Research and Innovation for Drug Development in Neglected Diseases: A Case Study of India

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Abstract

This study investigated the research and innovation in ‘neglected diseases’ in India and the various modalities being undertaken to develop ‘novel’ drugs for these diseases. In spite of increase in scientific research and patent filing, examination of Indian pharmaceutical firm’s activities shows that only a few firms are involved in the domain of neglected disease. Government is trying to bridge the ‘translational gap’ by stimulating public-private research partnership; however, private firms primarily exhibit profit motive for coming into public partnership. This model, as the evidence show, is not suitable for drug development in neglected diseases. The study explores other models that can broadly be placed under open innovation and argues that they are more promising for drug development in neglected diseases. It calls for more attention to these approaches as they provide incentives for actors to participate and moves away from the ‘market centric’ focus on drug development by firms leading to research only for lifestyle diseases effecting the north.

Keywords: Neglected disease, Tuberculosis, Malaria, Translational gap, India.

JEL Classification: I00, I10, I15.

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1. Introduction

Concept of Neglected Diseases

This article specifically examines research and innovation in neglected diseases, focusing on the Indian context. More than 1 billion—one sixth of the world’s poorest population are affected by them (Sinha, 2010). These diseases are mainly concentrated and endemic in over a hundred of the poorer countries in Africa, Asia and Latin America. So far, there is no standard definition of neglected diseases. Different organizations have looked at the problem from different perspectives. United Nation (2003) describes neglected diseases as those that “affect almost exclusively poor and powerless people living in rural part of low income countries”. However this is by no means an adequate description that covers all dimensions of neglected diseases. One of the difficulties in defining neglected diseases is that the concept of neglect is often different from the widely held notion. In broad terms, neglect here indicates and signifies the lack of investment in research and development. Broadbent (2011) has tried to offer a principled definition of these diseases on the basis of health burden on population, availability of treatments, alleviation measures and distribution. According to him, “a disease D is neglected to the extent that it poses a significant health burden on some reasonably large population, and preventive, curative or mitigation measures are either widespread among other populations, or would be much more actively sought if D imposed a similar burden on other population’ (ibid).

The World Health Organization (2010a) has in its latest report, provided a more informed assessment of neglected diseases; “They are named neglected because these diseases persist exclusively in the poorest and the most marginalized communities, and have been largely eliminated elsewhere and thus are often forgotten”. Most of these diseases are tropical and primarily vector borne, with tropical conditions acting as ideal breeding grounds for various vectors. The salient feature of neglected tropical diseases as described by WHO are (1) Poverty and disadvantage (2) Affects politically marginalized population (3) Restricted distribution (4) Morbidity and mortality (5) Stigma & discrimination, and (6) Can be controlled by appropriate healthcare. The Working Group of the WHO Commission for Macroeconomics & Health
has categorized neglected diseases according to the size and location of the market (National Commission on Macroeconomics and Health, 2005). On the basis of this categorization, the commission has pointed out the need for different policy actions to confront the challenges posed by each category of neglected diseases. AIDS, measles, respiratory diseases for example affects both developing and developed countries, whereas diseases like African sleeping sickness, Chagas disease, Leishmaniasis affect developing and improvised countries. Tuberculosis (TB), Malaria, GI nemotide infections although predominant health concern of developing countries do occur in developed countries.

Neglected Diseases and Concerns

Firms are mainly guided by ‘return to investment’ model and do not want to put money in research for drug development where returns do not commensurate with the investments made. A drug development process is a highly uncertain and risky venture. Investments in the order of $800 million to $1 billion have been estimated to successfully bring a drug in the market (Martin, 2010). It is understandable therefore that big pharmaceutical companies address diseases that are prevalent in the ‘North’, as these drugs have the potential to bring high end returns to their investment made (Herring, 2007). Thus, except for some neglected diseases like AIDS where clientele is also in the north, drug majors may not pay attention to majority of other neglected diseases. Low returns might not be the only reason for the non involvement of major pharmaceutical companies in drug development for ‘neglected diseases’. Potential infringement and high transaction costs involved in engaging with the South may also have prevented the development of drugs for ‘neglected diseases’.

New findings have increasingly shown that drugs that were effective against neglected diseases, such as tuberculosis and malaria are now found to be inefficient due to a number of factors —drugs used for treating them are more than fifty years old, difficult to manage and often toxic, the presence of new strains of these diseases, the fact that people carry different mutant genes, and others. Thus, for these diseases, highly complex research is now required to bring new drugs in the market that can cure or at least mitigate the sufferings.

