging as a serious health challenge in India particularly concentrated in the urban population.
- ◆ Cancers are another area of concern. In India, cancers account for about 3.3% of the disease burden and about 9% of all deaths. This is expected to rise significantly.
- ◆ 6.5% of the Indian population had some form of serious mental disorder, with no discernible rural–urban differences; women had slightly higher rates of mental disorder than men.
- ◆ It is also estimated that there were roughly 2.5 crore cases of asthma in 2001 which may increase by nearly 50% by 2015.

Fig 2: Priority Communicable Maternal and Child Health Condition In India, by share in Burden of Disease (1998)

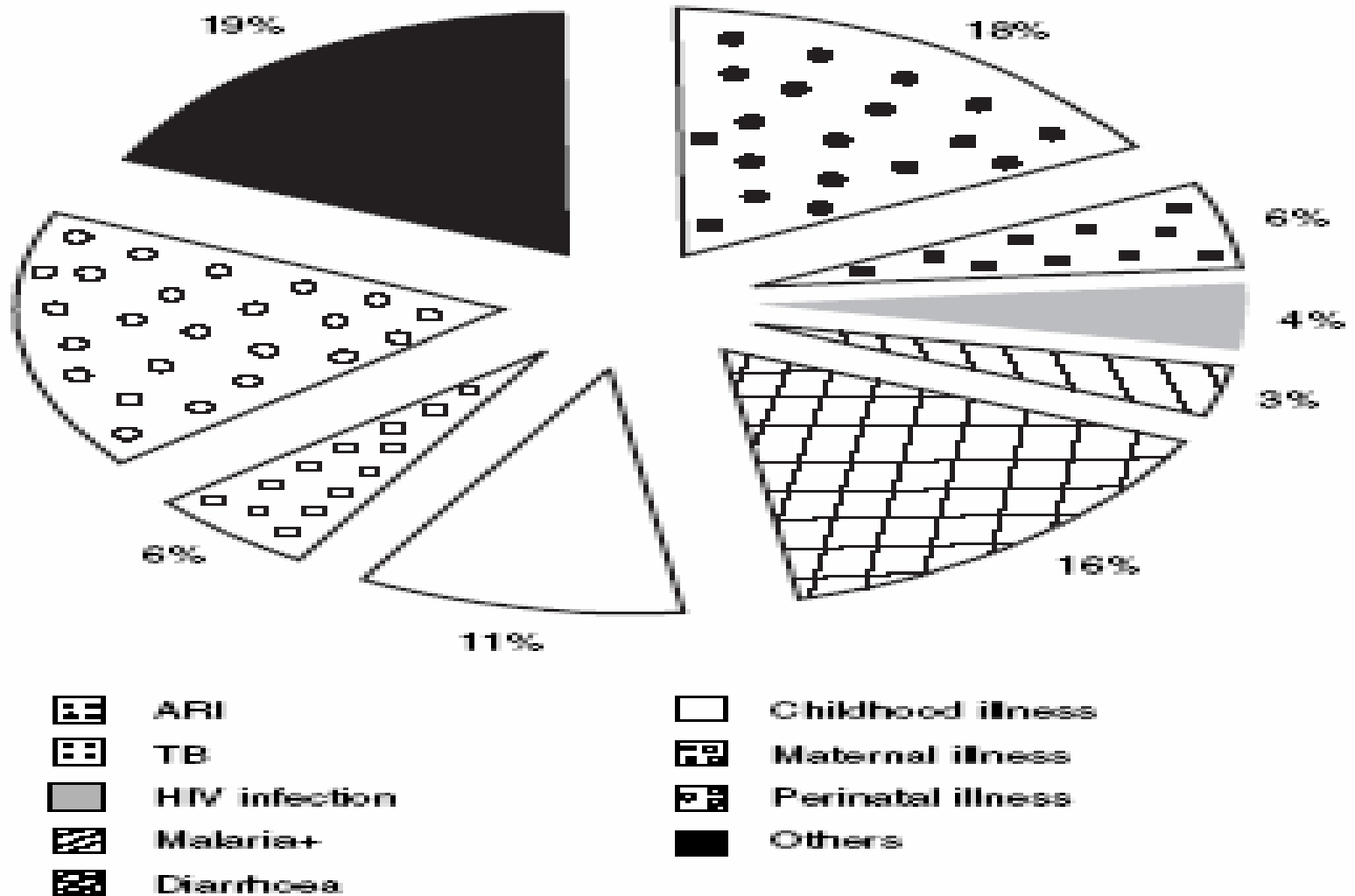
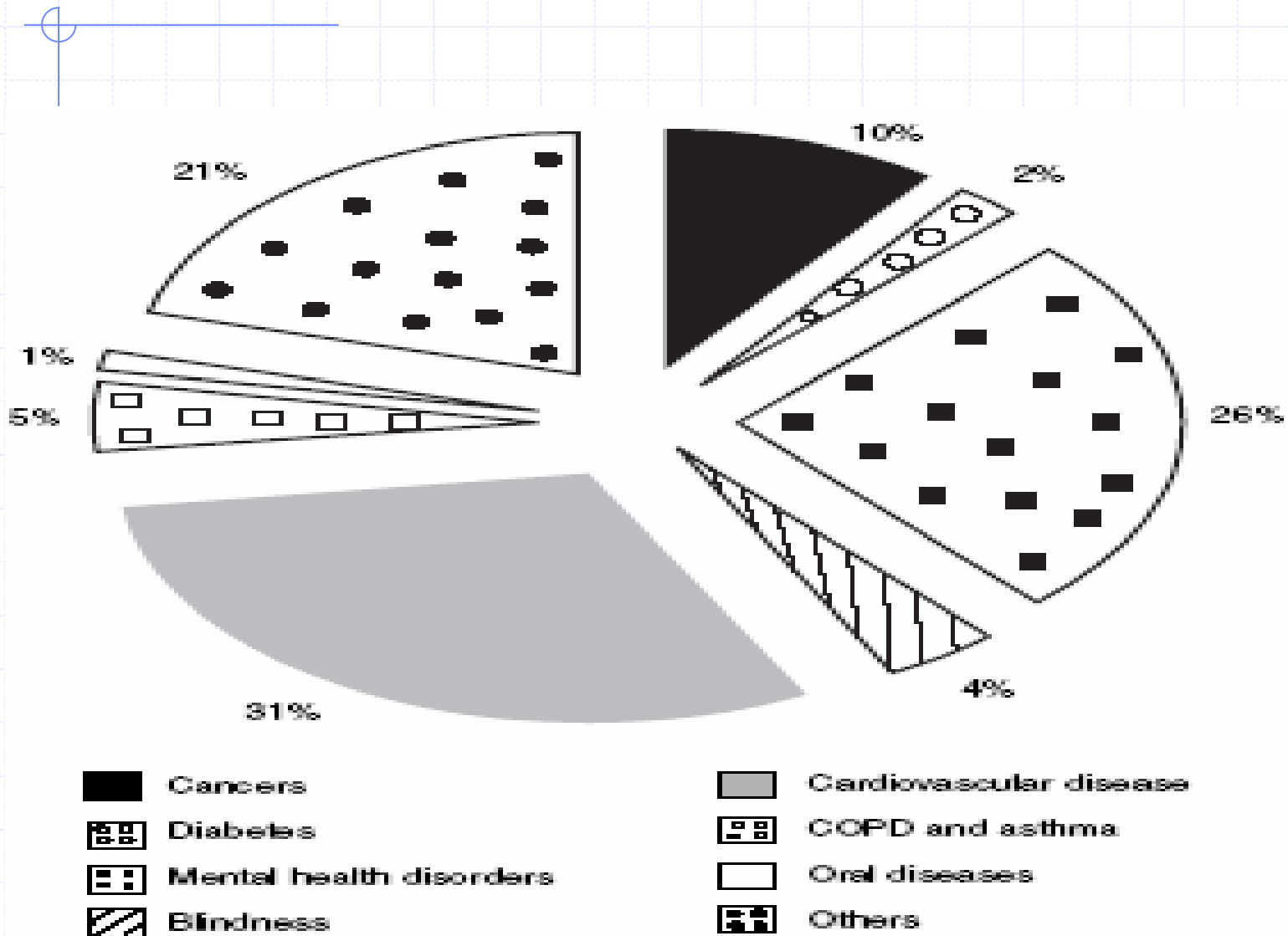


Fig 3: Priority Non-communicable Health Condition In India, by share in Burden of Disease (1998)



RESULTS

Addressing the Research Questions

Whether there has been a significant shift of domestic firms from reverse engineering towards process of innovation?

Research and Innovation by Indian Firms (Broad Observations)

- ◆ The ratio of R&D investment as %age of sales shows Indian firms spend 2 to 3% of their sales on R&D whereas global firms spend as high as 15 to 20% of their sales on their research.

