

# R&D for Development of New Drugs for Neglected Diseases

## How Can India Contribute\*

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March 31, 2005

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\* A study prepared for the World Health Organization Commission on Intellectual Property Rights Innovation and Public Health. The author benefited from discussions with Y K Hamied (Cipla), B Gopalan (Glenmark Research Centre), P Tewari and S K Misra (USV), K K Sharma (Lupin), Laxman Prasad (DST), G J Samathanam (DST), Rama Mukherjee (Dabur Research Foundation), D Yogeshwara Rao (CSIR), Bansi Lal (Nicholas Piramal), V Muthuswamy (ICMR), Rajen Shah (JB Chemicals & Pharmaceuticals). The author also thanks Charles Clift and Jean Lanjouw for comments on an earlier version of the paper.

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## Executive Summary

It is increasingly being realised that to take care of the market failure to generate R&D for new drugs for the neglected diseases, developing countries themselves will have to play an important role.

The focus of this paper is on India. India is important for several reasons. In line with TRIPS, India has introduced a product patent regime in pharmaceuticals from 1 January, 2005. Will this lead to an increase in resources devoted to R&D by Indian companies for the development of new drugs more suited to the needs of India and other developing countries? India has demonstrated strong innovation capabilities in developing manufacturing processes. Can such capabilities be utilized for developing new drugs particularly for neglected diseases? Can India contribute to lowering the cost of new drug development and hence make drugs more accessible?

Pharmaceutical R&D can be broadly classified into three types: (i) development of new chemical entities (NCEs); (ii) modifications of existing NCEs (new chemical derivatives, new formulations, new combinations) and (iii) development of new processes for manufacturing drugs (whether old or new). Till recently, R&D in the Indian pharmaceutical industry has been primarily of the third type. The indigenous sector has developed tremendous strength in developing cost efficient processes for manufacturing drugs satisfying international quality norms. India has received world wide recognition as a low cost producer of high quality bulk drugs and formulations. The product patent protection in India under the Patents and Designs Act, 1911 did not have any positive effect because the MNCs, who held the patents were not keen on manufacturing (and R&D) activities in India and prevented the Indian companies from doing so by using their patent rights. It was not product patent protection but its abolition under the Patents Act, 1970 which operated as a pull mechanism in India by provided the Indian companies the space of operations and the opportunity to develop and innovate. What helped the indigenous sector to realize its potential were significant public investments in manufacturing and R&D.

Despite the inadequate stress on R&D for new drug development, some new drugs did emerge in India primarily from the public sector laboratory, Central Drug Research Institute. It is one of the few public sector organizations in the world which have their own drug development infrastructure.

The drugs developed by CDRI were licensed to various Indian companies. Some of these drugs are available in the market. But these are yet to be commercially very successful. In fact none of the drugs developed has been registered in the large markets of developed countries. The basic limitation of the CDRI drug development programme has been the lack of commercial orientation. It is very difficult to take a product to the market without the help of MNCs. CDRI neither tied up with MNCs nor were able to develop alternative institutional marketing outlets.

So far as India is concerned, the MNCs disprove the hypothesis that strong intellectual property rights are important for their investments in R&D. Three MNCs started R&D for new drug development when India did not provide product patent protection. These have been stopped. After TRIPS, except AstraZeneca (which has set up a TB R&D centre in Bangalore) none of the MNCs is involved in any R&D for new drugs.

TRIPS has been accompanied by an increase in R&D for new drug development by Indian companies. But the Indian companies are not engaged in the entire process of drug development because they do not have the skills and the resources to do so. The model that Indian companies have adopted is to develop new molecules and license out these to the MNCs in the early phase of clinical development. As a result, Indian companies are not targeting the neglected diseases of the developing countries but the global diseases which interest the MNCs. The plans drawn up by the Indian companies suggest that this trend is unlikely to change in the foreseeable future. Indian companies have proved their competence as innovators of new processes. But they are yet to demonstrate their capability in new drug development. While some of the molecules developed are at clinical trials stages, no new drug has yet been approved for marketing.

Thus TRIPS has not led to much R&D for developing drugs for neglected diseases. What incentives can be put in place to foster such R&D? How can the different push and pull incentives be used? Can the developed country Orphan drug model be used for this purpose?

To analyse such questions, it is very important to be clear about the basic differences between a developed country such as USA and a developing country such as India. USA already has a well developed pharmaceutical R&D infrastructure. The issue there is how to generate a better outcome by changing the incentive structure. The Indian companies have just started R&D for new drugs. They lack the experience, the skills and the resources to be anywhere near the situation in USA.

Much of the pull incentives provided to the private sector in the developed countries (including market exclusivity in Orphan drug models, which has played such an important role there) are not relevant in India. Pull mechanisms offer a better return for the output of R&D. It presupposes that companies have the capacity and capability to undertake R&D. If they do not have this, if they cannot generate an output in the first place, obviously the question of benefiting from the higher value of the output promised does not arise. Unless Indian companies build up the competence to develop a drug, they cannot benefit from such exclusivity and hence such incentives would be inadequate.

The most important issue in India is how to develop the infrastructure for new drug R&D and how to fund it. Since the private sector in India is not yet prepared to undertake R&D investments on their own, the options are to collaborate with:

- MNCs
- Government
- International agencies

Collaboration with MNCs is not resulting in new drugs for neglected diseases. When asked, what they can do for neglected diseases, the typical answer of the Indian companies is that here government should play the main role.

A significant change which has taken place in India in recent years is a particular form of Public-Private Partnership (PPP). Traditionally, CSIR laboratories such as CDRI did not have much interaction with the pharmaceutical industry so far as R&D for new drugs was concerned. The situation has now changed with the Indian companies starting R&D for NCEs.

India has initiated two PPPs – one coordinated by the Department of Science and Technology and the other by CSIR. A summary of the important features and the status is as follows:

- Both funds and facilities are shared by the public sector and private partners
- Financial support is provided by government in two ways – grants and loans
- In the case of grants, the intellectual property, if any generated by the project will be jointly owned and the private partner will pay the government royalties @ 2 per cent of net sales in case of commercialization
- In the case of loans, the intellectual property will be owned by the private partner and the loan will be repaid with interest at 3 per cent
- The projects deal with different types of R&D including new drug development
- Of the two new drug development projects which have made substantial progress, one belongs to a global disease, cancer and another to a neglected disease, TB. As of now there has not been any progress in initiating and developing projects for most neglected diseases.
- The funds earmarked are abysmally small.

Both the PPPs are interesting and promising. There is substantial scope for improving and strengthening them.

## **Funding**

First and foremost, funding must improve. One of the ways of improving funding is to accept the recommendation of the Mashelkar Committee (1999) to impose a 1 per cent tax on pharmaceutical sales. It will fetch at least \$ 48 million, which is several times the current budget.

## **Cross subsidy**

So far as the private players are concerned, both the PPPs have been designed to subsidize their activities rather than as such to earn a return from public investments. The

projects of relevance to Indian and other developing country population can be classified into two groups:

- (i) Those for which market incentives exist for undertaking R&D, for example in R&D for global diseases, and to some extent for neglected diseases
- (ii) Those for which market incentives are absent, for example in the most neglected diseases.

Ideally, government should earn some return from the former group of projects to cross subsidize the latter group which require most public support and no projects have been initiated yet. Market incentives exist for Indian companies to participate in R&D for global diseases. Government should not subsidize R&D activities for which market incentives exist. If government participation can enlarge the scope of such activities and help to generate higher returns, then that can be a good justification for pursuing these. The higher returns can subsidize the R&D for the most neglected diseases.

It is indeed possible for the government to reduce costs and increase financial returns including its share. Indian companies developing promising new molecules are licensing out to MNCs. One of the important reason is the huge costs on clinical trials. The later the stage at which the molecule is licensed out, the higher is the cost (and the risk), but higher is also the return. The government by providing funds and sharing the risks can help to get a better deal. Particularly in view of India's advantages in clinical trials, the government can play a more proactive role here. In both the PPPs, another scientific agency in India, Indian Council of Medical Research (ICMR) is conspicuous by its absence. ICMR can be given the role of organizing clinical trials for new molecules developed. There are a large number of public hospitals and medical research institutes in India. There is tremendous scope for utilizing these facilities and ensuring clinical trials as per GCP norms.

### **Differential pricing**

The market for global diseases may be classified between domestic market and international market.

For the domestic market, a system of voluntary licensing may be introduced on payment of royalty at pre-determined rates. On the one hand, this will ensure market competition and more reasonable prices. On the other hand, the royalties payable will allow the PPP to earn some return.

For the international market, particularly for the large and lucrative market in developed countries the IPR rights (or other rewards systems, which may be put in its place in future) may be exercised. If product patent rights are exercised, and if this result in high prices there, then it should be the responsibility of the governments of the developed countries to subsidize the expenditure for the consumers in their countries. The government and the private sector in a poor country like India should not subsidize

the drug expenditure in rich countries. In fact the earnings of the PPP from any successful product should be used to subsidize R&D for the most neglected diseases in India.

### **Public initiatives for neglected diseases**

So long as opportunities exist for R&D for global diseases, and they do exist, the private companies obviously will be interested in pursuing these which promise much higher returns. Hence, the government will have to play the main role for neglected diseases. In fact it will have to be more a public initiative rather than a public-private partnership. Facilities at public sector research institutions, particularly CDRI, which has a full fledged new drug development infrastructure should be properly utilized and enhanced. Considering the enormity of the problem, it is also important to supplement national efforts by international initiatives.

### **How India can contribute to international efforts**

So long we have discussed what is being done and can be done to develop new drugs under Indian private and public sector initiatives. India can also contribute a lot to the international efforts. A number of international initiatives have already been taken for developing new treatments for neglected diseases. India's participation in the international initiatives has been piecemeal. There is much greater scope for Indian public and private sector to be part of these global PPPs and initiatives. More international funding can better exploit India's potential. Greater international awareness of the problem is expected to lead to more such efforts to develop drugs for neglected diseases. These international initiatives can take advantage of India's cost advantage and reduce the cost of new drug development and hence make these more accessible. Rather than just tying up with MNCs for global diseases, the Indian companies can be more involved in molecule development for neglected diseases. There are two other major ways in which India can contribute:

**Process development:** Developing the processes for manufacturing the NCEs and the intermediates required is an important component of the process of new drug development. Production of NCEs is required initially for laboratory testing, then for clinical trials and ultimately for producing and marketing these after regulatory approvals are obtained. India's world class skills in chemical synthesis and process engineering can be used for such purposes. A number of Indian companies have entered into such Contract Research and Manufacturing Services (CRMS). There is scope for much more.

**Clinical research:** About 40 per cent of the new drug development cost goes towards clinical trials. There are significant advantages of doing such trials in India and international initiatives can reduce both the time and the cost for developing new drugs for neglected diseases by organizing such trials in India. India's advantages include - huge patient population, speed of recruiting patients and conducting trials, large number of hospitals including specialty hospitals with state of the art facilities, skilled English speaking investigators including doctors trained in Western countries and low costs. India has not been able to fully exploit the advantages because of lack of experience and

exposure and an underdeveloped regulatory system. But things are changing. The regulatory environment has improved – guidelines have been issued and laws have been changed for making it mandatory to conduct clinical trials as per GCP norms. India has started attracting significant volume of international clinical trials.

# I Introduction

One of the major problems of the structure of the pharmaceutical industry dominated by the multinational corporations (MNCs) is that the diseases of poor countries are often neglected. The MNCs which are involved in the business of developing and marketing new drugs, do not find these diseases attractive enough for R&D investments because of the small size of the markets. The people in the poor countries who suffer from such diseases do not constitute a profitable market because of their poverty. Private R&D is driven by market considerations. Hence efforts of the MNCs are primarily directed towards developing new drugs for the large developed country markets (Correa 2001, p. 19).

The market failure to generate R&D for the neglected diseases, which exclusively or disproportionately affect the poor in developing countries, has not been compensated for by public funding for such R&D. Public funding remains insufficient. The result is that few or no drugs exist for these neglected diseases. While some neglected diseases, such as malaria and TB have attracted some attention, no drugs exist for diseases such as African trypanosomiasis, leishmaniasis and Chagas' diseases (the "most neglected" diseases).<sup>1</sup>

It is increasingly being realized that what is required to develop drugs for neglected diseases is a paradigm shift in the system of pharmaceutical innovation, both nationally and globally. The focus of this paper is on India – what can be done to promote R&D for new drugs for neglected diseases.

## Why is India important?

India is important for several reasons.

- In line with TRIPS, India has introduced a product patent regime in pharmaceuticals from 1 January, 2005. Will this lead to an increase in resources devoted to R&D by Indian companies for the development of new drugs more suited to the needs of India and other developing countries?
- India has demonstrated strong innovation capabilities in developing manufacturing processes. Can such capabilities be utilized for developing new drugs particularly for neglected diseases? Can India contribute to lowering the cost of new drug development?<sup>2</sup>

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<sup>1</sup> See, "R&D System Is Failing To Meet Health Needs In Developing Countries," MSF Briefing Note, November 2004, p. 6. See also Trouiller et al 2002; DND Working Group 2001; IFPMA 2004; Torreelle, Usdin and Chirac 2004.

<sup>2</sup> From the point of view of accessibility of drugs, it is also important to study the future developments in India because India has emerged as a major supplier of low cost quality drugs to the entire world. Another important issue is the role traditional medicine can play as a source of effective treatment (see the presentation of Ruth Dreifuss, chairperson of CIPIH, at the Confederation of Indian Industry Conference-

## II: Incentives for R&D for New Drug Development

Even for the development of drugs for developed country markets, different incentives have been devised/proposed to stimulate R&D. Usually, these incentives are classified into two categories: “push” and “pull.” Push programmes are designed to stimulate R&D by providing funds and inputs and reducing the costs. Pull mechanisms are essentially market enhancing. These create a market or increase the certainty of a market (Table 1).<sup>3</sup>

Table 1 Incentives to stimulate R&D

Push incentives	Pull incentives
Direct public spending	Patent system
R&D tax credits	Transferable market exclusivity
R&D grants to private sector	Advance purchase commitments
Public-private partnerships (PPPs)	Tax credit on sales
	Patent buyouts
	Prizes/other rewards
	Fast track regulatory approval

Source: Author’s own compilation from miscellaneous sources.

Most of the countries where pharmaceutical R&D is pursued, use some combinations of the push and pull incentives. Most common are the push from public subsidy (R&D grants; tax credits) and the pull from the market (market exclusivity through patent or other means). Public support has played a very important role in the development of new drugs. The pharmaceutical industry has been a major beneficiary of the output of publicly funded research projects particularly in the field of basic research. An investigation of 50 top selling drugs approved by US FDA from 1992-1997 reveals that 48 of these received funding from the government at some stage or the other (NIHCM 2000, p. 2).