Governmental and not-for-profit organisations have made efforts to simulate drug research for neglected diseases. The major players have
largely been emerging economies with reasonable scientific capacity (mainly India, China, Brazil), not-for-profit organisations (for example Welcome Trust) and, some developed economies health fund (such as National Institute of health- US, Department of health UK). It has led to more scientific research (visible through increase in scientific publications), but this has not finally resulted in the introduction of new drugs. In other words, investment has led to visible increase in scientific papers but less in terms of improvement in health research. One of the prime reasons that have been cited is the ‘translational gap’; this is the gap between the basic scientific research and development process (Butler, 2007). Development process and final creation of drug is a long, complex and expensive process (identification of candidate molecules, going through the different clinical phases, following the mandatory drug clearance guidelines etc) and requires a different skill-set which is difficult to replicate in academia, where scientific research takes place. Research in neglected diseases are not part of mainstream research, restrictive nature of academia that often tends to favour basic research i.e. reward systems (reward to publication), pressure to publish instead of practical contribution to disease ridden population make researchers less motivated to do the tedious work to narrow translational gap (ibid).

Seed financing\(^1\) can help bridge the translational gap. But more novel initiatives are required to address the translational gap. Thus it becomes an important policy research to examine research and innovation in neglected diseases and develop strategies that can stimulate the drug development process. The paper intends to address this. Among the questions that drive this research are: What is being done to promote R&D for discovery of new drugs for neglected diseases? What kind of incentives have been devised or proposed to steer the drug research to address neglected diseases? To what extent Indian pharmaceutical companies are engaged in research on ‘neglected diseases’? What are the models being deployed by public sector and private sector to stimulate drug research? More importantly what kinds of alternatives are emerging?

India was chosen since its health problems epitomizes the situation in other developing countries to a large extent i.e. it has a large population suffering from diseases which are typical in developing countries and has problems relating to access and affordability of medicines. Seventeen health conditions have been identified as priority conditions by the
Government of India (National Commission on Macroeconomics and Health – NCMH, 2005). A key finding of the NCMH study was that a large number of diseases, which were considered to be lifestyle-related and affecting the rich (such as CVD, cancer, diabetes), were also seen to affect the poor. In spite of the increase in lifestyle diseases, tropical and other neglected diseases constitute the greatest health problem in India. Tuberculosis is the single most important cause of death in India. According to the estimated epidemiology burden of TB in 2009, cases of mortality were 280,000 (16.7% of global TB mortality in 2009). Around (1.6-2.4) million TB patients are estimated to live in India (WHO 2010b). This amounts to one-fifth of the global figure and is home to the largest pool of partially treated patients with half of the 150,000 multi-drug resistant (MDR) TB cases in south-east Asia reported in India. Recent studies have shown that diabetes increases the risk of TB threefold. Malaria continues to be a serious health problem with 10,500,000 cases registered in India in 2009 and cause of 15,000 deaths in that year (WHO 2010c). It also accounts for roughly one-quarter of the world’s 120 million cases of lymphatic filariasis; a disfiguring and stigmatizing vector borne infection associated with elephantiasis (Hotze, 2010; ICMR, 2010; WHO 2010a).

The other important reason was that India, unlike the majority of other developing countries (with the exception of China and Brazil), has advanced S&T skills and ability to develop new drugs. India demonstrated its skills when it emerged as a leading country that could develop and supply low cost generics to the world market (Bhattacharya, 2004). In some cases, Indian firms have broken complex process patents to create generic drugs (Chaudhuri, 2003).

Section 2 describes the methodological approach of this paper. Section 3 highlights key findings of some major studies on research and innovation activities undertaken in neglected diseases. Sections 4 posit why Indian firms would be motivated to develop drug for neglected diseases. Section 5 examines scientific research and patenting activity in neglected diseases- Indian and Global scenario. Section 6 investigates involvement of Indian government and pharmaceutical firms in research and innovation in neglected diseases. Section 7 underscores new approaches that can address drug development in ‘neglected disease’. Section 8 concludes.
2. Methodology

This study is based on in-house created database, based on information on drug development for neglected diseases gathered from varied secondary sources: annual reports, newspaper clippings, stock market applications by firms (public listing i.e. red-herring prospectus), company web-sites, activities of multilateral health organisations/foundations, etc. Furthermore, detailed R&D and innovation profile sheets, including R&D undertaken by ninety-eight listed Indian pharmaceutical firms that have invested in R&D (sample included mid-size to bigger firms) were created (Bhattacharya et al., 2007). Profile sheets were constructed primarily from varied secondary sources (refer above) and a limited primary survey was also undertaken to address the missing gaps.