- ◆ However in the last few years there are some firms who were devoting more than 5% towards R&D as percentage of sales.

Ranbaxy, Wockhardt Ltd., Dr Reddy's Lab, Cadila healthcare Ltd., Lupin Labs were some of the prominent firms belonging to this category.

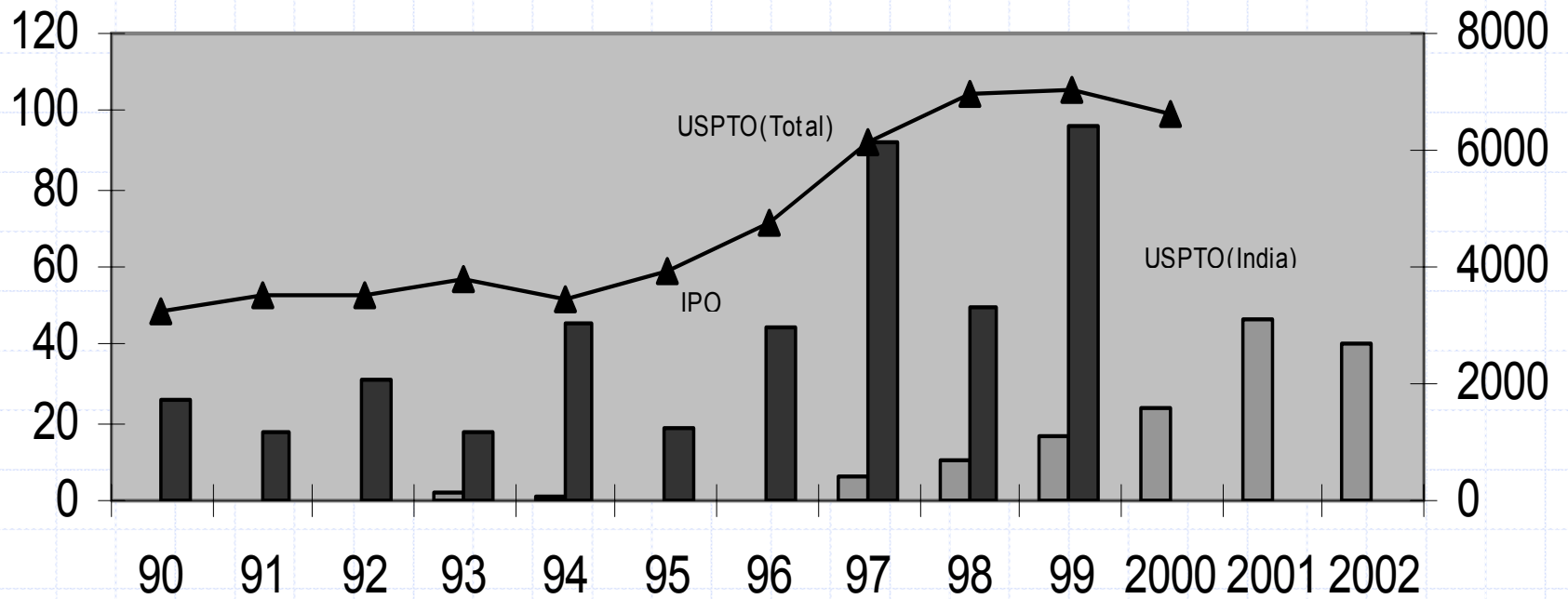
Matrix Laboratories, and Ajanta Pharma Ltd were two prominent firms devoting more than 15% of sales in R&D.

- ◆ On an average large pharmaceutical companies (Rs.500 crore and above) had witnessed 56 % increase to their R&D expenses (from 2001 to 2007).

As %age of sales turnover also, it had risen from 3.7 % to 4.4 %.

- ◆ Mid-sized companies (Rs.200-500 crore) on the other hand had witnessed 41 % growth to their research expenditure in the same period.

Figure 4: Pharmaceutical Patents in USPTO and IPO



Research and Innovation by Indian Firms

- ◆ Pharmaceutical sector accounted for 42% (284 patents) of the overall patents granted during 1990-2002.

Similarly, it had share of 32% (1579 patents) of the overall patents granted by the Indian Patent Office (IPO) during the same period.

- ◆ India was the leading country among the developing countries in terms of patent filing through the PCT (2001-2007).
- ◆ In the PCT patent filings by Indian entities, domineering position was held by pharmaceutical and biotechnological firms.
- ◆ Of the 8000 applications filed between 1995-2004 in the IPO under 'mailbox' provision, approx. 40% were from Indian Pharmaceutical Firms.