The patent system has been the most important pull incentive. Product patents by granting market exclusivity permits the innovators to charge higher prices. This helps them to recoup the R&D costs and earn higher returns on their investments. MNCs consider product patent protection as fundamental for their research efforts. It is widely accepted that some incentives may be necessary for R&D for new drug development. But the incentive need not be in the form of a patent monopoly. Arrow (1962), to whom much of the modern economic theorizing on patents is attributed, did not consider patents as the only possible incentive system. In theoretical works, patents have not been found to be

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"Building Innovative Pharma in India," 5 November, 2004, accessed from the CIPIH website: [www.who.int/intellectualproperty](http://www.who.int/intellectualproperty). We will not be discussing these issues in this paper.

<sup>3</sup> For a review of the different push and pull incentives, see Morris, Stevens and Gelder 2005, chapter 3; Center for Global Development Working Group 2004, chapter 2; Kettler and Collins 2002, pp. 13, 34-36.

necessarily the best option (see, for example, Arrow 1962, Nordhaus 1969 and Dasgupta and Stoneman 1987).

In the real world, the innovators were rewarded in USSR through prizes. But DiMasi and Grabowski (2004, p. 3) point out that the record of innovation has not been impressive and argue for the continuation of the patent system.

But the desirability of having marketing monopoly on patented invention to finance R&D is being contested even in developed countries. This is not only because of high prices. Doubts have been raised about the nature of R&D spending. Studies have shown that only about 10 per cent of the R&D is spent on developing new drugs. About three-fourths of the new drugs approved do not provide any therapeutic benefit over the existing products. The MNCs actually take patents to protect minor developments and delay the entry of generic products after patent expiry.<sup>4</sup>

Alternative models have been proposed, for example by Kremer (1998) for an auction system in which the government purchases most drug patents and places them in the public domain; by Hubbard and Love (2004) for a mandatory employer-based research fee to be distributed through intermediaries to researchers and by Hollis (2004) for zero-cost compulsory licensing patents, in which the patent holder is compensated based on social value of the drug. A review by Baker (2004) shows that these proposals are superior to the present patent system. Some of these models can also be used with appropriate changes for development of drugs for neglected diseases. Another scheme proposed by the Center for Global Development Working Group (2004) relates to advance purchase commitments. It has drawn up a scheme to stimulate vaccine development by providing a guarantee of a market and fixed subsidy per vaccine for the vaccine, which satisfy pre-established technical criteria.

For neglected diseases, as we will discuss below, the most important development has been the setting up of a number of PPPs and not for profit ventures. The objective is to combine the capacity, expertise and resources in both the public and private sectors to foster R&D for specific projects and diseases.

The pharmaceutical industry, understandably is against the abolition of patent incentives. The MNCs in fact want the patent system to be strengthened further and supplement these by other incentives. GlaxoSmithKline has demanded new tax credits and has proposed a system of "transferable exclusivity" for patents, where the development of a drug for a developing world disease is rewarded by an extension of patent protection for a developed world medicine.<sup>5</sup>

The developed countries also face a problem similar to neglected diseases. There are certain rare diseases (such as Huntington's disease, myoclonus, Tourette syndrome in USA) which cause suffering or premature death for a relatively small number of people.

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<sup>4</sup> See UNCTAD-ICTSD 2003, p. 97; Hubbard and Love 2004, p. 148.

<sup>5</sup> See Stephen Foley, "Glaxo tells Blair to press G8 for Patent Reform," in *The Independent*, 29 November, 2004.

The needs of these people are ignored by the pharmaceutical industry because of the small size of the market. USA responded by introducing the American Orphan Drug Act in 1983. It combines some aspects of the individual push and pull mechanisms to provide incentives for developing drugs for the orphan diseases which affect a very small number of Americans. Regardless of the status of the patent, it provides a market exclusivity of 7 years, tax credit for related clinical research and grants for investigation of treatment. Several other developed countries – Japan, Canada, Australia, EU – have similar orphan drug legislation. The Act has been quite successful in USA with a number of drugs now available for the treatment of rare diseases (Center for Global Development Working Group 2004, p. 28; Torreele, Usdin and Chirac 2004, pp. 44-45; Kettler and Collins, 2002, p. 24).

Can such orphan drug model for diseases neglected in developed countries be used for diseases neglected in developing countries? This is a very relevant question. We will take it up below.

### III: Structure of R&D Activities In India

As in most countries in the world, R&D activities are done in India by government R&D institutions, universities, colleges, academic institutions and by the private sector. As the table below shows, the government is far the largest sponsor of R&D in India.

Type of organization	R&D expenditure, Rs million, 1998-99	Per cent to total
Central government	87060.3	67.5
State government institutions	10265.4	8.0
Higher education sector	3785.6	2.9
Non-commercial private sector organizations	3808.3	3.0
In-house R&D units of private industry	24095.8	18.7
Total	129015.4	100.0

Source: DST, 2002, p.42

The institutional sector comprising of the central and state governments and the higher education sector accounted for 78 per cent of the R&D expenditure. The remaining 22 per cent comes from the private sector. The central government alone accounted for about 67.5 per cent of the total R&D expenditure of Rs 129015.4 million during 1998-99.<sup>6</sup>

<sup>6</sup> The main source of R&D statistics in India is the *Research and Development Statistics*, published by the Department of Science and Technology (DST) of the Government of India. The latest volume published is DST 2002, which provides actual data for the reference year 1998-99. The total R&D for 2000-01 has been estimated at Rs 176602.1 million. Actual R&D figures are not yet available after the post-1998-99 period.

The bulk of the central government R&D expenditure (83 per cent) is spent through 12 major scientific agencies such as Council of Scientific & Industrial Research (CSIR), Indian Council of Medical Research (ICMR), Department of Science & Technology (DST), Department of Biotechnology (DBT). Specially after the adoption of the Resolution of Scientific Policy in 1958, a chain of national R&D laboratories have been created in India under these scientific agencies. There are about 550 central government R&D institutions in the country.<sup>7</sup> The remaining 17 per cent of the total central government expenditure is spent through the ministries/departments, such as Ministry of Health & Family Welfare and the public sector enterprises within the administrative control of the concerned ministries.

In addition to directly performing R&D activities, for example in laboratories under CSIR, the government provides a number of push and pull incentives to promote R&D. As can be seen from Table 2, the fiscal incentives which are currently provided by the government, includes direct tax incentives, such as deduction of both current and capital R&D expenditure from taxable income, tax holidays and indirect tax incentives such as customs duty and excise duty exemptions. Under a number of schemes administered by the DST, Department of Scientific and Industrial Research (DSIR) and CSIR, the government also provides financial (loans/grants) and other assistance to R&D performers. Most of these schemes are of recent origin. As we will discuss below, an R&D programme specifically for the pharmaceutical industry was started in the mid-1990s.

## **Pharmaceutical R&D**

Total pharmaceutical R&D expenditure in India in 1998-99 has been estimated to be Rs 6000 million<sup>8</sup>. About 63 per cent of it (Rs 3775 million) was contributed by the pharmaceutical industry (DST 2002, p. 31). The remaining 37 per cent was spent by publicly funded laboratories, mainly under CSIR, ICMR, around 25 universities and a few pharmacy colleges (Mashelkar Committee 1999). Thus compared to the overall situation, the government in the pharmaceutical sector invests much less. Defence, space and atomic energy actually accounted for about 65 per cent of the total R&D by India's major scientific agencies. The shares of CSIR (including the laboratories involved in non-pharmaceutical R&D) and ICMR are only 9.9 per cent and 1.2 per cent respectively.<sup>9</sup>

CSIR has a full fledged institute devoted to drug R&D viz. Central Drug Research Institute (CDRI), Lucknow. Besides, six other institutions have major programmes on drugs, viz. Central Institute of Medicinal & Aromatic Plants (CIMAP), Indian Institute of Chemical Biology (IICB), Indian Institute of Chemical Technology (IICT), Institute of

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<sup>7</sup> DSIR 2003, p. 2.

<sup>8</sup> See Laxman Prasad. "Drugs & Pharma Research in India – Govt Initiatives", paper presented at the Workshop on TRIPS Pharmaceutical Industry and Health, October 7-8, 2002, Indian Institute of Management Calcutta. Prasad is Adviser, DST, which publishes the R&D Statistics in India.

<sup>9</sup> DST 2002, p. 6.

Table 2 Fiscal Incentives provided for R&D in India

Types of Institutions	Type of Incentives
Industrial units having in-house R&D centers	<ol style="list-style-type: none"> <li>1. Write off of revenue expenditure on R&amp;D</li> <li>2. Write off of capital expenditure on R&amp;D</li> <li>3. Duty free imports of pharmaceutical reference standards</li> <li>4. Duty free import of analytical &amp; specialty equipment for R&amp;D and production</li> </ol>
Sponsors of R&D in universities, academic institutions, national laboratories under CSIR, ICMR etc	<ol style="list-style-type: none"> <li>1. Weighted tax deduction of 125% on R&amp;D expenditure</li> </ol>
Companies engaged in bio-technology, drugs & pharmaceuticals etc	<ol style="list-style-type: none"> <li>1. Weighted tax deduction of 150% on R&amp;D expenditure</li> </ol>
Commercial R&D companies ( companies with main objective of doing R&D)	<ol style="list-style-type: none"> <li>1. Tax holiday for 10 consecutive years</li> </ol>
Investments on plant & machinery based on indigenous technology	<ol style="list-style-type: none"> <li>1. Accelerated depreciation allowance @ 40%</li> </ol>
Public funded R&D institutions	<ol style="list-style-type: none"> <li>1. Duty free import of equipment and consumables</li> <li>2. Excise duty exemption on equipment and consumables</li> </ol>
University or scientific research associations	<ol style="list-style-type: none"> <li>1. Income tax exemption @ 125% to donations</li> </ol>
Non-commercial Scientific and Industrial Research Organizations	<ol style="list-style-type: none"> <li>1. Duty free import of equipment and consumables</li> <li>2. Excise duty exemption on equipment and consumables</li> </ol>
Any wholly owned Indian company	<ol style="list-style-type: none"> <li>1. Excise duty exemption for 3 years on goods designed and developed and patented in any two countries out of: India, USA, Japan and any one of European Union</li> </ol>
Any Indian company	<ol style="list-style-type: none"> <li>1. Exemption from price control under Drug price Control Order for drugs which have been developed</li> </ol>

	indigenously or produced through a process developed indigenously
R&D projects funded by Government of India	1. Exemption from customs duty on imports

Sources: DSIR 2003; Website of Department of Scientific & Industrial Research, www.dsir.nic.in.

Microbial Technology (IMT), National Chemical Laboratory (NCL) and Regional Research Laboratory (RRL-Jammu).<sup>10</sup>

The total amount of Rs 3726 million spent by the 126 private pharmaceutical companies, constituted only 0.76 per cent of their sales turnover in 1998-99.<sup>11</sup> As we will see below, the spending by the private companies has been increasing and some big companies now spend a much larger proportion of their turnover on R&D. But compared to the global scenario, such levels of R&D expenditure remain abysmally low.

Pharmaceutical R&D can be broadly classified into three types: (i) development of new chemical entities (NCEs); (ii) modifications of existing NCEs (new chemical derivatives, new formulations, new combinations) and (iii) development of new processes for manufacturing drugs (whether old or new). Till recently, R&D in the Indian pharmaceutical industry has been primarily of the third type. The indigenous sector has developed tremendous strength in developing cost efficient processes for manufacturing drugs satisfying international quality norms. India has received world wide recognition as a low cost producer of high quality bulk drugs and formulations. In the next section we will analyse the factors which accounted for such a success.

## New drugs developed in India

Despite the inadequate stress on R&D for new drug development, some new drugs did emerge in India primarily through public initiatives. We have listed in Table 3, the new drugs developed in India.<sup>12</sup> It may be noticed that most of these drugs came from CDRI, which was set up by the Central government in 1951. It is engaged in the development of

<sup>10</sup> In addition there are eight other laboratories which have activities relating to the sector namely Centre for Cellular & Molecular Biology (CCMB), Central Leather Research Institute (CLRI), Central Salt & Marine Chemicals Research Institute (CSMCRI), Institute of Himalayan Bioresource Technology (IHBT), Industrial Toxicology Research Centre (ITRC), National Botanical Research Institute (NBRI), National Institute of Oceanography (NIO) and Regional Research Laboratory, Jorhat (RRL-Jorhat) (information accessed from CSIR website: www.csir.res.in).

<sup>11</sup> The 7 public sector pharmaceutical companies spent Rs 49 million (1.9 per cent of sales) – see DST 2002, pp. 82-83.

<sup>12</sup> Few others are in the development stage including streptokinase, a blood clot dissolver (Institute of Microbial Technology, Chandigarh), asmon, an anti-asthma drug (Indian Institute of Chemical Biology, Kolkata) and few others are undergoing efficacy-cum-safety clinical trials (CDRI) (see Answer of the Minister of Health to a question in the Lok Sabha, as reproduced in *IDMA Bulletin*, 31 December, 2002.

both new drugs and processes for manufacturing drugs and intermediates. But the stress has always been on the former. It is one of the few public sector organizations in the world which have their own drug development infrastructure. The other notable example is Walter Reed US Army Institute of Research (Nwaka and Ridley 2003, p. 919). CDRI has all the facilities for new drug development under one roof. It has facilities not only for designing and synthesizing molecules but also for undertaking preclinical studies and clinical trials necessary for developing and marketing drugs. As Table 3 shows, it has developed 10 new drugs such as centchroman (oral contraceptive), guggulipid (hypolipidaemic) and centimzone (anti-thyroid). Regional Research Laboratory, Hyderabad, now known as the Indian Institute of Chemical Technology has developed 2 drugs. The other CSIR laboratories with R&D focus on drugs and pharmaceuticals are primarily engaged with development of processes for manufacturing drugs.

None of the new drugs marketed by the MNCs globally have been developed in India. But three of them, Ciba Geigy (now part of Novartis), Hoechst (now part of Aventis) and Boots set up facilities for new drug development in India. After synthesizing a few new drugs, including Sintamil, an anti-depressant, Ciba Geigy discontinued new drug research in India. Boots India developed an anti-diabetic compound. But when it was at the clinical trials at phase II, the ownership of the company changed and the new discovery programme was discontinued in India.<sup>13</sup> The Hoechst outfit has been purchased by an Indian company, Nicholas Piramal.

The drugs developed by CDRI were licensed to various Indian companies. But most of these could not survive in the market because of competition from similar products of MNCs.<sup>14</sup> Some of these drugs are available in the market (see Table 3). But these are yet to be commercially very successful. In fact none of the drugs developed has been registered in the large markets of developed countries.