Scientific publications can be useful in assessing the research efforts/priorities undertaken by individual countries. It can also highlight the alarming gaps, areas where research is urgently needed (Lewison, 2005). On the other hand, patent applications can provide an indication of activity in different stages of the innovation process in drug development. The Scopus database (provides a more detailed coverage of journals emerging from developing countries then web-of-science and thus more suitable for this study) was used to extract data on scientific papers; search terms created through MESH (Medical Subject Heading). The extraction of data from Scopus covered the period 1990 -2007. Patent data was extracted using same subject headings from the following patent offices: (1) Application data filed through Patent Cooperation Treaty (PCT)2, (2) Patent grant by US patent office3 (USPTO), (3) Indian Patent Office (IPO).

Government role in drug research and especially in neglected disease was examined through investigation of one major programme, namely the Drugs and Pharmaceuticals Research Programme (DPRP).

3. Status of Research and Innovation in Neglected Disease: Evidence from Global and Indian Studies

Some of the influential studies that have attracted world attention to the mismatch between drug development in high profile diseases (diseases like cancer, CVD, Obesity) and neglected diseases are examined to provide grounding to the present study. Kettler (2000) showed a low
priority of research for neglected diseases. This study estimated that only 5-10 percent of health R&D is going to LDC diseases and only 1 percent of the new products developed during 1975-1997 were for tropical diseases. Human development report highlighted that of the 1,223 drugs introduced between 1975 and 1996, only thirteen were aimed at tropical diseases. In 1998, the world spent $70 billion on health research, but only $300 million was directed at developing an AIDS vaccine and a miniscule $100 million was devoted to malaria research (HDR, 2001). Lanjouw (2003) reported 137 drugs in development for infectious diseases by big pharmaceutical companies, of which only two drugs were related to the most neglected diseases.

Global Forum for Health Research (2004) has brought world attention towards research on diseases affecting the poor and vulnerable population. It describes the “10/90 gap” which occurs since 90% of the world’s biomedical research (measured by expenditure) is carried out on diseases such as cancer and cardiovascular diseases, that mainly affect 10% of the world’s population, and vice versa. The PhRMA website mentions only two products for malaria, one for leishmaniasis, one for African trypanosomiasis and three for TB. There are currently twelve alliances in research that might relate to malaria, seventeen for TB and six for the AIDS vaccine (Kettler, 2005).

Some of the studies on India’s involvement in drug research with specific reference to neglected disease drug research that were influential are highlighted. The Scherer and Watal (2001) study showed that in 1999, only 16% of R&D expenditure in India targeted towards tropical diseases or developing country markets. Lanjouw and Cocklum (2001) surveyed top twenty Indian firms as to their extent of R&D investment on neglected diseases. They found that firms are preferably investing on R&D for diseases that can be classified ‘global illnesses’. The study by Cheric Grace (2004) for the British Government’s Department for International Development (DFID) found that in order to compensate for revenue loss in the domestic market (since generic copies of newer drugs will become illegal post TRIPs) Indian firms have increased their emphasis on export. Gehl Sampath (2006) in a study commissioned by CIPH (Commission on Intellectual Property Rights), WHO, investigated 104 pharmaceutical firms core activity and direction of research. She found that fifteen firms focused only on local diseases; sixteen reported to devote 50% of their research on local disease, and sixty-two of them reported less than 25% or no research at all on local disease. The main
conclusion of the study was that export demands shaped innovation strategies of Indian firms.

4. Possible Motives for Indian Firms Involvement in Drug Development for Neglected Disease

Drug major’s reluctance to involve in drug research for neglected disease provides an opportunity for Indian firms to enter and assert in this domain of drug. The strategy of catering to a high volume, low priced segment has earlier helped Indian firms to capture more than 20% of the global consumption (this however amounts to only 1.5% of the global pharmaceutical market of $480 billion). This business model, based on selling generic versions of patent drugs worked in the pre-TRIPs era as lax patent rules in developing countries allowed circumventing the research and innovation drug development path. This model is severely constrained in present TRIPs regime where only off-patent generics can be sold (Bhattacharya, 2004). Drug manufacturers in India can overcome this market of generics of patented drugs in developing/improvised markets by aggressively entering neglected disease segment. These drugs can again provide Indian firms the advantage of monopoly in the low-priced high-volume markets of the South.