Research and Innovation by Indian Firms

- ◆ Some of the major pharmaceutical firms **Ranbaxy, Nicholas Piramal, Wockhardt, Reddy's Lab** had started investing in biotechnology research in a big way to develop more cost effective and reliable platform for drug discovery.
- ◆ The generic manufacturers were leveraging their research skills by developing **NDDS** for the existing molecules. Ranbaxy Ltd., Dr Reddy's Lab, Cipla, Wockhard were some of the labs that were following this route.
- ◆ One of the new entrant was **Reliance Life Sciences**. This firm is concentrating on stem cell research and had already been listed among the best labs worldwide in this field.

Research and Innovation by Indian Firms

- ◆ In **bio-informatics** beginning has been made. Major IT firms like TCS are investing in this sector and developing software tools.
- ◆ Indian firms were increasingly involved in contract manufacturing and clinical trials.
- ◆ A few firms such as Ranbaxy, Dr Reddy had licensed their novel molecules (in pre-clinical stage) to major MNCs. The target areas were diabetes and oncology.

R&D and Innovation Activity of the 98 Pharmaceutical Firms

Broad Statistics

Year	Sales	R&D	R&D as %age of Sales	Export	Import
1990-91— 1994-95	15,123.40	105.92	0.70	1,863.67	2,197.15
1995-96— 2000-01	30,327.58	311.86	1.02	4,953.87	4,833.33
2000-01— 2004-05	23,327.18	177.46	0.76	3,576.34	3,317.38
1990-91— 2004-05	68,778.16	595.24	0.86	10,393.88	10,347.86

All Figures in Rs. Crores

R&D and Innovation Activity of the 98 Pharmaceutical Firms

- ◆ R&D Investment, Establishment of R&D Centres, R&D Collaborations, Higher Quality Standards, Patenting Activity, were phenomena's observed mainly post 1995.
- ◆ R&D investment exhibited strong correlation to sales.
- ◆ R&D investment also showed strong correlation to export
- ◆ One fifth of the firms had separate R&D centres established mainly after 1998.
- ◆ R&D collaborations ranged from technology transfer to joint research partnership

21 firms were involved in collaborative partnerships.

R&D and Innovation Activity of the 98 Pharmaceutical Firms

Firms were taking all necessary steps/safeguards to enter regulated market in the west.

(a) Filing ANDAs (Abbreviated New Drug Applications) for marketing generic drugs in USA.

(b) Filing DMFS (Drug Master Files) to export their bulk drugs.

27 of the 68 firms had filed ANDAs and DMF in the USA.

(c) Obtained US-FDA, WHO-GMP plant certifications, UK MCA, etc.

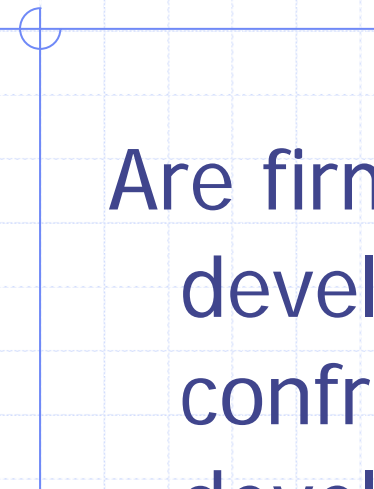
R&D and Innovation Activity of the 98 Pharmaceutical Firms

- ◆ Only a few of the 98 firms were involved in patenting activity in the USPTO and the IPO (Indian Patent Office).
- ◆ Only 9 firms were involved in patenting activity- granted and application filed in the two systems.
- ◆ No patents were issued before 2004 (USPTO).
- ◆ Application filing data in the USPTO covered for the period 2001-2007 showed only a few applications filed before 2005.
- ◆ 1998 was primarily the cut-off date for the patents granted by the IPO.
- ◆ 7 firms accounted for 78 patents of which only 2 were granted before 1998.

This result is not different from the overall population involved in patenting activity. Only 10 pharmaceutical firms were primarily involved in patenting activity (1990-2007) in the USPTO & EPO.

Product and Processes Developed by the 98 Pharmaceutical Firms

- a) New processes in the field of extraction and analysis of drug compounds and bacterial cultivation, etc.
- b) New or improved manufacturing processes for drugs
- c) New drugs in various therapeutic segments.
- d) New drug delivery systems (NDDS) in the form of sprays, inhalers, rubbing creams, gels etc.
- e) Various kinds of medicinal equipments and kits (HIV test kit, syphilis test kit, continuous dialysis equipment, colorimeters) etc.
- f) Plant based drugs and, cosmetic & health products
- g) Development of various types of vaccines such as vaccines for Hepatitis A&B, anthrax, Tetanus, Whooping Cough, Chicken Pox etc.