The basic limitation of the CDRI drug development programme has been the lack of commercial orientation. What is important is not only to develop a drug but to promote it for marketing. As we will discuss below, if an organization from a developing country develops a new drug and tries to establish it in the market, it faces immense difficulties not only in the developed countries but in their own country. In the late 1970s a small Croatian pharmaceutical company called Pliva developed a new antibiotic, azithromycin. Rather than trying to promote itself, in 1981 it entered into a licensing agreement with Pfizer to sell the drug world-wide, except in Central and Eastern Europe where the company retained the selling rights.<sup>15</sup> Today Zithromax (Pfizer's brand name) is one of the largest selling antibiotics in USA. In 2003, it sold about \$ 1.8 billion (Kermani 2004, p. 6). It is unlikely that the product would have been so successful, if

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<sup>13</sup> Interview with B Gopalan, (currently with Glenmark Research Centre), Navi Mumbai, 11 February, 2005. Gopalan worked for Boots and in fact was the patent holder of the anti-diabetic drug developed.

<sup>14</sup> Personal communication from C M Gupta, Director, CDRI, 31 January, 2005.

<sup>15</sup> Fiona Fleck, "Developing countries take a creative approach to R&D," in IN FOCUS, December 29, 2004, World Health Organization.

Table 3 New Drugs Developed in India

Drug	Year	Use	Institution	Marketing status
Urea Stibamine	1921	Kala-azar	School of Tropical Medicine, Calcutta	
Methaqualone	1956	Non-barbiturate Hypnotic	Regional Research Laboratory (RRL), Hyderabad/ Lucknow University	
Hamycin	1961	Anti-fungal	Hindusthan Antibiotics Ltd, Pune	
Centimizone	1972	Anti-thyroid	CDRI, Lucknow	
Sintamil	1978	Anti-depressant	Ciba-Geigy, Mumbai	
Tinazolin	1978	Nasal decongestant	Ciba-Geigy, Mumbai	
Tromaril	1980	Anti-inflammatory	RRL, Hyderabad	
Isaptent	1985	Cervical dilator	CDRI, Lucknow	
Gugulipid	1986	Hypolipidaemic	CDRI, Lucknow	Available
Centbucridine	1987	Local anaesthetic	CDRI, Lucknow	
Centbutindole	1987	Neuroleptic	CDRI, Lucknow	
Centchroman	1991	Nonsteroidal oral Contraceptive	CDRI, Lucknow	Available
Chandonium Iodide	1994	Neuromuscular blocking agent	CDRI, Lucknow/Punjab University, Chandigarh	
Centpropazine	1996	Anti-depressant	CDRI, Lucknow	
Arteether	1997	Anti-malarial	CDRI, Lucknow/ Central Institute of Medicinal and Aromatic Plants, Lucknow	Available
Standardized Brahmi extract	1997	Herbal remedy for memory improvement	CDRI, Lucknow	Available
Bulaquin	2000	Anti-malarial	CDRI, Lucknow	Available
Consap	2004	Local contraceptive cream	CDRI, Lucknow	Available

Sources: CDRI, *Annual Reports* (various issues); CDRI website: [www.cdriindia.org](http://www.cdriindia.org); Anand 1988; Mehrotra, Tandon and Dhawan 1991; Business World, 7-21 July, 1998; personal communication from Director, CDRI, Dr C M Gupta, 31 January, 2004.

Note: The above list does not include immunodiagnostic kits for early Diagnosis of Filariasis and Leishmaniasis developed by CDRI

Pliva had tried to promote it on its own. It is in fact difficult to find a single instance of a drug developed elsewhere but successfully marketed in developed countries, particularly in USA and Western Europe without the involvement of MNCs. In recent years, biotechnology companies have challenged the traditional methods of drug development concentrated in the MNCs. They have been successful in developing novel molecules. But few have been able to take the product to the market without the help of MNCs (Kettler, White and Jordan 2003, p. 3).

Cipla, tried to introduce a new drug after doing clinical trials in India. As narrated in Box 1, Cipla found it extremely difficult to introduce and promote it in the country despite being a reputed and large company.

Unlike the recent private and public-private initiatives for new drug development discussed below, CDRI did not have a proper strategy for commercializing the products.

#### **IV: Process Innovation and the Growth of Pharmaceutical Industry in India**

Till 1972, when the Patents and Designs Act, 1911 was replaced by the Patents Act, 1970, India effectively provided product patent protection in pharmaceuticals. The indigenous sector had a long tradition of entrepreneurship in pharmaceuticals. The first pharmaceutical unit, Bengal Chemicals and Pharmaceutical Works was set up as early as in 1892. By the 1970s, a large number of companies were involved in the industry, including the bigger companies such as Ranbaxy, Cipla, Alembic, Unichem. But using the product patent rights, the MNCs prevented the indigenous companies from producing the new drugs. On the other hand, they themselves were not very keen to invest in manufacturing operations in the country. The MNCs considered the Indian market as too small for setting up separate plants in the country. They were also not keen to lower the prices of drugs and to try to enlarge the market, fearing adverse impact in their home countries. They were content with the small market of those who could afford the high prices charged by them. They preferred imports to local production. Even when they started production, they were more keen to formulate imported bulk drugs or those bought from others rather than to produce the bulk drugs themselves and develop the basic raw materials production base. As a result, on the one hand, because of lack of competition, drug prices in India were very high. On the other hand, India was dependent on imports for many of the essential bulk drugs. The import dependence constricted consumption in a country deficient in foreign exchange and inhibited the growth of the industry. Compared to the present status of the industry, the size of the pharmaceutical industry was relatively very small in the early 1970s.<sup>16</sup>

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<sup>16</sup> See author's forthcoming book, Chaudhuri 2005. This section relies extensively on chapters 2 and 4 of the book.

The situation underwent a complete transformation with the introduction of the Patents Act, 1970. The most striking feature of the new law was that it did not recognize product patent protection in drugs (and food). Complete elimination of product patent

**Box 1 Promoting New Drugs: Cipla's Kelfar**

Cipla introduced in 1995 a new drug, deferiprone (brand name: Kelfar). This drug is used for the removal of iron from blood (iron chelators) of thalassaemia patients. The drug was developed by Robert Hilder and George Kontoghiorghes of UK in 1983. Phase I and early phase II clinical trials were done in UK and Switzerland. Novartis, the innovator and manufacturer of the only other iron chelator, desferrioxamine bought the patent rights from the National Research Development Corporation, UK (later British Technology Government – BTG). But, Novartis did not develop the drug for marketing. Y K Hamied, Chairman of Cipla became interested in the drug in 1988 after being told about the trials by one of his managers, whose son happened to be a thalassaemia patient. Cipla contacted Kontoghiorghes, who agreed to help since Novartis was not interested in developing it further. Cipla conducted phase II and phase III clinical trials in India and got the drug approved for marketing in December 1993.

Cipla's Kelfar has two advantages over the Novartis product. First, it is easier to administer. It is taken orally, whereas the Novartis product is administered as a slow subcutaneous injection over 8-12 hours for at least five days a week. Secondly, the Cipla product is considerable cheaper over the other product imported by Novartis. Both the products have side effects, neurotoxicity (for Novartis) and agranulocytosis and neutropenia (related to blood count) reported in less than 1 per cent and 5 per cent of patients respectively (for Cipla). Because of the latter, Cipla's product is sold directly to the patient party on satisfactory results of blood count tests of the patients.

Cipla found it very difficult to promote the drug. Once a drug is approved for marketing abroad, usually neither the Drug Controller who approves the drug for marketing nor the doctors who prescribe the drug doubt the efficacy and the safety of the product. For any drug developed in India the typical question asked is where else has it been approved? If the answer is not yet, as in the case of Cipla's Kelfar, doubts are expressed. Cipla in fact had a tough time getting the marketing approval. It had to bring Kontoghiorghes to Delhi to impress upon the Drug Controller

Source: Discussion with Cipla officials, Mumbai, 10 February, 2005.

protection brought about significant changes in the pharmaceutical industry in India. The indigenous firms were quick to respond to the favourable provisions in the Act of 1970. They were no longer prevented from producing and marketing the new drugs.

As a result, India now occupies an important position in the international pharmaceutical industry (see Box 2). India is now a major source of drugs for the entire

world. India produces about 350 bulk drugs ranging from simple pain killers to sophisticated antibiotics and complex cardiac products.<sup>17</sup> Most of the bulk drugs are produced from basic stages, involving complex multi-stage synthesis, fermentation and extractions.

**Box 2 Status of India's Pharmaceutical Industry**

- Size of India's pharmaceutical market is \$ 4.9 billion (2003). This constitutes about 1 per cent of the global pharmaceutical sales and about 10 per cent of the total generic market in the world.
- In value terms, India is the 14<sup>th</sup> largest market in the world. In volume terms, India's share is around 8 per cent and is the 4<sup>th</sup> largest after USA, Japan and China
- India is among the top five bulk drugs manufacturers of the world. India has the largest number of US FDA approved manufacturing facilities outside USA.
- India exported drugs worth \$ 3.2 billion to more than 65 countries. India is the 14<sup>th</sup> largest exporter of drugs in the world

*Sources:* Miscellaneous sources cited in Chaudhuri, 2005 (forthcoming).

What helped indigenous entrepreneurship to realize its potential were public investments in manufacturing and research.

The setting up of the public sector plants under Hindustan Antibiotics Ltd in 1954 and Indian Drugs and Pharmaceuticals Ltd in 1961 to produce antibiotics and synthetic drugs was an important factor in the development of the industry. These were set up with help, from USSR at a time when the MNCs were not very enthusiastic about setting up basic manufacturing facilities themselves, did not want to provide technology to others and the Indian private sector were not matured enough to undertake production of many of the bulk drugs. IDPL and HAL created a new climate and confidence that India could also manufacture bulk drugs in a big way (Anand 1988). Indian universities did not provide the type of specialized training required by pharmaceutical companies. By creating the demand for and helping the supply of inputs in the form of skilled labor, specialized capital, and other relevant services, both IDPL and HAL sparked industrial development in up and downstream businesses (Smith 2000, pp. 32-33). Though foreign technical help was involved in these two companies, Indian technologists played an important role. The technologies provided by USSR to IDPL could not always be implemented in the form in which these were supplied. Various modifications were necessary due to technological imperfections and due to the different physical and economic environment in which the technology was being implemented (Joshi 1977). IDPL gave a tremendous boost to indigenous efforts in the private sector. The city of Hyderabad where the synthetic drug

<sup>17</sup> See Dr Reddys Laboratories Ltd, *Annual Report, 2002-03*.

plant of IDPL was located has developed into the main bulk drug manufacturing centre in the country. The founders of many of the private sector bulk drug manufacturing firms had at one time worked for IDPL's production or R&D departments. This includes Dr K Anji Reddy the founder of the highly successful company, Dr Reddy's Laboratories.

As the pharmaceutical industry developed, a closer link was established between some CSIR laboratories and the manufacturers. The former developed technologies on their own and offered them for sale. They also did research and provided technical consultancy services on problems referred to them by Indian companies. Among the CSIR laboratories, CDRI, IICT and NCL have been relatively more active. The CSIR laboratories developed the processes for a large number of drugs, including ciprofloxacin, omeprazole, salbutamol, vitamin B6, lamivudine, diclofenac sodium and azithromycin. Typically what they developed were laboratory scale processes. These were scaled up and manufacturing plants were set up by the companies themselves. Almost all the top pharmaceutical companies in India, for example, Cipla, Ranbaxy, Lupin, Nicholas Piramal, Wockhardt, Unichem, Torrent, Cadila, Neuland, Sun Pharmacaeticals, Orchid have used the services of the CSIR laboratories.<sup>18</sup>

### **Importance of the absence of product patent protection**

The product patent protection in India before 1972 did not have any positive effect because the MNCs, who held the patents were not keen on manufacturing (and R&D) activities in India and prevented the Indian companies from doing so by using their patent rights. It was not product patent protection but its abolition which operated as a pull mechanism in India by provided the Indian companies the space of operations and the opportunity to develop and innovate. What Indian companies innovated are processes for manufacturing. And it is this capability which has permitted India to have an international presence and be a global source of drugs.

It may be mentioned in this connection that the Indian generic industry has often been depicted as a “copycat” industry implying that everything has been copied and is the same and there is no innovation involved.<sup>19</sup> Actually only the molecule is the same. In the patent regime under the Act of 1970, India did not provide product patent protection in pharmaceuticals but did recognize process patents. To produce the drugs developed abroad, Indian generic companies had to develop their own processes and what they developed were often superior to the processes developed by the innovator companies. A number of MNCs have been outsourcing some of their requirements from Indian companies because of lower costs. Even after the product patent expires abroad, a generic company cannot enter the market unless it can develop a process of manufacturing which does not infringe on any existing patented process. Innovator companies usually patent a large number of processes to prevent the entry of generics. Unless one is really skilled, it is difficult to develop a new non-infringing process. Eli Lilly, for example protected the

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<sup>18</sup> See the websites of CDRI ([www.cdriindia.org](http://www.cdriindia.org)); NCL ([www.ncl-india.org](http://www.ncl-india.org)); IICT ([www.iictindia.org](http://www.iictindia.org)).

<sup>19</sup> See the editorial, “India’s Choice,” in *The New York Times*, 18 January, 2005 and the critical comment on it by K Weerasuriya, 21 January, 2005 in e-drug archives, in [www.essentialdrugs.org](http://www.essentialdrugs.org).

production of cefaclor through 32 processes. What earned the Indian generic company, Ranbaxy international recognition is that it managed to develop a new and superior process. This in fact paved the way for collaboration between Eli Lilly and Ranbaxy.<sup>20</sup>

## **V: Private Initiatives for Development of New Drugs in India**

During the TRIPS negotiations, the MNCs argued that the developing countries too would benefit from stronger patent protection because it will stimulate private R&D investment for developing country diseases. (Lanjouw and Cockburn 2001, p. 266). It has also been more specifically claimed that local companies will be prompted to do more R&D for the development of new drugs more suited to their needs.<sup>21</sup>

So far as India is concerned, the MNCs disprove the hypothesis that strong intellectual property rights are important for their investments in R&D. As we mentioned above, three MNCs started R&D for new drug development when India did not provide product patent protection. These have been stopped. After TRIPS, except AstraZeneca none of the MNCs is involved in any R&D for new drugs. AstraZeneca has set up a research facility in Bangalore in India to develop novel compounds for TB. (The other two such dedicated R&D centers for developing drugs for neglected diseases set up by MNCs are in Madrid and Singapore) (IFPMA 2004, Table 8).