We explore in the latter sections to what extent the Indian firms and other stakeholders involved in research and innovative activity in neglected diseases are finding this as a useful strategy.

5. Scientific and Patenting Trends in Neglected Diseases- Indian and Global

Figure 1 displays the research trend in the neglected diseases whereas Figure 2 shows combined scientific research output affecting Indian population from 1990-2007.
The publication trends from 1990-2007 shows growth being most intense for the three diseases Tuberculosis, AIDS and Malaria. Kalazar, leprosy, encephalitis, dengue, and polio have highest incidence in Indian population. Researches in these diseases are more specific to the Indian context unlike TB, AIDS, and Malaria. Thus research even within neglected disease category have different priorities and are not committed enough to work where global attention is the least. Figure 2 provides an aggregated picture to show the research contribution of the major neglected diseases.

Figure 2 reasserts the findings of Figure 1. The three disease AIDS, Malaria and TB account for 71% of the output in comparison to other prevalent neglected disease. Figure 3 shows the aggregated global scenario of research in these neglected diseases.
Figure 2: Aggregated Scientific Research Output in Major Neglected Diseases in India (1990-2007)

Source: Constructed from Scopus database

Figure 3: Aggregated Global Scientific Publications in Neglected Diseases (1990-2007)

Source: Constructed from Scopus database

The three dominant areas of scientific research in neglected disease are AIDS, TB and Malaria. India’s scientific research activity mirrors global activity.

Patenting Activity
Patenting activity provides an indication of activity in drug development. Table 1 highlights patent filing in the Indian Patent office (IPO) in neglected diseases.

**Table 1: Applications Filed in the Indian Patent Office in Neglected Diseases**

(1993-2007)

<table>
<thead>
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<tbody>
<tr>
<td>Tuberculosis</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Malaria</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>AIDS</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Polio</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Leprosy</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Cancer</td>
<td>4</td>
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<tr>
<td>Diabetes</td>
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<td>6</td>
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<td>Cardiac</td>
<td>2</td>
<td>2</td>
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</table>

Source: Constructed from Indiabigpatents.com
Note: Italics indicate lifestyle diseases

<table>
<thead>
<tr>
<th>Year</th>
<th>PCT Applications</th>
<th>USPTO Grant</th>
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<tbody>
<tr>
<td></td>
<td>Cancer WD IN CVD</td>
<td>Malaria WD IN</td>
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<tr>
<td>2000</td>
<td>2727 8 865 3</td>
<td>23 3 78</td>
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<tr>
<td>2001</td>
<td>4164 12 1044 7</td>
<td>29 5 11 0</td>
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<tr>
<td>2002</td>
<td>4975 20 1452 9</td>
<td>34 6 11 8</td>
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<td>2003</td>
<td>5429 28 1702 19</td>
<td>37 16 1 2</td>
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<td>2004</td>
<td>5588 34 1844 18</td>
<td>39 4 13 3</td>
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<tr>
<td>2005</td>
<td>6025 32 2132 19</td>
<td>29 4 14 2</td>
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<tr>
<td>2006</td>
<td>6299 39 2152 17</td>
<td>38 16 5</td>
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<tr>
<td>2007</td>
<td>6365 83 2179 33</td>
<td>44 10 18 0</td>
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</table>

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Table 1 underscores the limited invention activity in drug research in general. India is now having the maximum people affected by polio and leprosy. Patenting activity shows that not much effort is undertaken to develop new drugs in these two diseases.

Table 2 highlights patent filed though the PCT route and patents granted by the US patent office globally and by India in two major global and neglected diseases.

Table 2: Applications filed (PCT) and Patents Granted in Dominant Global Diseases and Most Prevalent Neglected Diseases

<table>
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<tr>
<th>Year</th>
<th>Applications</th>
<th>Patents Granted</th>
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<td>2008</td>
<td>7021</td>
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<td>216</td>
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<td></td>
<td>3</td>
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<td>2009</td>
<td>888</td>
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<td>1914</td>
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<td>67</td>
<td>84</td>
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Table 2 highlights the difference in patenting activity in two diseases (cancer, CVD) which are typically global disease with high prevalence in the north in comparison to two neglected disease predominant in all developing and improvised economies. The table clearly brings out the difference in activity globally in the two global diseases. Almost similar pattern of difference is observed in India.