Are firms paying attention to development of drugs that are confronting diseases mainly prevalent in developing countries?

Development of Drugs for 'Neglected Diseases'

- ◆ Evidence so far has shown that private intellectual property rights promote research only for drugs and therapies with large expected returns.
- ◆ In 1996, WHO estimated that whereas 50% of all global health R&D was conducted by the private sector, less than 5% of this was spent on diseases of importance to low income countries.
- ◆ In 1999, Pecoul *et al.* reported similarly that out of 1233 drugs licensed world-wide between 1975 and 1977 only 13 were for the tropical diseases of which five were for veterinary diseases.

Development of Drugs for 'Neglected Diseases'

- ◆ In India too, private sector investment in health priorities of the developing world has been scarce, even before 2005.
- ◆ A study conducted by Lanjouw and Cocklum (2001) surveyed top 20 Indian firms as to their extent of R&D investment into neglected diseases. They found that firms are investing in R&D for diseases that can be classified under 'global illness'.
- ◆ Study by Cheric Grace (2004) for DFID Health System Resource Centre found that to compensate for revenue loss of the domestic market (since generic copies of newer drugs will become illegal) Indian firms have increased their emphasis on export market more aggressively.

Development of Drugs for 'Neglected Diseases'

- ◆ Recent study by Gehl Sampath (2006), commissioned by CIPH, WHO, surveyed 103 Indian firms.

In the context of addressing disease category, the study found that:

- 15 firms focussed only on local diseases

- 16 reported to have 50% of their entire work on local disease

- 62 of them had less than 25% to no activity on local disease.

- ◆ The export demand shaped innovation strategies.

Development of Drugs for 'Neglected Diseases' (Evidence from 98 Pharmaceutical Firms)

- ◆ Our Broad level Industry Analysis and more In-depth analysis of 98 firms show only a limited involvement of firms in diseases that are confined mainly to India and other developing countries.
- ◆ Diabetes, Cancer, Pulmonary disease were found to be the main research domain of Indian firms. Other areas that can be categorised as health cosmetic such as Anti-ageing, facial hair removal were also a domain of research.

Development of drugs for 'Neglected Diseases' (Evidence from 98 Pharmaceutical Firms)

Among the 98 firms, only a few firms had addressed 'neglected diseases' segment.

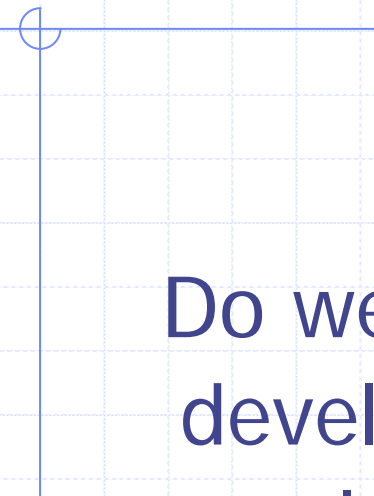
Only 3 Firms had indicated their specific area of operation in 'neglected disease'.

3 Firms had partnership with Global Working Alliance for TB drug development.

Product development (in 'neglected' disease')

One firm had a TB drug molecule in pre-clinical stage

Seven firms have developed various medicinal equipments & Kits (including HIV, Syphilis test kits)



Do we observe new opportunities for development/access of drugs in 'neglected' diseases?

Governments Efforts to Mitigate the Effect of TRIPs Governed IPR Changes in Indian Patent Act (2005)

- ◆ Introducing a special caveat in the IPR provision (Section 3(d))
- ◆ Establishing the National Commission on Macroeconomics and Health (NCMH).
- ◆ Introducing pre-grant opposition
- ◆ Changing compulsory license provision as per Doha Declaration
- ◆ Increasing participation with international organisations involved in new initiatives for drug development
- ◆ Targeted public-private partnership programs for drug development in 'neglected diseases'.
- ◆ Vaccine R&D initiative
- ◆ Fiscal and Non-fiscal R&D Incentive
- ◆ Price-control mechanism

MNC Strategies and their Effect on Access & Affordability of Medicines

- ◆ MNC drug companies (In India) were evolving new strategies to
 - Help them battle generic companies i.e. position themselves favourably in the price sensitive and pre-dominant generic driven Indian market.
 - Try to reach a wider group of patients
 - Avoid chances for compulsory licensing by the government.
 - Challenge unfavourable court rulingStrategies may have long term effect for:

- ◆ Introduction of novel patented drug at affordable prices and accessible to poor patients
- ◆ Co- partnership for the development of drug including drugs for 'neglected disease'. Four MNCs exhibited major involvement namely: GSK, Roche, Novartis, and Eli-Lilly.