But unlike in Italy where introduction of product patent protection in pharmaceuticals did not induce Italian pharmaceutical companies to spend more on R&D for new drugs (Scherer and Weisburst 1995), the Indian private sector has started investing in R&D for new drugs since the mid-1990s when TRIPS came into effect.<sup>22</sup> It was initiated by Dr Reddy's Laboratories and Ranbaxy Laboratories. Since then a few other companies have also joined in.<sup>23</sup> At present there are about 15 Indian companies which are involved in R&D for development of new drugs (Table 4). Most of these companies have set up or are in the process of setting up new research centers with new drug discovery research (NDDR) as a major objective. Ranbaxy, for example set up its new research centre at Gurgaon. It employs about 400 scientists and spent the largest amount of Rs 2761 million in 2003-04 for R&D. It is followed by Dr Reddys (Rs 2261 million), Sun (Rs 1077 million), Cadila Healthcare (Rs 882 million) and others. The 12 companies listed in Table 4 spent Rs 10021 million on R&D during 2003-04. It amounts

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<sup>20</sup> Ranbaxy Laboratories Ltd and Management Development Institute n.d., "Ranbaxy Laboratories Ltd: On its way to becoming a Research-based International Pharmaceutical Company."

<sup>21</sup> See WHO 1999, p.37, for a reference to such views.

<sup>22</sup> As we will discuss below this may not have happened because of the incentive effect of TRIPS.

<sup>23</sup> Among the large Indian companies, a notable absentee is Cipla. As the chairman of Cipla, Y K Hamied pointed out in a personal discussion with us (Mumbai, 10 February, 2005), Cipla is not yet prepared to invest in R&D for new drugs. Citing the huge resources required and that even Japanese companies have not been able to develop new drugs independently without international partners, he pointed out that the prospects of Indian companies developing new drugs on their own are very bleak.

Table 4 R&D Expenditure by Indian companies involved in development of new drugs

Company	R&D expenditure in Rs million, 2003-04	Percentage of total turnover, 2003-04	R&D expenditure in Rs million, 2002-03	Percentage of total turnover, 2002-03	R&D expenditure in \$ million, 2003-04
Ranbaxy Laboratories	2761	7.80	1922	6.80	60
Dr. Reddy's Laboratories	2261	12.99	1635	9.92	49
Sun Pharmaceuticals	1077	10.20	658	7.70	23
Cadila Healthcare	882	7.52	383	3.72	19
Wockhardt	604	7.89	462	6.23	13
Nicholas Piramal India	559	3.90	185	1.63	12
Lupin	460	3.90	360	3.49	10
Torrent Pharmaceuticals	397	8.90	312	6.98	9
Orchid Chemicals & Pharmaceuticals	397	5.56	278	5.13	9
Glenmark Pharmaceuticals	372	9.67	306	9.16	8
Dabur Pharma	182	8.5	175	1.42	4
J B Chemicals & Pharmaceuticals	69	2.20	50	1.73	2
Total	10021	7.73	6726	5.55	218

*Sources:* Company annual reports and websites. Figures for Ranbaxy and Wockhardt are for year ending December 2003 and December 2002 respectively.

*Notes:* (i) The figures for Dabur for 2002-03 are for Dabur India before demerger of pharmaceutical business on 1 April 2003. Other companies which are involved in R&D for NCEs include Alembic, FDC and Kopran. Few other companies such as Biocon have initiated plans to venture into R&D for NCEs and NBEs (new biological entities) in the near future. (ii) Expenditure in rupees have been converted to dollars at the 2003-04 average foreign exchange rate of 1 \$ = Rs 45.95 (see Reserve Bank of India, *Handbook of Statistics on Indian Economy*, 2003 (accessed from [www.rbi.org.in](http://www.rbi.org.in))).

Table 5 NCE pipeline of Indian companies

Company	NCE <sup>a</sup>	Indication	Development stage
Dr Reddys	DRF 10945	Dyslipidemia	Phase I clinical trials
Dr Reddys	DRF 11605	Diabetes & dyslipidemia	Pre-clinical stage
Dr Reddys	DRF 1042	Cancer	Phase II clinical trials
Dr Reddys	DRF 1644	Cancer	Phase I clinical trials
Dr Reddys	DRF 5265	Cancer	Pre-clinical stage
Dr Reddys	RUS 3108	Cardiovascular	Pre-clinical stage
Dr Reddys	DRF 13792	Bacterial infection	Pre-clinical stage
Ranbaxy	RBx 7796	Respiratory	Phase II clinical trials
Ranbaxy	RBx 6198	Urology	Early discovery
Ranbaxy	RBx 9001	Urology	Pre-clinical stage
Ranbaxy	RBx 9841	Urology	Pre-clinical stage
Ranbaxy	RBx 8700	Bacterial infection (TB)	Pre-clinical stage
Ranbaxy	RBx 7644	Bacterial infection	Phase I clinical trials
Ranbaxy	OZ 222/RBx 11160	Malaria	Phase I clinical trials
Wockhardt	WCK 771	MRSA <sup>b</sup> responsive anti-infective	Phase II clinical trials
Wockhardt	WCK 1152	Respiratory tract infections in community patients	Ready for phase I clinical trials
Wockhardt	WCK 1457	Activity against vancomycin resistant enterococci	Pre-clinical stage
Lupin	NCE	Anti-migraine	Phase II clinical trials
Lupin	LL 4858	Anti-TB	Phase I clinical trials
Lupin	LL 4218	Anti-psoriasis	Phase I clinical trials
Lupin	LL 3348	Anti-psoriasis	Phase I clinical trials
Glenmark	GRC 3886	Asthma/chronic obstructive pulmonary disorder	Phase I clinical trials completed
Glenmark	GRC 1087	Obesity/diabetes	Pre-clinical stage
Glenmark	GRC 8200	Diabetes	Pre-clinical stage
Torrent	NCE	Anti-arrhythmic agent	Phase II clinical trials
Torrent	NCE	AGE breakers( diabetes; heart diseases)	Late-pre clinical stage
Kopran	KNC 6	Anti-ulcer	Ready for phase I clinical trials
Kopran	KNC 1206	Bulk laxative	Pre-clinical studies completed
Dabur	DRF 7295	Cancer	Phase II clinical trials
Dabur	NCE	Cancer	Phase I clinical trials
Orchid	BL 1002	Diabetes	Phase I clinical trials

(Bexel <sup>c</sup> )			
Cadila Healthcare	ZYH1	Dyslipidemia	Pre-clinical stage
Cadila Healthcare	ZYH2	Diabetes	Pre-clinical stage
Cadila Healthcare	ZYH3	Dyslipidemia and diabetes	Pre-clinical stage
Cadila Healthcare	ZY1400	Inflammation and pain	Pre-clinical stage

*Notes:*

(a): The list is not exhaustive. A number of other NCEs are at various stages of development by Indian companies such as Nicholas Piramal, Sun Pharmaceuticals, Cadila Healthcare, J B Chemicals & Pharmaceuticals. Further details are not available in annual reports or websites of these companies.

(b): MRSA - methicilin-resistant staphylococcus aureus

(c): The NCE has been developed by Bexel Pharmaceuticals, a US based 50:50 JV between Orchid Chemicals and Pharmaceuticals and an R&D company headed by an Indian.

*Sources:* Company annual reports and websites.

to 7.73 per cent of their total turnover. As a percentage of turnover, the largest spender on R&D is Dr Reddys (12.99 per cent) followed by Sun (10.2 per cent), Glenmark (9.67 per cent), Torrent (8.9 per cent) and others. The R&D expenditure has been increasingly at a very rapid rate in recent years. The R&D expenditure of these 12 companies increased from Rs 6726 million in 2002-03 to Rs 10021million in 2003-04, i.e., by almost 50 per cent. Companies such as Cadila Healthcare, Nicholas Piramal and Sun Pharmaceuticals have undertaken huge expansion programmes recently (Table 4). While process R&D still continues to be dominant, a rising proportion of the expenditure is being devoted to discovery research. Thus expenditure on drug discovery by Dr Reddys increased by 52 per cent from Rs 480 million in 2002-03 to Rs 729 million in 2003-04 and now accounts for 37 per cent of the total R&D budget.<sup>24</sup>

A number of Indian companies have reported some successes. Table 5 provides a list of 35 NCEs, which are at different stages of development.<sup>25</sup> The largest spenders, Ranbaxy and Dr Reddy's have been most active with the discovery of about 14 molecules to their credit (7 each), followed, for example by Lupin (4), Glenmark and Wockhardt (3 each), Torrent and Dabur (2 each) (Table 5). None of these has yet been approved for

<sup>24</sup> Dr Reddys Laboratories Ltd, *Annual Report, 2003-04*.

<sup>25</sup> The list does not include NCEs which were developed but later suspended/dropped (see text below).

marketing. But 19 of these NCEs have successfully completed pre-clinical studies and are at different stages of clinical trials. Some of these are at phase II clinical trials, for example Dr Reddy's anti-cancer molecule (DRF 1042), Ranbaxy's respiratory, RBx 7796, Lupin's anti-migraine NCE and Dabur's anti-cancer, DRF 7295 (Table 5).

It is important to note that none of these companies is engaged in the entire process of drug development. The reason for such an approach is simple. Indian pharmaceutical companies are not yet ready for a start-to-finish model in NCE research because they do not yet have all the skills and the funds required. Let us elaborate.

### **Skill sets for new drug development**

The process of drug development is a long and elaborate process which involves a variety of skills primarily from chemistry and biological sciences (Figure 1). For our purposes, the skills required can be classified into two groups:

- Those which were acquired and used during the previous phase of process development in the pre-TRIPS period and
- The skills to which the Indian companies have not been adequately exposed to.

As we have mentioned above, Indian companies earlier did not pursue any R&D for new drug development. What they did was to innovate new processes for new drugs developed abroad. This required organic chemistry skills. But to design and synthesize new promising molecules, both organic chemistry and medicinal chemistry skills are required. Indian companies did not have much experience of the latter. They were not familiar with the knowledge and experience of modern medicinal chemistry required for the critical task of identifying lead compounds which have some desirable properties to inhibit the target, and of optimizing the efficacy/safety of the compounds.

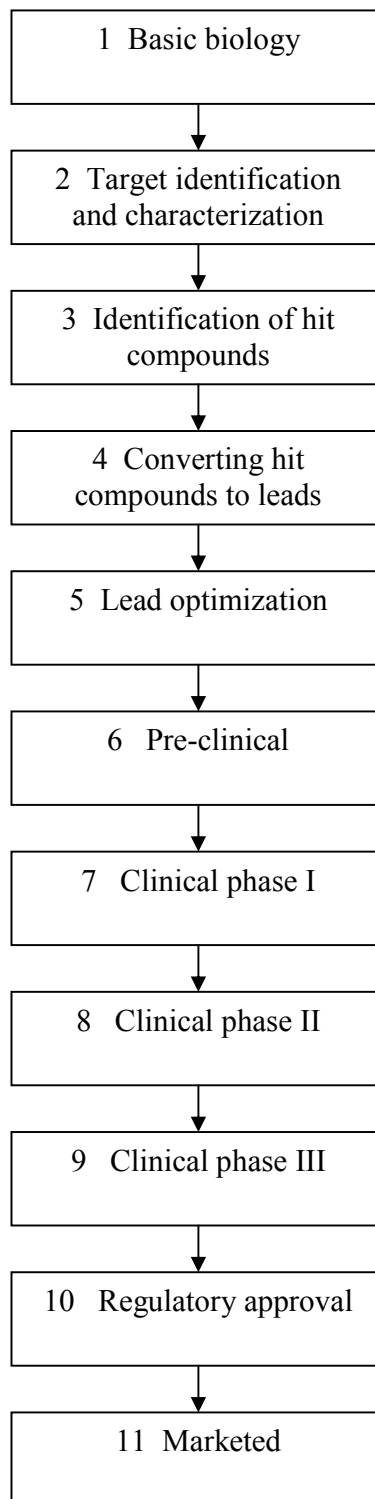
The other skills which are scarce are:

- target identification: basic biology skills to understand how the disease works and to identify a specific target, the inhibition of which plays a crucial role in the particular disease (stages 1 and 2 of Figure 1).
- Pre-clinical testing on animals and clinical trials to determine the efficacy and safety of the molecule (stages 6 to 9).

The other aspects of NDDR related to stage 6 onwards, for which Indian companies have capabilities are:

- Manufacturing aspects of the compound including process chemistry, scaling up, manufacturing process development
- Formulation development of proper dosage forms and delivery systems.

Figure 1 The Drug R&D Process



Source: Kettler, White and Jordan 2003, p. 4

## Funds for new drug development

The cost of developing and bringing a drug to the market is considered to be \$ 802 million abroad.<sup>26</sup> As we have mentioned above, 12 Indian companies together spent in 2003-04, Rs 10021 million, i.e., about \$ 218 million on R&D, including R&D on new drug development (see Table 4). Thus the entire Indian private sector spend on new drug development an amount which is about a quarter of what it costs to develop a single new drug abroad. This would suggest that it is pointless for Indian companies at this stage to participate in new drug development.

But comparison of such figures may not be very meaningful. The figure of \$ 802 million per new drug is not the actual expenditure incurred. These are estimates based on assumptions, which critics have contested.<sup>27</sup> The figure is based on an unrepresentative sample. It excludes the majority of new drugs which are extensions of existing ones and those which are developed through public research and licensed in by the MNCs.

Moreover, the cash outlays on R&D are adjusted upwards, for example for the opportunity cost of capital and to compensate for R&D failures.<sup>28</sup> These estimates ignore several factors which reduce R&D costs, for example contributions of publicly funded research and tax benefits for R&D. It also does not exclude the substantial R&D expenditure wasted in pursuing drugs of no medical significance. Starting from a chemical already identified, the Global Alliance for TB Drug Development, 2001 (p. 3) has estimated the cost of developing a new anti-tuberculosis drug to be less than \$ 40 million, if the cost of failure is excluded and \$76-\$115 million if it is included (depending on total development time and discount rate).

R&D costs in India are much lower. The international consultancy organisation, Mckinsey & Company has estimated that physical infrastructure and overhead costs are 40 per cent to 60 per cent of the US rates. A skilled Ph.D can be employed at 20 per cent of the US salaries. CDRI estimates are that a new drug can be developed in India at 30 per cent of the US costs (Garg *et al* 1996). According to the Mashelkar Committee (1999), it costs less than 10 per cent of the costs overseas to develop a molecule at the pre-clinical stage.

## Strategy of Indian companies

The model that the Indian companies have adopted is to develop new molecules and license out the molecules to the MNCs in the early phase of clinical development. There has been a marriage of interests. It is the development of biotechnology companies which

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<sup>26</sup> This widely quoted figure in 2000 dollars is based on R&D costs of 68 new drugs of 10 large pharmaceutical manufacturers during the 1980-1999 period (DiMasi, Hansen and Grabowski (2003).