Examination so far reveals that scientific activity is happening as reflected through growth in scientific research papers. At least this is true in three neglected diseases, malaria, TB and AIDS; all these have more global spread. AIDS and to some extent TB also effects the developed countries. Inventive process is much less visible as the patenting examination reveals. We posit that the problem of drugs not being developed is possibly due to ‘translational gap’. Primarily publications and also patents (in neglected diseases) are coming from academia and thus for translation towards developing a potential drug entails a long, elaborate and complex process. Drug majors are reluctant to exploit this knowledge.
6. Involvement of Firms and Government in Research on Neglected Diseases

Involvement of Pharmaceutical Firms

Our findings are based on the examination of ninety-eight pharmaceutical firms (Bhattacharya, et al., 2007). Only three out of ninety-eight firms were engaged in research on ‘neglected disease’. These findings are similar to those other influential studies: Lanjouw and Cockbum (2001), Grace (2004) and Gehl Sampath (2006). We found significant commitment of firms towards R&D post 1995. This was reflected by parameters such as R&D investment, establishment of R&D centres, R&D collaborations, and patenting activity. One fifth of the firms had separate R&D centres established mainly after 1998. R&D collaborations ranged from technology transfer to joint research partnership. R&D investment exhibited significant correlation to sales as well as exports. This implies that bigger firms (delineated in terms of sales) and export oriented firms are investing more in research. Firms had taken various steps/safeguards to enter regulated markets in the west such as (a) Filing ANDAs (Abbreviated New Drug Applications) for marketing generic drugs in the USA. (b) Filing DMFs (Drug Master Files) to export their bulk drugs. Twenty-seven of the sixty-eight firms had filed ANDAs and DMFs in the USA. (c) Obtained US-FDA, WHO-GMP plant certifications, UK MCA, etc.

Diabetes, cancer, pulmonary diseases were found to be the main research domain of the firms. Even anti-ageing and facial hair removals were areas of research. Specialty generics (alternate dosage formulation, new drug delivery systems) were primary targets of research. We observed that firms’ involvement in neglected disease research was poor. Only three firms were active in research on ‘neglected diseases’. Three firms had partnership with Global Working Alliance for TB drug development. One firm had a TB drug molecule in pre-clinical stage. Seven firms had developed medicinal equipments and kits for AIDS, Syphilis, etc. Only one firm, namely Lupin Laboratory, was involved in patenting in ‘neglected diseases’ (AIDS and TB). Six process patents were granted to an AIDS diagnostic kit and one to a TB composition by the Indian patent office. It has filed seven process patents in TB (four in diagnostics and five in drug composition), and four patents in HIV diagnostic kits in Indian patent office.
Involvement of Government in the Development of Drugs for Neglected Diseases

India is the fifth largest public funder of neglected diseases, with the Indian Council of Medical Research (ICMR) alone contributing to 60 percent share (Bakshi, 2010). It allocates $0.40 per individual per year for the treatment of its population at risk for visceral leishmaniasis (Hotez, 2010). The ICMR, the Department of Biotechnology (DBT), the Department of Science and Technology, and the Council of Scientific and Industrial Research are major government organisations involved in undertaking research and providing grants for drug research in India. The government efforts are catalysing research and innovation activity in drug research. No special initiative was observed for ‘neglected disease’ research except TB. However, much of the efforts are being made in vaccine research for neglected diseases. Dhar and Rao (2002) also showed that Government sponsored networks/ knowledge partnerships are primarily concentrated on diseases such as cancer, diabetes and cardiovascular, while only a few are targeted towards tropical diseases. In recent years, a number of new programs have been initiated to mitigate the consequences of the TRIPS compliance regime.