MNC Strategies and their Effect on Access & Affordability of Medicines

Strategies Include:

- (a) Differential pricing (Government supply; Patient Access programme; Hospitals in rural areas , and NGO)
- (b) Developing public-private partnership
- (c) Targeted funding for 'neglected disease' research
- (d) Associating themselves with international programs/multi-lateral organisations in drug development for 'neglected disease'

Actions already Initiated (Differential Pricing)

- ◆ Pfizer Ltd has worked out a three-tier pricing system for Sutent (the first patent protected product launched in India by the company)
Drug priced at about Rs. 1.96 lakh for a 45 day treatment has been offered at 3 different prices through the company's patient assistance program's launched in association with a non-profit organisation.
- ◆ Gilivec — a blood cancer drug launched by Novartis India Ltd offers two types of pricing (a) full cost (b) free.

Both these drugs are facing challenge by local Indian firms who have got injunction to sell copycat version of these drugs at much lower price.

International Organisations in Drug development for 'Neglected Diseases'

- ◆ Multi-lateral organizations, Non-profit entities, Foundations involved in health research were playing the central role in drug development for 'neglected diseases'.
- ◆ Initiating public-private partnership, patient access support, research for drug development were some of the methods in which these organizations were involved.
- ◆ Following international organisations were identified as major players involved with Indian firms, research organisations and government:
 - WHO (Special programme for research and training in Tropical Disease, Green Light Committee- MDR-TB programme)
 - Gates Foundation (Funding for drug development in Leishmaniasis; purchase commitment for new vaccines)
 - MSF- Medicins Sans Frontiers (Drugs for neglected disease imitative DNDi)
 - Clinton Foundation (ARV supply to developing countries)

Conclusion and Lessons Learned

The primary objective of this study was to ascertain whether TRIPs challenge has provided the stimulus for enhanced commitment to health research in developing countries'. To address this objective we examined three main research questions

(A) Shift from Reverse Engineering towards Research and Innovation Activity

The evidences strongly imply that Large and Mid-Size firms are focusing on research and innovation as a strategy to survive in the post-TRIPs era.

Making a global presence particularly in regulated markets seems to guide their R&D activity.

From simple generics the firms have been able to move towards 'specialty generics'.

The firms have been able to do incremental innovations resulting in new dosage forms, mode of administration etc.

Conclusion and Lessons Learned

A few firms have developed molecules which have been licensed at the pre-clinical stage to major MNCs.

For regulatory approvals, Indian firms were actively involved in fulfilling the required norms.

A few firms have obtained process patents and secondary patents (i.e. patents for incremental innovations allowed in the USPTO).

Conclusion and Lessons Learned

Whether firms were paying attention to development of drugs that are confronting diseases mainly prevalent in developing countries.

We examined this in the context of India. We tried to map with the diseases affecting the Indian population, mainly those affecting the poor/rural population.

Addressing regulated market in the north as the primary objective has resulted in the Indian firms research focus mainly towards the diseases that have high incidence in the north.

Their involvement in research in any of the 'neglected diseases' were motivated by partnership with MNCs, International organisations, and targeted public-private government programmes.

The sample of 98 firms examined were a true reflection of the broader picture. They re-assert the above observations.

New opportunities for development/access of drugs in 'neglected' diseases

International Organisations/Foundations were playing a key role as intermediary organisations in various capacities for research, access and affordability of medicines in 'neglected diseases'.

Government own initiatives, public-private partnership and partnership with international organisations are showing results.

MNCs mainly for strategic reasons are getting involved in a limited way in research in 'neglected diseases'. A few partnerships with Indian firms are developing.



Lessons Learned

In spite of strong, adverse consequences of IPR provisions for developing countries in public health, there are possibilities of mitigating the effects to some extent by exploring new initiatives.

The options available would be dependent on the capability of developing countries i.e. the means to achieve the end (health care).

The present case study of India provides some indications in this context.



THANKS!
LOOKING FORWARD TO YOUR QUESTIONS.