<sup>27</sup> See Correa 2001, p. 16; DND Working Group 2001, p. 17 and Light and Lexchin 2004, pp. W3-W4, Goozner 2004, chapters 8-9 for a brief review of some of the issues involved and the estimates.

<sup>28</sup> The average out-of-pocket cost per new drug estimated by DiMasi, Hansen and Grawobski (2003) is actually only \$ 403. Capitalizing this cost for the time between investment and marketing at a real discount rate of 11 per cent raises the cost to the figure of \$ 803 million.

has encouraged specialization according to stages of the drug development process. The MNCs seek and contract out specific activities (Nawka and Ridley 2003, p. 920). As the NCE pipeline of the MNCs started drying up, they in fact intensified efforts to in-licensing promising compounds developed by others. In fact most of the major MNCs have opened compound acquisition departments in their companies. There are also specialized companies, which keep track of promising compounds, maintain libraries, catalogue them and offer for sale to prospective clients.<sup>29</sup>

The main reason why Indian companies have been licensing out clinical trials is the huge costs involved. As Table 6 shows, 40 per cent of the new drug development goes for funding clinical trials. Nearly half the cost goes for clinical trials and for taking regulatory approvals. Clinical trials costs have been increasing at a faster rate than other costs of new drug development (Kermani 2004, p. 4). To appreciate the funds required for new drug development in general and clinical trials in particular, one should not focus on costs per drug. New drug discovery process is a risky business. According to the estimates of PhRMA, out of every 10,000 compounds synthesized, only 20 reach animal testing stage and 10 the clinical trials stage and ultimately only one gets marketing approval. Moreover, only around three out of 10 drugs approved recover R&D costs.<sup>30</sup> Hence for undertaking any viable NDDR, an organization should have a sufficiently large NCE pipeline. The number of products under development in the top 10 MNCs in 1999, varied between 74 (Eli Lilly) and 112 (Roche).<sup>31</sup>

Table 6 Stage-wise breakup of R&D costs for new drug development

Stage	Percentage
Clinical evaluation	40
Basic research	27
Development of production process	19
Implementing regulatory requirements	7
Others	7

*Source:* Pharmaceutical Research and Manufacturers of America (PhRMA) data for the USA in 1998 quoted in WHO 2004, p. 17

The paucity of resources at the disposal of the Indian companies will be clear if we compare Tables 4 and 7. During 2003, the largest MNC, Pfizer spent \$ 7.13 billion (18 per cent of sales) on R&D and the second largest, GlaxoSmithKline, \$ 4.54 (15.2 per cent). The tenth largest, Eli Lilly spent \$ 2.35 billion (18.7 per cent) (see Table 7). In contrast the largest Indian company, Ranbaxy spent only \$ 60 million on R&D and Dr Reddys only \$ 49 million. Most of them in fact spent around \$ 10 million or less (see Table 4).

<sup>29</sup> Personal discussion with B Gopalan, Glenmark Research Centre, Navi Mumbai, 11 February, 2005.

<sup>30</sup> PhRMA figures quoted in ICRA 2002, p. 16.

<sup>31</sup> WHO 2004, p. 19.

Apart from costs, there are also other reasons why Indian companies are keen to partner with the MNCs. Previously in the pre-TRIPS period, when Indian companies developed new processes and introduced in India new drugs developed abroad, they as such were not required to promote the drugs. They did not face much difficulty in getting these drugs approved for marketing by Drug Control authorities<sup>32</sup> or getting these prescribed by doctors. Anything which is already in use in developed countries and particularly sold by the reputed MNCs, are typically well accepted in developing countries such as India. Just the opposite if products are not yet available in developed countries. Hence as we have mentioned above, non-MNC companies which may develop drugs, typically tie up with MNCs for promoting and marketing the drug.

## New Molecule development

Even at the pre-clinical stage, Indian companies are not engaged with all the stages. Indian companies are not involved in basic research of target identification for new drugs. They rely on basic research of others and adopt an approach called ‘analogue research.’ This entails working on certain pre-identified targets for specific diseases to develop molecules that alter the target’s mechanism in the diseased person.<sup>33</sup>

Table 7 R&D Expenditure by top Pharmaceutical MNCs, 2003

MNC	R&D expenditure, \$ billion	R&D expenditure as per cent of sales
Pfizer	7.13	17.99
GlaxoSmithKline	4.54	15.23
Merck	3.17	9.47
Johnson & Johnson	4.68	24.00
Aventis	3.23	17.01
AstraZeneca	3.45	18.30
Novartis	3.07	19.16
Bristol-Myers Squibb	2.27	15.21
Wyeth	2.09	16.56
Eli Lilly	2.35	18.68
Total (10 companies)	35.98	16.63

Source: “Special Report – Pharm Exec 50,” in *Pharmaceutical Executive*, New York, May 2004.

<sup>32</sup> Under India’s Drugs and Cosmetics Act, limited phase III clinical trials are necessary in India for drugs developed abroad. But as we will see below, these were mere formalities.

<sup>33</sup> Glenmark Pharmaceuticals Ltd, *Annual Report, 2003-04*.

But even this requires medicinal chemistry and biology skills, which as we have discussed above are still scarce in India. The Indian companies are filling up this gap in various ways. As we have mentioned above, in the previous regime too some R&D for new drug development took place in India though not by the Indian companies. Notable here are CDRI (public sector), Ciba Geigy, Hoechst and Boots (all MNCs). As a result of these efforts not many drugs have come to the market. But it generated skills. CDRI in particular has been a source of R&D personnel for the industry. This included J M Khanna the ex-head of R&D of Ranbaxy and Bansi Lal, the ex-head of R&D at Nicholas Piramal. The new drug development activities of the MNCs in India also generated skills which are now being found to be very useful. B Gopalan, one of the main persons behind the development of the anti-asthma molecule (GRC 3886) at Glenmark, worked for about 10 years at Boots at their new drug research centre in India.

Another important source has been the recruitment of NRIs (non-resident Indians or persons of Indian origin) by Indian companies for R&D. It has been estimated that about 15 per cent of those who work in the laboratories of pharmaceutical companies in USA and Europe are of Indian origin.<sup>34</sup> It appears that both pull (from India) and push (from USA for a number of reasons including personal) have prompted the return of many such skilled persons to India. Compared to \$ 40,000 in USA, a post-doc with few years of experience gets about Rs 1 million (approximately \$ 22,000) per annum plus housing in India. This appears to be attractive enough to return home, considering that cost of living is significantly lower in India and non-economic factors are also involved in such decisions. At senior levels (few in number), the Indian companies can afford to pay much higher salaries to attract NRIs. NDDR at a number of Indian companies are headed by NRIs with years of experience at MNCs. The present head of R&D at Ranbaxy, Rajinder Kumar (a British national) worked at GlaxoSmithKline and other companies. The immediately preceding head at Ranbaxy, Rashmi H Barbhैया also had experience of new drug development at Bristol Myers Squibb in USA. Other previously NRIs now heading R&D centres in India include Uday Saxena at Dr Reddys and Somesh Sharma at Nicholas Piramal.

Licensing was initiated by Dr Reddys Laboratories when it developed a molecule for treating diabetes in 1997 and licensed it out to Novo Nordisk, the world leader in the field.<sup>35</sup> Since then the other companies which have made some progress in new drug development, for example Ranbaxy, Torrent, Glenmark (Table 5) have essentially followed the same model.

When a company licenses out a molecule, the subsequent expenditure is incurred by the licensee and the licensor gets milestone payments depending on the stages through which the molecule passes. The later the stage at which the molecule is licensed out, the higher is the cost incurred by the Indian company and hence higher is the risk – the entire cost would be a sunk cost if the product fails. But higher is also the return – they will get

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<sup>34</sup> *Chemistry World*, November, 2004, p. 56.

<sup>35</sup> See Dr Reddys Laboratories Ltd, *Annual Report*, 2001-02.

higher payments for the licensed product.<sup>36</sup> The agreement between Torrent Pharmaceuticals, an Indian company and Novartis, an MNC, typifies such arrangements. Torrent entered into an agreement with Novartis for the development of its AGE (Advanced Glycosylation Endproducts) breaker compound (for the treatment of heart diseases and diabetes related vascular complications) when the compound was at the late pre-clinical stage. To start with, Torrent received an amount (\$ 0.5 million). Torrent will be responsible for developing the compound till a pre-defined stage. At this point Novartis will have the option to acquire global rights for further development. If Novartis exercises this option, Torrent will receive an initial payment of \$ 3 million and subsequent milestone payments depending on the progress. If the product is commercialised, Torrent will get royalties and will also lead the co-promotion of the product in India. In July, 2004, Novartis has exercised the option to further develop the molecule in return for payment of \$ 3 million.<sup>37</sup>

The company which has been most active in licensing out, is Dr Reddy's – the company which started it all. But it is Glenmark a medium size company in India which has entered into the single largest licensing deal by any Indian company as of now. Glenmark has developed a NCE for treatment of asthma and other indications. After successfully completing preclinical testing in India, it initiated Phase I clinical trials in UK through a well known contract research organization (CRO), Quintiles. While Phase I trials was in progress, it (through its wholly owned subsidiary in Switzerland) entered into a licensing agreement with Forest Laboratories of USA. Under the terms of the agreement, Forest will develop, register and commercialize the product for the North American market, while Glenmark retains the right for the rest of the world. Forest has paid an upfront amount of \$ 10 million on signing the agreement. Depending on development and commercialization of the product, other milestones payment will be paid totaling \$ 190 million. In addition, Glenmark will get “mid-teens” royalty from Forest on net sales of the product and will supply the bulk drugs.<sup>38</sup>

## **New drugs for neglected diseases?**

Such licensing is not unknown in the international pharmaceutical industry. In fact a number of blockbuster drugs, for example Lipitor, Procrit, Paxil have been in-licensed molecules.<sup>39</sup> But if the Indian companies want to license out molecules, as they are trying to do, then naturally, the molecules should be those which the MNCs are keen to develop further. As we have mentioned above, the MNCs are keen to develop drugs which cater to their main markets in the developed countries. The diseases affecting world's population can be classified into three groups:

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<sup>36</sup> See “Indian Pharma Sector: Manual of Risks for Growth Opportunities”, Industry Report, Salomon Smith Barney, September, 2002.

<sup>37</sup> “Novartis Acquires Rights in Torrent's AGE Compound”, Press Release, October 31, 2002 and “Torrent Licenses AGE Compound to Novartis,” Press Release, July 29, 2004, Torrent Pharmaceuticals Ltd (accessed from website: [www.torrent-india.com](http://www.torrent-india.com)).

<sup>38</sup> Personal discussion with B Gopalan, Glenmark Research Centre, Navi Mumbai, 11 February, 2005;

“Glenmark Pharmaceuticals and Forest laboratories Announce Collaboration Agreement on PDE4 Inhibitor for Asthma and COPD,” 23 September, 2004.

<sup>39</sup> See Glenmark Pharmaceuticals Ltd, *Annual Report, 2001-02*, p. 22.

1. Global Diseases (e.g. cancer, cardiovascular diseases) which affect people everywhere and constitute the major focus of the R&D-based pharmaceutical industry.
2. Neglected Diseases (e.g. malaria, TB, HIV/AIDS) which mainly affect people in poor countries, but there is a small market in wealthy countries which prompts some R&D efforts.
3. Most Neglected Diseases (e.g., sleeping sickness, Chagas disease, Buruli ulcer, Dengue fever, leishmaniasis, leprosy, lymphatic filariasis and schistosomiasis) which almost exclusively affect people in developing countries who are too poor to pay for treatment.<sup>40</sup>

Not surprisingly, Indian companies are targeting not the neglected diseases of poor countries, but diseases which interest the MNCs. “Most neglected diseases” are absent from the list of NCEs developed. As Table 5 shows, the NCEs being developed by the Indian companies are related primarily to the “global diseases.” Thus the situation has not changed since Lanjouw and Cockburn (2001, p. 281) reported on the basis a sample of interviews with Indian companies that their targeted markets are for global diseases. There are only two exceptions in the “neglected diseases” category – malaria and TB. Ranbaxy is participating in an international project sponsored and funded by the Medicines for Malaria Venture (MMV), Geneva to develop an anti-malarial drug.<sup>41</sup> Ranbaxy and Lupin are experimenting with the development of anti-TB drugs. As we will discuss below, Lupin in partnership with some publicly funded research institutions has developed an anti-TB molecule. Both these molecules are at phase I clinical trials stage (see Table 5).

The NCE R&D pattern is unlikely to change in the foreseeable future. The critical neglected diseases do not specifically find a place in the target R&D areas drawn up by the Indian companies. Dr Reddy’s Laboratories mentions the following areas in its *Annual Report, 2001-02* (p. 44), as its future plan of action:

“Development of new products in the therapeutic segments of women’s healthcare, gastrointestinal disorders, pain management, anti-diabetics, nutraceuticals, anti-cancer, cardiovascular, dental care, respiratory, anti-infectives”.

The therapeutic focus of new drug development research by Ranbaxy is on urology, anti-infection, respiratory, cardiovascular and cancer segments.<sup>42</sup> Other companies too, such as Nicholas Piramal and Torrent, mention diseases such as diabetes and cardiovascular rather than the neglected diseases, as their thrust areas. As Glenmark mentions, the criteria adopted by the Indian companies are to target areas of global potential in terms of growth and value, which are of interest to the international pharmaceutical industry.<sup>43</sup>

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<sup>40</sup> “R&D System Is Failing To Meet Health Needs In Developing Countries,” MSF Briefing Note, November 2004, p. 2.

<sup>41</sup> See Ranbaxy Laboratories Ltd, *Annual Report, 2003*.

<sup>42</sup> See company website, [www.ranbaxy.com](http://www.ranbaxy.com).

<sup>43</sup> See company website: [www.glenmarkpharma.com](http://www.glenmarkpharma.com).