Our study examined one major programme, namely the Drugs and Pharmaceuticals Research Programme (DPRP), and investigated the role played by this programme in promoting research in ‘neglected diseases’. The mainstay of this programme is to support public-private partnerships in drug development for diseases affecting the Indian population. The programme provides support on:

**Collaborative projects:** Eighty-one collaborative projects have been funded so far under this programme (data captured till January 2008) in five categories, namely New Chemical Entity (thirty-four projects), Assay Systems (six projects), Drug Delivery Systems (nine projects), herbal drugs & Indian system of medicine (twenty-seven projects), Veterinary drugs (one project). Only four of the thirty-four projects under New Chemical Entity target neglected diseases (one in AIDS, two in TB and one in malaria). However, all four collaborative projects under ‘vaccines & diagnosis’ are in ‘neglected diseases’ (three in AIDS and one in rabies). Of the six projects under Assay systems, one targets tuberculosis, while of
the nine projects under Drug delivery systems, three target tuberculosis. Of the twenty-seven projects funded under Herbal drugs & Indian system of medicine, only three target malaria. Cancer and other lifestyle related diseases dominate the collaborative projects.

**National Facility projects:** Thirty facilities have been created at the National level - seventeen in national laboratories, and thirteen in academic institutions. Only one national facility in ‘screening drugs and their biological effects for cancer, AIDS and Malaria’ had direct involvement in neglected diseases.

**Extending loans for pharmaceutical industry R&D:** Thirty one industries were involved in R&D drug discovery projects received loans under this scheme, twenty four in modern medicine and seven in herbal medicine. Only three R&D projects in modern medicine were for the development of vaccines for neglected diseases; one each in dengue, encephalitis, and AIDS. Under this DRPP programme, so far fifteen product patent applications have been filed. However, none are associated with ‘neglected diseases’. It is evident that the DRPP programme does not seem to address strongly research in neglected diseases.

Partnerships for the development of vaccines for neglected diseases are now encouraged by the government. Vaccine research involves lower risk, cost, commitment and uncertainty than drug development since clinical trials are not so extensive and costly. Three specific R&D projects in vaccine development by the industry are currently supported by the government under the DPRP programme. Some of the specific outcomes are highlighted. A rota-virus vaccine is now in clinical trial, and is anticipated to achieve considerable reduction in diarrhoeal diseases among infants. It has been developed through the collaboration between the ICMR, Bharat Biotech, Centre for Disease Control, Atlanta and NIH, Washington, the Institute of Genomics and Integrative Biology, New Delhi, and the National Institute of Virology, Pune. The multi-caccina ankara epitope candidate vaccine for HIV/AIDS was developed under an agreement between the ICMR, the National AIDS Control Organisation and the International AIDS Vaccine Initiative (IAVI). The pre-clinical trials of the vaccine are being carried out by a biotech company in the US. A vaccine for HIV-1 sub-type ‘C’ DNA (the clade prevalent in India) is also being developed at the National HIV Reference Centre, Department
of Microbiology, All-India Institute of Medical Sciences. The vaccine is still to undergo pre-clinical testing in animals.

The examination so far clearly demonstrates Indian research activity is not leading to drug development for neglected disease. Return to investment in health research is in terms of scientific papers being produced in larger numbers but less in terms of tangible outcomes. We examine what would be possible innovative solutions, bridging institutions and innovative funding mechanisms that can lead to tangible outcomes.

7. Novel Approaches for Drug Development in ‘Neglected Disease’

Hope emerges from a new set of actors, structures and alliances that have started addressing the demands of population suffering from neglected diseases. Gradually, an increase in R&D for neglected diseases drug development mainly by not-for-profit organizations can be seen. For instance, programs such as Drugs for Neglected Diseases Initiative, Medicines for Malaria Venture (MMV) and initiatives by multinational pharmaceuticals such as AstraZeneca and GlaxoSmithKline are picking up in this direction (Chaudhuri, 2010). Involvement of multinational firm’s motive and to what extent they will bridge the translational gap still remains to be seen. Given the dismal state of drug research on neglected diseases, commentators have unanimously indicated the need for large and informed approaches (see for example Herder, 2008). In the past few years India saw the emergence of multi-lateral agencies, novel institutional arrangements, partnerships involving various actors, loose coupling strategy for creating partnership, that are trying to provide the needed incentive for drug research in neglected diseases. These different arrangements and involvement of varied actors and stakeholders are examined below.

International Organisations

WHO (Special programme for research and training in Tropical Disease, Green Light Committee- MDR-TB programme); Gates Foundation (Funding for drug development in Leishmaniasis; purchase commitment for new vaccines); MSF- Medicins Sans Frontiers; Clinton Foundation were identified as major players involved with Indian firms,
research organisations and government. Gates foundation has created competitive funds for addressing research in global diseases with specific emphasis to neglected disease. The objective is to attract firms/researchers with innovative projects to work on disease research that may not be mainstream but can make a major difference to health of a large population. For example, Bharat Biotech, a dedicated Indian biotechnology firm has been given grants to develop two new vaccines targeting malaria and rota-virus infection.

MNC Involvement

Different motivations are leading pharmaceutical MNCs to get involved in drug development for ‘neglected diseases’. This may be a ‘goodwill strategy’ similar to one posited by Grace (2004) while examining MNC’s approach to develop drugs for neglected disease in China with the primary motive to gain foothold in the lucrative Chinese market. Among the major MNC involvements in India is Eli Lilly involvement in the MDR-TB programme. The partnership involves the international organisation ‘the Green light Committee’ of the WHO and the US Department of Health. The Italian pharmaceutical firm Farmitalia has transferred technology of its Leishmaniasis drug candidate molecule for further chemical trials and has extended the manufacture to the Institute for One World Health via WHO. Roche has transferred technology of various malaria products to “Medicines for Malaria Venture”. Chiron vaccines, in joint venture with Aventis and in alliance with the Indian firm Panacea Biotech are undertaking R&D for ‘rabies’ vaccine. Astra Zeneca is undertaking R&D in India for target discovery research in tuberculosis.

Novel institutional arrangements

For the past two decades, policy makers, donor agencies and health organizations have been deliberating on the ways to align research and the product profile of drugs to the needs of patients. Lately a new kind of drug research model has been gaining ground especially in drug development for neglected diseases. The premise of this model is based on large scale collaboration structured through tasks and functions rather than hierarchical commands as prevalent in academia and industry (Maurer, 2007). Collaborative efforts are expected to reduce the time
spent in the conventional drug discovery process and provide dedicated funding for research. This model borrows from ‘open innovation’ model which can be understood as the antithesis of the traditional vertical integration model where internal R&D activities lead to internally developed products that are then distributed by the firm (Chesbrough, 2003) and the ‘invisible college’ concept of Wagner (2007). Open innovation extends the concept of open source further, by articulating a business model as source of both value creation and value capture. It exploits among others the concept of loose coupling strategy (Brusoni et al., 2001) wherein actors are linked together with a common purpose and value constellations (Norman and Ramirez, 1993) which again highlights the linked concept but with a central node acting as key driver. A parallel view of this concept in science is articulated by Wagner (2008); she talks of a new structure of science whose central thesis is global network of researchers- an ‘invisible college’ and uses cases studies to demonstrate how scientific breakthroughs are increasingly the result of collaborative research.

Two variants’ of this model in India can be seen working for drug development in neglected diseases (i) The Drugs for Neglected Diseases Initiative and (ii) Open Source Drug Discovery Project (OSDD).

The DNDi Approach: This novel partnership involves different actors leading to a new institutional arrangement- a loose coupling with a strong mission oriented objective. The ICMR along with four other international medical research organisations formed in 2003 an independent, not-for-profit entity, the ‘The Drugs for Neglected Diseases initiative (DNDi)’. Along with the ICMR the other partners in DNDi are - the Malaysian Ministry of Health, the Kenya Medical Research Institute, the Oswaldo Cruz Foundation Brazil, and the Institut Pasteur - as well as an international humanitarian organisation, Médecins Sans Frontières. The UNICEF/UNDP/World Bank/WHO’s special programme for research and training in tropical diseases (TDR) is a permanent observer. The DNDi also has partnerships with firms/drug majors such as GlaxoSmithKline (GSK), Sanofiaventis. With a current portfolio of 18 projects, the DNDi aims to develop new, improved, and field-relevant drugs for neglected diseases, such as malaria, leishmaniasis, human African trypanosomiasis, and Chagas disease that afflict the very poor in developing countries. In 2007, the DNDi delivered its first product, a
fixed-dose antimalarial "ASAQ" in partnership with Sanofiaventis. Recently, new treatment regimes involving combination therapies of three drugs- liposomal amphotericin B (AmBisome), miltefosine and paromomycin have been developed for visceral leishmaniasis in India. The trial of these drugs in Bihar, India was sponsored by DNDi (DNDi, 2011).

**Open Source Drug Discovery Project (OSDD):** This novel approach involves universities, research organizations, and private players in a collaborative mode with a central driving institution. It also has a global research alliance that consists of governmental, non-profit organizations bodies across the world supporting it (CSIR, 2008). The central driver of this network is CSIR (a public funded Indian scientific research organisation with 37 laboratories covering natural and engineering sciences) that initiated this network in 2008.