The collaboration between the Indian companies and the MNCs for new drug development that we have witnessed in recent years have been essentially product specific. But in a significant departure from the past trends, the second largest drug MNC in the world, GlaxoSmithKline and the largest Indian drug company, Ranbaxy have announced in October, 2003 that they have entered into a drug discovery and clinical development collaboration covering a wide range of therapeutic areas. Ranbaxy's role will be to develop compounds and also in some cases to conduct early clinical work. GSK will complete the development and in return get world-wide exclusive marketing rights except in India. Ranbaxy will promote any successful drug in India and also may co-promote in USA and EU with the consent of GSK.<sup>44</sup>

Such an agreement is basically a sub-contracting arrangement. The difference with manufacturing sub-contracting is that here the risks and also the benefits are much higher. The initial investments will have to be made by the Indian companies and unless they are able to develop prospective compounds, there may not be much returns. The Indian companies have demonstrated that they can do the initial research of developing potential drug candidates at a fraction of the developed country costs. The experience of the PPP, NMITLI discussed below suggests that molecules are being developed at the cost of \$ 4-5 million.<sup>45</sup> According to Dr Reddy, the cost of developing their first 8 molecules till the pre-clinical stage was only \$ 57 million.<sup>46</sup> Hence it makes sense for MNCs to take advantage of such activities to reduce R&D costs. For the Indian companies too the prospects of royalties and other earnings would be an important attraction.<sup>47</sup> In fact, if such collaboration results in the development of a block buster drug, then the royalty from the huge global sales will mean a significant change in the fortune of the company. This type of collaboration is likely to be more popular in future with other Indian companies and MNCs entering into similar agreements. But Indian companies are basically operating as a part of the MNC R&D chain. The drug candidates which the MNCs will select for further development will obviously be those relevant for their main markets in developed countries. Hence such R&D activities are unlikely to be directed towards the neglected diseases of the poor countries.

## Not yet proved

India has proved its competence as innovators of new processes. But India is yet to demonstrate its capability in new drug development. Within a few years of starting NCE

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<sup>44</sup> "GSK and Ranbaxy to Collaborate on Drug Discovery and Development," Corporate Press Release, October 22, 2003 (accessed from [www.gsk.com](http://www.gsk.com)).

<sup>45</sup> "R&D outsourcing to India substantially reduce MNC drug development costs: Dr. Mashelkar," in *Chronicle Pharmabiz*, October 9, 2004.

<sup>46</sup> K Anji Reddy, "The Future of Medicine," in *Business Today*, January 16, 2005.me

<sup>47</sup> In the GSK-Ranbaxy agreement, there is no provision for fees since Ranbaxy is a partner, not a contractor. The rewards will be in the form of milestone payments and royalty depending on the progress and the success (see Gauri Kamath, "The GSK-Ranbaxy R&D model could be the way forward," in *Business World*, November 17, 2003).

R&D in India, Dr Reddys outlicensed two anti-diabetic compounds, DRF 2593 and DRF 2725 in 1997 and 1998 respectively to Novo Nordisk, the world leader in diabetes.<sup>48</sup> Licensing of compounds by Dr Reddys Laboratories and the milestone payments, attracted widespread publicity both in India and abroad and is believed to have lured other Indian companies into new drug development. No new drug has yet been developed and put to market. Perhaps it is too early to expect this. But there has been a number of setbacks. After completing phase II clinical trials, Novo Nordisk decided to terminate the further development of the both the molecules which generated so much of optimism. In Novo Nordisk's assessment, DRF 2593 did not suggest a sufficient competitive advantage compared to similar products marketed products.<sup>49</sup> Earlier it called off the trials of DRF 2725 because of some adverse results of animal tests discovered later.<sup>50</sup> Ranbaxy outlicensed its molecule RBx 2258 for the treatment of Benign Prostate Hyperplasia (BPH) to Schwarz Pharma. The latter has discontinued the clinical phase II trial due to unclear preclinical findings. Until final resolution, the development programme has been put on hold.<sup>51</sup> Dr Reddys and Ranbaxy have made the largest investments on NDDR in India. Their profitability has been under pressure for the last two years with inadequate financial return from NDDR.<sup>52</sup>

## Summary

Thus, to sum up our discussion in this section so far:

- TRIPS has been accompanied by an increase in R&D for new drug development by Indian companies
- But the Indian companies are not engaged in the entire process of drug development because they do not have the skills and the resources to do so
- The model that Indian companies have adopted is to develop new molecules and license out these to the MNCs in the early phase of clinical development
- As a result Indian companies are not targeting the neglected diseases of the developing countries but the global diseases which interest the MNCs
- The plans drawn up by the Indian companies suggest that this trend is unlikely to change in the foreseeable future
- Indian companies have proved their competence as innovators of new processes. But they are yet to demonstrate their capability in new drug development. While some of the molecules developed at clinical trials stages, no new drug has yet been approved for marketing.

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<sup>48</sup> See the website of the company, [www.drreddys.com](http://www.drreddys.com).

<sup>49</sup> "Novo Nordisk terminates further clinical development of Balaglitazone (DRF 2593) out-licensed by Dr. Reddy's," Press Release, Dr Reddys Laboratories Ltd, Hyderabad, October 27, 2004

<sup>50</sup> *The Economic Times*, February 6, 2003.

<sup>51</sup> "Schwarz Pharma stops clinical trial in Ranbaxy molecule," in *Chronicle Pharmabiz*, November 8, 2004.

<sup>52</sup> "New Rules for Clinical Trials," in *Chronicle Pharmabiz*, February 2, 2005.

## **Product patent protection as an incentive for new drug development**

Introduction of product patent protection in pharmaceuticals in India in line with TRIPS has two implications:

- It is supposed to provide incentives to Indian companies to undertake new drug R&D themselves
- It will result in a shrinkage of market opportunities of the Indian companies because they will no longer be able to reverse engineer and produce the new drugs invented abroad and protected by patents.

The new drug development programme of the Indian companies has been more a response to the latter rather than a result of the former.

As we have seen above, the Indian companies are not yet ready for undertaking new drug R&D independently. They are subcontracting out the molecules developed and their motivation is not only milestone payments, but royalties from sales in patent protected large markets in developed countries. Their target is not the Indian market, where product patents have been introduced after TRIPS. The developed countries had product patent protection even before TRIPS. Thus TRIPS does not make any difference to the prospects of such sales though it may have prompted them to go for it due to the second factor mentioned above.

The motivation of the MNCs in licensing molecules developed by the Indian companies is reduction of their R&D costs. If costs are considered to be important, then even if product patent protection is not provided, the MNCs are unlikely to deprive themselves of such low cost sources. In the absence of TRIPS, these molecules could not have been patented in India. But it could be and would have been patented abroad in developed countries and hence the licensee would have enjoyed the market exclusivity.

## **Incentives to stimulate R&D for new drugs for neglected diseases**

Thus TRIPS has not led to much R&D for developing drugs for neglected diseases. What incentives can be put in place to foster such R&D? How can the different push and pull incentives be used? Can the developed country Orphan drug model be used for this purpose?

To analyse such questions, it is very important to be clear about the basic differences between a developed country such as USA and a developing country such as India. USA already has a well developed pharmaceutical R&D infrastructure. The issue there is how to generate a better outcome by changing the incentive structure. The Indian companies have just started R&D for new drugs. They lack the experience, the skills and the resources to be anywhere near the situation in USA.

Much of the pull incentives provided to the private sector in the developed countries are not relevant in India. Pull mechanisms offer a better return for the output of R&D. It presupposes that the companies have the capacity and capability to undertake R&D. If they do not have this, if they cannot generate an output in the first place, obviously the question of benefiting from the higher value of the output promised does not arise. As Lacetera and Orsenigo 2001 (p. 26) have pointed out, product patents (a pull mechanism) magnify incentives to innovate, but do not create them in the absence of the competencies to make innovation possible in the first place.

Similarly, consider the interesting proposal of Hollis (2005) to promote new drugs for neglected diseases. The idea is to create an optional reward fund. Drugs which are of low market value, but high therapeutic value would be rewarded from this fund to promote new drugs. This can act as an incentive for pharmaceutical companies in developed countries. The incentive of the reward will not be adequate for Indian companies which do not yet have the capacity to develop drugs independently.

Though Orphan drug models in developed countries are a combination of push and pull incentives, what has actually played a more important role is the pull incentive of market exclusivity (Center for Global Development Working Group 2004, p. 28). Unless Indian companies build up the competence to develop a drug, they cannot benefit from such exclusivity and hence such incentives would be inadequate.

The most important issue in India is how to develop the infrastructure for new drug R&D and how to fund it.<sup>53</sup> Since the private sector in India is not yet prepared to undertake R&D investments on their own, the options are to collaborate with:

- MNCs
- Government
- International agencies

As we have discussed above, collaboration with MNCs is not resulting in new drugs for neglected diseases. When asked, what they can do for neglected diseases, the typical answer of the Indian companies is that here government should play the main role. We discuss the role of the government in the next section. We discuss in Section VII below, what role India can play in the international efforts under way to develop new drugs for neglected diseases.

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<sup>53</sup> A number of fiscal incentives are available as we have mentioned above (see Table 1). But some of the studies which have been done show that availability of fiscal incentives has not been a major consideration for starting R&D activity. Mani (2002, p. 257) found that pharmaceutical companies (and electrical industry companies) attach greater importance to tax incentives, but their response too has been quite low. In a survey done specifically for the pharmaceutical industry, it was found that the decision to establish R&D units was not influenced by these incentives. However such incentives provide them some financial benefits and they very much want these to be continued (Ray 2003, chapter 5).

While push incentives would be more relevant to create and support new drug R&D infrastructure (see Table 1), once such infrastructure is created, and new drugs are developed, it will also be important to devise pull mechanisms to create a market. The incentive of market exclusivity in orphan drug models in the developed countries operated because the companies could charge very high prices via the health insurance system and earn an adequate return despite the very small number of patients. But in the developing countries, even if drugs were to be developed for neglected diseases, the return despite market exclusivity would be very low because of the low purchasing power and virtual absence of any health insurance (Kettler and Collind 2002, p. 24; Torrelee, Usdin and Chirac 2004, p. 44). Thus developing new drugs is not enough. Appropriate funding mechanisms will have to be devised to make these drugs accessible to the target population, viz., the poor in the developing countries. Here too government has a large role to play.

Thus in promoting new drugs for neglected diseases, the government in developing countries such as India has a dual role to play: to provide push incentives to develop the drugs and pull mechanisms to create a market.

## **VI: Public-Private Partnerships for Development of New Drugs in India**

A significant change which has taken place in India in recent years is a particular form of Public-Private Partnership (PPP). Traditionally, CSIR laboratories such as CDRI did not have much interaction with the pharmaceutical industry so far as R&D for new drugs was concerned. Neither the MNCs, nor the Indian companies were interested in the drugs developed by the publicly funded laboratories. In the previous patent regime, the Indian companies actually were more interested in developing processes for the new drugs and so far as this activity is concerned, the Indian companies did collaborate with the CSIR laboratories, as we have discussed above. The situation has now changed with the Indian companies starting R&D for NCEs.

### **Drugs and Pharmaceuticals Research Programme**

The Department of Science & Technology (DST), Government of India has initiated a Drugs and Pharmaceuticals Research Programme (DPRP) in 1994-95. The basic idea is to synergise the strengths of publicly funded R&D institutions (such as the laboratories under CSIR, universities and academic institutes) and the Indian pharmaceutical industry. Different CSIR and academic institutions have different types of expertise. It was felt that if these islands of expertise can be integrated, then R&D will be much more effective. Such integration and collaboration are particularly important because of the paucity of R&D funds in India. This DST programme supports joint research projects of industry and public R&D institutions in all systems of medicines. Both facilities and funds are shared.<sup>54</sup>

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<sup>54</sup> See “Drugs and Pharmaceuticals Research Programme: Salient Features”, DST, New Delhi, July, 2002; “Pharmaceuticals Research And Development Support Fund (PRDSF) Programme: salient Features,” DST,

Under DPRP, jointly formulated research project proposal is submitted to DST by the pharmaceutical company (ICP) and publicly funded R&D institutions (IRI) for approval. The research is jointly done by IRI and ICP and the project is monitored by DST. The project costs are shared by the public and private sectors as follows::

1. IRI provides the use of existing facilities and the time of the R&D personnel
2. ICP funds 100 per cent of both the recurring and capital costs for the research undertaken by it for the project. In addition it provides 30 per cent of the recurring costs of research at IRI.
3. DST funds 70 per cent of the recurring costs and 100 per cent of the capital costs of the research for the project at IRI.

The duration of the project is usually 3 years, which can be extended maximum by another year. However new follow up projects can be taken up.

Any intellectual property generated by the project will be jointly owned by the IRI and ICP. The ICP will have the first right to commercialize the IP. The ICP will pay royalty @ 2 per cent of the net sales. The royalty received will be shared by IRI and DST in the proportion of 75 per cent (IRI) and 25 per cent (DST).

No special provisions are there for R&D for new drugs for neglected diseases. Research is collaborative and the Indian private companies are participating in areas where they find it worth while. They do not seem to be interested in investing funds for developing drugs for neglected diseases.

Till 2004-05, the annual DST budget for the programme was Rs 100 million. During 1994-95 to 2003-04, 58 projects have been approved under the scheme. All the major national laboratories in the drugs field (such as CDRI, IICT, NCL, CCMB, IICB), well known academic institutes (such as Indian Institute of Science, Bangalore, All India Institute of Medical Sciences, New Delhi, National Institute of Pharmaceutical Education and Research, Chandigarh) and about 50 pharmaceutical companies (such as Dr Reddys, Ranbaxy, Dabur, Glenmark, Lupin, Cadila Pharmaceuticals, Alembic) have been involved in the projects.

Under this programme, funds have been provided for different activities – (i) NCE research, (ii) process development, (iii) setting up research facilities, (iv) drug delivery system, (v) assay systems, (vi) veterinary drugs and (vii) Indian system of medicine. So far as commercial implementation of the output of the projects are concerned, a number of processes developed have been put into use. Another area where a number of successes have been achieved is bio-efficacy and analytical evaluation of the active molecules in herbal medicines (for example the project between IICB and Dey's

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New Delhi, Januray, 2005; Inputs were also received from personal discussions (New Delhi, 8 January, 2003) with Laxman Prasad, Adviser, DST and with G J Samathanam, Director, DST ( New Delhi, 8 September, 2004 and 17 February, 2005), who co-ordinates the DST programme on drugs.

Medical). Some of the facilities created, for example for pharmacokinetics and metabolic studies at CDRI are highly used research by others.

A number of projects of programme relate to NCEs. But no NCE has yet been developed. Actually DST funds only piecemeal projects dealing with particular aspects of the new drug development process. A number of projects have been completed dealing with design, screening and biological evaluation of novel compounds in different disease areas including cancer, tuberculosis, obesity, and asthma. Adequate follow up activities have often not been done. As a result, though these studies have generated insights which may be of use for future researches, no concrete action has been initiated for new drug development.

One promising exception is Dabur. Starting from 1995-95, DST has sanctioned 6 projects involving Dabur for development of anti-cancer agents. The total project costs of the five projects since 2000-01 are Rs 154.9 million, of which Dabur's share has been 67 per cent and DST's 33 per cent. To this must be added the costs of the time of the R&D personnel and the use for existing equipments at the R&D institutions, for example, ICT, CCMB, IICB, JNCASR, CDRI, which jointly did the R&D together with Dabur. It is important to note that Dabur's two anti-cancer NCEs and one NDDS are undergoing clinical trials – two are at phase II and one has completed phase I trials.<sup>55</sup>

The Department of Chemicals & Petrochemicals, Government of India constituted a Pharmaceutical Research and Development Committee (PRDC) under the Chairmanship of R.A. Mashelkar, Director General, CSIR. One of the important terms of reference of the committee was to suggest measures to boost R&D in the pharmaceutical industry in India. Mashelkar Committee (1999) stressed the need for intensifying R&D activities including R&D for new drugs of relevance to the Indian population. The Committee recommended the setting up of a Drug Development Promotion Foundation to execute the R&D strategy with a one-time contribution of Rs 500 million by the government. The Committee also suggested a surcharge of 1 per cent of the maximum retail price of all formulations sold within the country. The proceeds estimated to generate an amount of Rs 1000 million annually (in 1999) could be used to fund R&D projects, through the Foundation, particularly for malaria, TB, filaria, leprosy, kala-azar and the like which are neglected by commercial R&D but are important for the disease profile for India.

The Government of India has not yet accepted the recommendation of setting up of the Foundation or the 1 per cent surcharge. What it has done is to announce a one-time Pharmaceutical Research and Development Support Fund (PRDSF) of Rs 1500 million in 2004. PRDSF has come into existence in 2004-05 and has replaced DPRP. The fund will function as a corpus, with the interest earning being used for R&D projects. During 2004-05, the budget for the drugs programme has been increased from Rs 100 million to Rs

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<sup>55</sup> Personal discussion with Rama Mukherjee, President – R&D, Dabur Research Foundation, Ghaziabad, 2 December, 2004.

240 million (\$ 5.5 million).<sup>56</sup> The interest from the corpus of Rs 1500 million (\$ 35 million) is expected to be available next year.

It has been decided that collaborative R&D projects will continue as before under PRDSF. But in addition to that, a new scheme has been started to provide loans to the private industry as under the other PPP discussed below. Out of Rs 240 million, Rs 90 million has been earmarked for loans for 2004-05. DST will fund normally maximum 50 per cent of the project cost. But in case of risky projects, DST will fund upto 70 per cent of the cost.

As we noted above, in the earlier programme there was no focus on R&D for neglected diseases. But it has been decided that for disbursement of financial assistance under the new programme, preference will be given to R&D projects for neglected diseases.

### **New Millennium Indian Technology Leadership Initiative**

Another programme which has been initiated by the Government of India is the New Millennium Indian Technology Leadership Initiative (NMITLI) coordinated by CSIR. Here too, the basic objective is to synergise the facilities and competencies of publicly funded R&D institutions, academia and private industry for developing technologies for Indian industry. Unlike the stress of the DST scheme on collaborative projects, here financial support is provided through loans to the private industry (and grants to institutional partners).

The loan are unsecured and the simple interest payable is 3 per cent per annum. Repayment of principal and interest will start after the project implementation period. The intellectual property rights will accrue to the company. But one of the conditions of the loan is that “in case the output of the project leads to products used in/for healthcare, education R&D purposes, the industrial partner undertakes to sell these at concession prices to Indian customers in these sectors.”<sup>57</sup>

Another notable feature of the programme is that in addition to industry originated projects, where the private companies approach CSIR for funds, there is provision for “nationally evolved projects.” On the basis of wide ranging consultation including screening by experts, broad areas for projects are identified and the best players in the field are invited to participate in the project.<sup>58</sup>

The NMITLI programme is much bigger in scope compared to PDRSF. The outlay for the 33 projects sanctioned since its inception in March 2001 and till December 1, 2004 has been Rs 2200 million, i.e., almost Rs 600 million (\$ 14 million) per year.

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<sup>56</sup> The Planning Commission promised an amount of Rs 3500 million. But the Ministry of Finance has made available only Rs 2400 million.

<sup>57</sup> “Terms and Conditions for the Loan,” NMITLI, CSIR, mimeo.

<sup>58</sup> Personal discussions (New Delhi, 7 January, 2003) with D Yogeswara Rao, Scientist-in-charge, NMITLI Cell, CSIR; “New Millennium Indian Technology Leadership Initiative”, CSIR, New Delhi, 2004

This is in fact the biggest PPP in India.<sup>59</sup> But unlike PDRSF, it is not restricted to drugs. Out of these 33 projects, 6 are in the area of drugs and pharmaceuticals and 6 in biotechnology. In drugs and pharmaceuticals, the most promising development has been for a new anti-TB molecule. It has mounted an Rs 150 million TB programme. No new drug has been introduced to treat TB in the last 40 years. Multi drug resistant strains of the disease have emerged. Under NMITLI, Lupin, the world's largest manufacturer of anti-TB drugs is engaged in a collaborative research project with 12 research institutions IICT, NCL, Indian Institute of Science, Bangalore, for design, synthesis and biological evaluation of new anti-TB compounds. Several promising leads have been obtained which are at various stages of pre-clinical development. Drug Controller of India has approved Lupin for conducting phase-I clinical trials for the molecule (code named LL 4858). Another promising development relates to a herbal formulation for the treatment of psoriasis. Here Lupin is involved in collaboration with CDRI and NIPER. Lupin has got phase-I clinical trials for this drug too (code named LL 4218).<sup>60</sup>

## Summary

- India has initiated two PPPs in recent years which are related to pharmaceutical R&D. Both funds and facilities are shared
- Financial support is provided by government in two ways – grants and loans
- In the case of grants, the intellectual property, if any generated by the project will be jointly owned and the private partner will pay the government royalties @ 2 per cent of net sales in case of commercialization
- In the case of loans, the intellectual property, will be owned by the private partner and the loan will be repaid with interest at 3 per cent
- The projects deal with different types of R&D including new drug development
- Of the two new drug development projects which have made substantial progress, one belongs to a global disease, cancer and another to a neglected disease, TB. As of now there has not been much progress in initiating and developing projects for most neglected diseases.
- The funds earmarked are abysmally small.

## How can the PPPs be strengthened

Both the PPPs are interesting and promising. There is substantial scope for improving and strengthening them.

## Funding

First and foremost, funding must improve. So far as public investment is concerned, internationally government has played a very important role in the development of new

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<sup>59</sup> “New Millennium Indian Technology Leadership Initiative”, CSIR, New Delhi, 2004.

<sup>60</sup> “New anti-TB molecule discovered under NMITLI initiative”, in *Chronicle Pharmabiz*, September 8, 2004; “Lupin gets DGCI nod for phase I clinical trials for two IND,” in *Chronicle Pharmabiz*, December 2, 2004.

drugs. Public funding of health R&D in high-income and transition economies was \$ 34.5 billion in 1998. It accounted for 47 per cent of global health R&D (WHO 2004, p. 13). In contrast the total amount spent by the government in India through CSIR, ICMR and DST in 1998-99 was only Rs 10986 million or about \$ 260 million. This is the total expenditure on R&D by these scientific agencies including areas other than drug R&D. Recently public funding in drugs has improved. The budget of the DST drugs and pharmaceutical programme has gone up from Rs 100 million per annum earlier to Rs 240 million (\$ 5.5 million) in 2004-05. The total outlay of the other PPP, NMITLI, is about Rs 600 million (\$ 14 million) per annum (including for projects other than drugs and pharmaceuticals). The interest from Rs 1500 million (\$ 35 million) Pharmaceutical Research and Development Support Fund set up by the government will be available 2005-06 onwards. But at say 6 per cent rate of interest, this will add only another \$ 2 million to R&D funds. If the PPPs are to play any significant role, there is no question that public funding of new drug development has to improve substantially in India.

The incremental cost to the government of setting up any significant pharmaceutical fund in India would be much higher compared to that in developed countries. Consider, for example Hollis (2004)'s proposal to set up a Pharmaceutical Investment Fund to reward the innovators of new drugs in exchange for zero-priced licenses to permit others to produce and market the drug. The government in USA, for example will make substantial savings because of lower drug prices resulting from such free licensing and competition. As a result, it has been estimated that the net cost to the government to set up the fund will be marginal (Hollis 2004, pp. 15-16).

But in most developed countries, particularly in India, the government is a low spender on health and drugs. So any enhanced public funding presupposes a quantum jump in the role of the government. The involvement of the government in healthcare in India is among the lowest in the world. Government expenditure as a per cent of total expenditure on health was only 17.8 per cent<sup>61</sup> in India in 2000. Only two countries out of the 191 countries considered by (WHO 2002, Annex Table 5) have a lower proportion of government expenditure – Georgia (10.5 per cent) and Myanmar (17.1 per cent). It is not only that government health expenditure is low. Government health statistics reveal a declining trend. Government health expenditure as a per cent of GDP has gone down from 1.5 per cent in 1988 to 0.9 per cent in 2000. Similarly the government share in health expenditure has declined from 32 per cent in 1994 to less than 20 per cent in 2000 (CII & Mckinsey 2002). About 15 per cent of the total public health funding is contributed by the central government. In India's constitutional structure, public health is the responsibility of the state governments. But the state governments in particular are experiencing fiscal stress for quite some time now. Health expenditure has been a victim of the difficult fiscal situation. While the central budgetary allocation for health, as percentage of the total budget has remained stagnant at around 1.3 per cent in the 1990s, that in the states has declined from 7 per cent to 5.5 per cent.<sup>62</sup>

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<sup>61</sup> This figure is marginally higher than the CII and Mckinsey & Co (2002) estimate of 16.5 per cent (Rs 170 billion as a per cent of Rs 1030 billion).

<sup>62</sup> See the text of the National Health Policy 2002, accessed from the website of the Ministry of Health and Family Welfare ([www.mohfw.nic.in](http://www.mohfw.nic.in)).

Because of such difficulties and also to make the PPPs sustainable in the longer run, it is important to supplement the budgetary support from government.

While more funds should be allocated from the general budget of the government, it is also important to think of industry specific solutions. Mashelkar Committee's (1999) proposal for a tax on pharmaceutical sales is worth considering. It recommended a mandatory contribution @ 1 per cent of formulation sales by all the pharmaceutical companies. The retail store audit of ORG-MARG (2004) reported formulations sales of Rs 204987.3 million in 2004. A 1 per cent surcharge would fetch an amount of Rs 2049.9 (\$ 48 million). This would mean a quantum jump in the funding position.

## **Selection of projects**

A plan should be drawn up for selecting a manageable number of projects and focusing on them rather than dissipating scarce resources in a large number of projects. The stress should be on development of new treatments rather than on process development, where already adequate skills are available in the private sector. As in NMITLI, projects should be “nationally evolved” and experienced and reputed companies which have demonstrated some competence in the field should be chosen to lead the project from the private sector. (Incidentally, both Dabur and Lupin satisfy this criterion in the two projects mentioned above and that may be one of the reasons for their relative success).

The projects selected should naturally be of relevance to the disease pattern in developing countries, particularly to India. Some of these diseases are also major health concerns in developed countries. It may be seen from Table 8 that cardiovascular disease is the most important cause of deaths not only in India and other low income countries, but also in high income countries. Malignant neoplasms (cancer) which is the second largest killer disease in high income countries, is the third largest killer in low and middle income countries. Similarly there are some other diseases, such as respiratory infections, respiratory diseases, digestive diseases, neuropsychiatric disorders, diabetes, which are major causes of death in both low and high income countries.

The priority R&D plan drawn up by the Mashelkar Committee (1999, p. 11) for diseases relevant to Indian population includes a number of global diseases, such as cardiovascular diseases, cancer, diabetes, arthritis, Alzheimer disease, asthma (Table 9). Similarly Kaplan and Laing (2004) did a very interesting exercise of identifying “pharmaceutical gaps” which affects Europe but are also relevant for developing countries. The pharmaceutical gaps are those diseases of public health importance for which pharmaceutical treatments either do not exist or are inadequate and hence there is need for intensifying R&D. They used a variety of methods to identify the gaps including the current disease burden and public health trends based on past and present experience. Most of the diseases in the priority list drawn up by Kaplan and Laing are global diseases (Table 9).

Table 8 Causes of death in 1998

Disease	Number of deaths in India in 000	Rank in India	Rank in low and middle income countries	Rank in high income countries
Cardiovascular diseases	2820	1	1	1
Respiratory infections	987	2	4	6
Injuries	923	3	2	3
Diarrhoeal diseases	711	4	7	21
Malignant neoplasms	653	5	3	2
Perinatal conditionsg	612	6	8	10
Childhood diseases	429	7	9	20
Tuberculosis	421	8	10	18
Respiratory diseases	284	9	5	4
Digestive diseases	240	10	11	5
Other infectious diseases	209	11	19	12
HIV/AIDS	179	12	6	16
Congenital abnormalities	153	13	16	14
Maternal conditions	125	14	15	24
Neuropsychiatric disorders	104	15	14	7
Diabetes mellitus	102	16	18	8
Diseases of the genitourinary system	102	17	13	9
Nutritional deficiencies	100	18	17	17
STDs excluding HIV	55	19	20	25
Meningitis	36	20	21	23
Tropical diseases	30	21	22	
Malaria	20	22	12	
Hepatitis	16	23	24	22
Dengue	10	24	30	
Other neoplasms	5	25	25	13
Musculoskeletal diseases	3	26	26	15
Intestinal nematode infections	3	27	29	
Nutritional/endocrine disorders	2	28	23	11
Skin diseases	2	29	27	19
Leprosy	1	30	33	
Japanese encephalitis	1	31	31	

Source: Calculated from WHO, 1999, Annex table 2. Separate figures for India are not available for later years.

Note: The rank is in terms of the number of deaths caused by the diseases in descending order.

## Cross subsidy

So far as the private players are concerned, both the PPPs have been designed to subsidize their activities rather than as such to earn a return from public investments. In the collaborative projects, the royalty payable is only 2 per cent of net sales and in loans the interest rate is only 3 per cent.

The projects of relevance to Indian and other developing country population can be classified into two groups:

- (iii) Those for which market incentives exist for undertaking R&D, for example in R&D for global diseases, and to some extent for neglected diseases
- (iv) Those for which market incentives are absent, for example in the most neglected diseases.

Ideally, government should earn some return from the former group of projects to cross subsidize the latter group which require most public support and no projects have been initiated yet. For the former group, the projects should be collaborative as in the case of the DST programme rather than loan financed. The government should jointly take the risk and also expect a return much larger than the current 2 per cent royalty.

It is clear from our discussion in Section V above that market incentives exist for Indian companies to participate in R&D for global diseases. Government should not subsidize R&D activities for which market incentives exist. If government participation can enlarge the scope of such activities and help to generate higher returns, then that can be a good justification for pursuing these. The higher returns can subsidize the R&D for neglected diseases.