Operationally, the OSDD is inspired by the Wiki model, a web portal which allows the OSDD community to contribute and share the data and the entire information is available as ‘protected collective information’. Web portal has been set up to assemble data on the pathogens. The relevant laboratory process is performed in CSIR laboratories. The potential drugs are to be made generic after their discovery to ensure speedy introduction and low cost of medicines. The core committee would keep the entire activity in public domain to enhance transparency and to eliminate any forms of competition. The Government of India has committed 150 crores (US $38 million) towards this project. An equivalent amount of funding would be raised from international agencies and philanthropists. About 46 crores (US $12 million) have been already released by the Government of India. The first task taken up in the initiative was to develop drug for tuberculosis.

The first initiative was taken for TB as no new drug has been developed in the last fifty years inspite of this disease continues to be a major health hazard. The drug therapy for TB evolved around 1950s such as Isoniazid and Pyrazinamide in 1952, Esthabetol in 1961 and Rifampicin in 1966, and no development in treatment has come up for more than half century(Paramasivan and Venkataraman, 2004). The OSDD programme for TB drug development is divided into two phases. The phase one (2008-12) will focus on new chemicals (primarily on drugs against TB bacillus (Mycobacterium tuberculosis)) and phase two (2012-2017) will include preclinical and clinical trials of drugs.
Under this initiative, so far TB genome has been mapped and a group of researcher have found out an inhibitor that binds multiple targets of M. Tuberculosis to make it an effective bactericidal (Ibid). In addition, About 20 Mtb-derived antigens found in the early stages of the infection have been identified and are now under evaluation as potential vaccines for TB. CSIR has also proposed to apply open source model for malaria research with global participation. This approach will have wet lab approaches in addition to the collaborative and computational components (Ministry of Science and Technology, 2011).

8. Conclusions and Lessons Learned

The study highlights the need for ‘novel’ initiatives to stimulate drug research in ‘neglected diseases’. Firm centric approach will not bring the desired results, as a major lesson one learns from the case study of India. India firms have similar motivations and approaches as their counterparts in the West, the only major difference being their financial restrictions. Thus, firms are not interested in drug development for ‘neglected diseases’ on its own. Indian firms are currently shifting from plain vanilla generics to specialty generics. Some big firms are also investing in NCE and trying to license molecules at the early stage to a drug major. However, their research and product development are targeted towards lifestyle diseases anticipating big profits by exporting in western countries. This is the mainstay of survival of Indian firms. The urban disease pattern of India includes diseases prevalent in the North. The Indian firms are also targeting this lucrative segment. Firms are involved in drug research for ‘neglected diseases’ only when there are other incentives.

Public-private partnerships, involvement of international foundations, partnerships with drug majors are major stimulants. But this involvement requires novel initiatives, new business models to be developed so that it makes the partnerships strong and lead to deliverance and can help bridge the ‘translational gap’ i.e. gap between academic research and product development. This study has presented some of the approaches/models which could be effective. Different variants of the ‘open innovation’ model are the mainstay of both the programmes that seems most promising DNDi and OSDD. The paper calls for novel initiatives like this to address drug research for neglected disease,
allowing a different approach than the firm-centric model for drug development.

It is useful to look at other country’s approach which can be future research in this direction. For instance Brazil has opted for a procurement policy as a key strategy for a targeted progress to address the needs of its population. In this context it has articulated public buying policies and a law on innovation in 2004 which strengthens the procurement process and supports domestic industry. This policy has been very affective for stimulating vaccine research and development in Brazil (de Brito Cruz and Chaimovich, 2008). It combines seed stage financing and further support to the domestic industry to be involved in areas that may not be lucrative to private firms. Making this procurement policy as a legal act makes it more affective.

Notes

1 Seed financing is a step upon the funding ladder and is designed to bridge a gap between pure research and the product development stage. It provides researchers with sufficient resources to develop their ideas (research) to a stage where it can be taken to the next stage of development by firms. It makes the firm with less uncertainty of the viability of the research for the product and thus makes them more attracted to get involved in varied ways.

2 PCT acts as single office, an international depository, for filing in multiple countries. Thus PCT filing in a particular technology is a good indication of inventive activity in a said technology field/area.

3 US is the most important technology market and thus, US is generally first choice for patenting and future exploitation of their technology.

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