It is indeed possible for the government to reduce costs and increase financial returns including its own share. As we have discussed above, Indian companies developing promising new molecules are licensing out to MNCs. One of the important reason is the huge costs on clinical trials. The later the stage at which the molecule is licensed out, the higher is the cost (and the risk), but higher is also the return. The government by providing funds and sharing the risks can help to get a better deal. Particularly in view of India's advantages in clinical trials, the government can play a more proactive role here. In both the PPPs, another scientific agency in India, ICMR is conspicuous by its absence. ICMR can be given the role of organizing clinical trials for new molecules developed. There are a large number of public hospitals and medical research institutes in India. There is tremendous scope for utilizing these facilities and ensuring clinical trials as per GCP norms as mentioned below.

Table 9 Diseases for Priority R&D

Mashelkar Committee (1999) for India	Kaplan and Laing (2004) for Europe and the World
Communicable and infectious diseases (TB, malaria, kalaazar, HIV/AIDS, lower respiratory diseases)	Infections due to antibacterial infections, HIV AIDS, TB, malaria
Cardiovascular diseases	Cardiovascular diseases
Cancer	Cancer
Eye and ear diseases	Smoking cassation
Metabolic diseases (diabetes, arthritis, dyslipidaemia, obesity)	Diabetes, osteoarthritis
Neurological diseases (Alzeimer disease, Parkinsonism, Epilepsy)	Alzeimer disease, depression
Respiratory diseases (asthma and other allergic respiratory disorders)	Chronic obstructive pulmonary disease
	Acute stroke
Nutritional linked diseases	Pandemic influenza
Paediatric diseases	Smoking cassation
Reproductive diseases	Postpartum haemorrhage and maternal mortality
	Alcohol use disorders
	Most neglected diseases (trypanosomiasis, baruli ulcer, Chagas diseases)

Sources: Mashelkar Committee 1999, p. 11; Kaplan and Laing 2004, p. 121.

## Differential pricing

One of the conditions of NMITLI funding is that any output generated from the project should be sold at concessional prices to Indian customers. No such qualifications are there in the DST collaborative projects.

The market for global diseases may be classified between domestic market and international market.

For the domestic market, a system of voluntary licensing may be introduced on payment of royalty at pre-determined rates. On the one hand, this will ensure market competition and more reasonable prices. On the other hand, the royalties payable will allow the PPP to earn some return.

For the international market, particularly for the large and lucrative market in developed countries, the IPR rights (or other rewards systems,<sup>63</sup> which may be put in its place in future) may be exercised. If product patent rights are exercised, and if this result in high prices there, then it should be the responsibility of the governments of the developed countries to subsidize the expenditure for the consumers in their countries. The government and the private sector in a poor country like India should not subsidize the drug expenditure in rich countries. In fact the earnings of the PPP from any successful product should be used to subsidize R&D for the most neglected diseases in India.

For a developing country new drug to be accepted and successful in developed countries it is important to either tie up with MNCs, or devise alternative institutional arrangements. CDRI, which developed a number of new drugs did neither and it is not surprising that its products are not commercially successful. Perhaps learning from this experience, in the new drug development programme, the Indian companies are collaborating with MNCs not only because they lack the skills and the funds, but also to ensure that successful products get proper marketing outlets. Similar strategy should be followed for the PPPs. In the collaborative projects, the IPR is jointly owned, but the responsibility of commercializing the product lies with the private partners. If and when to license out, whether to license out at all or look for other institutional outlets should be decided commercially.

It is important to note that any successful venture can bring immense financial returns if the commercial potential is fully utilized. Consider the agreement between Glenmark of India Forest Laboratories of USA referred earlier. If the product which has completed phase-I clinical trials is successful with say a sales of a billion dollar, at 15 per cent royalty Glenmark will get each year \$ 150 million during the life of the patent. This is in addition to the milestone payment totaling \$ 190 million.

### **Public initiatives for development of drugs for neglected diseases**

Lupin is involved in the NMITLI PPP to develop a new anti-TB drug, a neglected diseases. But Lupin is world's largest manufacturer of anti-TB drugs. Hence, Lupin may have some business interest in the project. For most of the neglected diseases, particularly the most neglected ones, it is difficult to find much private sector interest. So long as opportunities exist for R&D for global diseases, and they do exist, the private companies obviously will be interested in pursuing these which promise much higher returns (Kettler and Collins 2002, p. 22; CIPR 2002, p. 33).

Here the government will have to bear most of the burden. In fact it will have to be more a public initiative rather than a public-private partnership. Facilities at public sector research institutions, particularly CDRI, which has a full fledged new drug development infrastructure should be properly utilized and enhanced.

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<sup>63</sup> For example the one suggested by Hollis 2004.

In addition, as we have mentioned, because of the low purchasing power of the patients and absence of insurance facilities, the government will also have to subsidize the marketing and distribution of the products.

Thus public funding must improve. And considering the enormity of the problem, it is also important to supplement national efforts by international initiatives.

## **VII How can India Contribute to International Efforts to Develop New Drugs for Neglected Diseases**

So long we have discussed what is being done and can be done to develop new drugs under Indian private and public sector initiatives. India can also contribute a lot to international efforts. A number of international initiatives have already been taken for developing new treatments for neglected diseases. These include: (i) the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) (ii) Public/private partnerships (PPPs) and not-for profit drug development initiatives, for example, the Global Alliance for TB Drug Development (TB Alliance), the Medicines for Malaria Venture (MMV), the International AIDS Vaccine Initiative (IAVI), the Institute for One World Health (IOWH), Drugs for Neglected Diseases Initiative (DNDi) and (iii) some pharmaceutical industry initiatives, for example, by AstraZeneca, GlaxoSmithKline and Novartis.<sup>64</sup>

India's participation in the international initiatives has been piecemeal. AstraZeneca's TB research centre is located in India. Ranbaxy is involved in a MMV initiative for developing anti-malarial drugs. ICMR has been associated with the development of the drug, miltefosine for visceral leishmaniasis. There is much greater scope for Indian public and private sectors to be part of these global PPPs. More international funding can better exploit India's potential. Greater international awareness of the problem is expected to lead to more such efforts to develop drugs for neglected diseases. These international initiatives can take advantage of India's cost advantage and reduce the cost of new drug development and hence make these more accessible. Rather than just tying up with MNCs for global diseases, the Indian companies can be more involved in molecule development for neglected diseases. There are two other major ways in which India can contribute:

### **Process development of NCEs**

Developing the processes for manufacturing the NCEs and the intermediates required is an important component of the process of new drug development. Production of the NCEs is required initially for laboratory testing, then for clinical trials and ultimately for producing and marketing these after regulatory approvals are obtained. India's world class skills in chemical synthesis and process engineering can be used for such purposes (see Section IV). About 19 per cent of the cost of new drug development goes for

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<sup>64</sup> "R&D System Is Failing To Meet Health Needs In Developing Countries," MSF Briefing Note, November 2004, pp. 5-6; IFPMA 2004.

development of production process (WHO 2004, p. 17). So competitive supplies here will have a significant impact on the cost of drug development and hence on accessibility of drugs. The Indian companies also will be very keen to play such a role. With the introduction of product patent protection in India from 1 January, 2005, domestic opportunities will shrink. Indian companies are now looking for new opportunities for growth. A number of Indian companies have entered into such Contract Research and Manufacturing Services (CRMS). These include specialized companies such as Suven Pharmaceuticals, Avra Laboratories. A number of diversified big Indian companies, such as Dr Reddys Laboratories, Ranbaxy, Alembic have also entered into the area. Specialized bulk drugs manufacturers such as Divis and Shasun which currently export commodity generics are diversifying to CRMS activities.

## **Clinical research**

We have discussed above that because of lack of funds to do the costly clinical trials themselves, Indian companies are licensing out new molecules developed at the early clinical stage. But there are advantages of doing such trials in India and international initiatives can reduce both the time and the cost for developing new drugs for neglected diseases by organizing such trials in India.

India's advantages are:

- Huge patient population (including those with neglected diseases) and genetically distinct groups willing to participate in clinical trials
- Speed of recruiting patients and conducting trials
- Large number of hospitals including specialty hospitals with state of the art facilities
- Skilled English speaking investigators including doctors trained in Western countries
- High levels of computer efficiency
- Lower costs even if done as per international standards.

A survey found that clinical trials costs in India are half or even lower when compared with that prevailing in developing countries.<sup>65</sup> The Indian company, Nicholas Piramal did a clinical trial for visceral leishmaniasis in India following US FDA standards and monitored by an international CRO, Quintiles. The costs were 25 per cent lower.<sup>66</sup>

But India has not been able to fully exploit the advantages because of lack of experience and exposure and an underdeveloped regulatory system. India's Drugs and Cosmetics Act classifies new drug substances as follows:

1. New drug substances already approved for marketing abroad

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<sup>65</sup> Reshma Ratil and Toufiq Rashid, "Strong Medicine," in *The Indian Express*, 28 December, 2003.

<sup>66</sup> Gina S Krishnan, "Entering a New Phase," in *Business World*, November 24, 2003.

2. New drug substances discovered abroad, but not yet approved for marketing abroad
3. New drug substances discovered in India

***New drug substances already approved for marketing abroad***

Almost all the modern drugs used in India have been developed abroad. For new drugs developed abroad, India's Drugs and Cosmetics Act does not insist on repeating the entire clinical trials here. Only confirmatory phase III clinical trials are required. The idea is to ensure that the new drug is effective and safe for Indian people too. Indian companies which developed processes for new drugs developed abroad and wanted to introduce these in India, essentially prepared product dossiers based on published data and supplemented these with some limited phase III trials. Good Clinical Practices (GCP) were not followed in India. It was not thought to be important because in any case these have already been approved for marketing abroad. The phase III trials here essentially turned out to be a technical requirement. There has not been any instance where a new drug approved for marketing, say in USA has been rejected in India.

***New drug substances discovered abroad, but not yet approved for marketing abroad***

From time to time clinical trials have also been done in India for drugs which been discovered abroad and not yet approved for marketing anywhere. For drug substances discovered abroad, phase I trials are not allowed in India. For other stages, clinical trials were allowed to be initiated at one stage earlier to the phase of trials in other countries. Reliability of such trials depended basically on who it.

Some of the MNCs, for example Pfizer, Eli Lilly, Novo Nordisk have been doing clinical trials in India. These again were primarily for phase III. MNCs often had to do phase III clinical trials in developing countries because regulators such as US FDA insist on trials on a huge number of patients and it is difficult to recruit so many volunteers from only developed countries. These MNCs however followed the international GCP and hence the reliability as such was not questioned. GCP basically tries to ensure that the clinical data are credible and reliable and the rights, safety and well-being of people participating in such trials are protected. It is a standard for the design, conduct, monitoring, recording, analysis, and reporting of clinical trials.

Again in the case of clinical trials for a drug (miltefosine) for treatment of visceral leishmaniasis (VL), where WHO/TDR was involved, the facilities in a hospital in Bihar, which accounts for 90 per cent of VL cases in India were not found to be suitable. But with the help of TDR clinical coordinators, proper facilities and standards were put in place and clinical trials were successfully implemented. These were the first clinical trials conducted in a developing country setting of a drug developed in a developed country but serving the medical needs of developing countries.<sup>67</sup>

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<sup>67</sup> Sujit Bhattacharya, "Experiences from miltefosine trials in India," TDR News, Vol 69, Nov 2002

But in general in India, in the absence of a proper regulatory system, the reliability of clinical trials has often been questioned. Not collecting and recording data properly, exaggerating claims and downplaying risks, recruiting volunteers unethically are among the complaints made.<sup>68</sup>

### ***New drug substances discovered in India***

For such drugs, clinical trials are required to be done in India from Phase I stage. But as we have discussed above, only few drugs have been discovered in India. When Indian companies started investing in new drug R&D, Drug Controller found it quite difficult to process their applications for clinical trials. Drug control administration was simply not organized for such activities. Processing of such applications requires expertise which the Drug Controller's office did not have in-house. Ultimately a procedure was started with help from other organizations, such as ICMR and the Department of Biotechnology. Now it takes much less time to process applications in India.

If India is to attract significant volume of clinical trials work from abroad, the system should appear creditable. It should not only depend on the integrity of the sponsors and investigators. Proper regulation should be in place to ensure reliable and acceptable data generation.

Things are changing. During 2000-01, Central Drugs Standard Control Organization issued the GCP Guidelines and ICMR issued the "Ethical Guidelines for Biomedical Research on Human Subjects." These were mere guidelines and were often ignored. In January, 2005, the government has amended Schedule Y and now much of these are mandatory. Facilities for clinical trials are also being strengthened. ICMR has undertaken programmes for enhancing facilities in different hospitals and institutions, for example KEM Hospital, Mumbai, All India Institute of Medical Sciences, New Delhi, National Institute of Nutrition, Hyderabad for both pre-clinical studies and clinical trials.<sup>69</sup>

The confidence level on India's capacity to perform clinical trails satisfactorily and efficiently has gone up. The following is the assessment of Pfizer, which is among the first MNCs to set up a dedicated clinical research division in India:

"The Future of clinical research in India: India possesses significant potential to become a preferred location for research and development for the global biotechnology and pharmaceutical sector. .... Recent studies have estimated that India can become the most preferred destination for global pharmaceutical and biotech companies looking for partnerships or setting up

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<sup>68</sup> K S Jayaraman, "Outsourcing clinical trials to India rash and risky, critics warn," in *Nature Medicine*, Vol 10, No 5, May, 2004.

<sup>69</sup> "ICMR proposes 15 to 20 pre-clinical study centres for new drugs," in " *Chronicle Pharmabiz*, June 27, 2001; Personal discussion with V Muthuswamy, Senior Deputy Director-General, ICMR, New Delhi, December 2, 2004.

new operations. Furthermore, the outsourced clinical research market in India will increase to \$ 500 mn by 2010.”<sup>70</sup>

Pfizer has not only been conducting phase II-IV clinical trials in different therapeutic areas. It has set up an “Academy for Clinical Excellence,” in collaboration with the Bombay College of Pharmacy and Suven Pharma. The academy will provide training programmes in clinical research methodology, data management and biostatistics. GlaxoSmithKline also has plans to set up clinical research facilities in India to undertake trials for its NCE pipeline.<sup>71</sup> A number of international CROs, such as Kendle of USA and Chilern of UK are in the process of opening offices in India to enter the clinical trials business.<sup>72</sup>

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<sup>70</sup> “Pfizer Clinical Research in India,” in [www.pfizerindia.com](http://www.pfizerindia.com).

<sup>71</sup> “GSK to set up clinical research facility in India to start in-house trials soon,” in *Chronicle Pharmabiz*, February 10, 2004.

<sup>72</sup> :India is inevitable for us: MNCs,” in *Chronicle Pharmabiz*, December 2, 2004.

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