Chapter 4
R&D Crisis in Pharma for Neglected Diseases – Scope for an Open Source Approach

Pharmaceutical R&D begins with the basic research to understand a particular disease and its conditions. Once this understanding has reached a critical point, research shifts to the discovery or synthesis of a molecule that will influence or palliate the disease condition and thus has the potential to be a medicine. This involves finding out of how and where a disease or condition can be successfully attacked. The development part of pharmaceutical research has a pre-clinical and clinical stage. In the pre-clinical stage potential drug candidates are studied for their effect on animals. Drug candidates that qualify this stage will be taken to the clinical stage where they will be tested on humans. The entire process is indeed very complex, expensive and the success rates are very low. According to Pharmaceutical Research and Manufacturers of America (PhRMA) the average cost to develop a new medicine is estimated to be around US $ 2.6 billion\(^1\). Pharmaceutical industry has asserted that only one in five thousand of the potential drug candidates that are put through these stages, make to the market\(^2\). The recent years has seen the industry propounding a theory of R&D Crisis. The 2011 Oliver Wyman report interestingly divided the history of drug discovery from 1996 to 2004 into Era of abundance (1996-2004) and Era of scarcity (2005-2010) characterized by a fall in drug approvals by 40 percent\(^3\). It is argued that over the period of time, pharmaceutical

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R&D has grown more complex that, the productivity challenge has become particularly difficult to overcome. They point out that, productivity in drug discovery research has experienced a down turn since 1990's. From 1998 to 2008 the number of 'new molecular entities' approved per year has declined.

Pharma funded researches have tried to statistically establish that in spite of the rate of introduction of new molecular entities remaining low, drug discovery costs have increased like never before. They say, after 2005 Industry R&D spending has skyrocketed to an average of US $ 125 billion per year compared to US $65 billion per year in the era of abundance. The January 2010 issue of the Morgan Stanley report even advised the pharma companies to exit research and create value by reallocating the R&D capital into in-licensing of external innovations. Some scholars are of the view that this is because easier targets has been exhausted making the drug discovery research much more complex and thus raising the bar for future research. Some economists propose the view that this is the result of industry's shift in focus towards riskier and larger market targets which are characterized by high uncertainty and difficulty, but lower expected post launch competition. This reorientation of investment is thus pointed out as the reason for most of the recent decline in productivity. But despite this theory of crisis, it is interesting to note that the big

4 Fabio Pammolli, Laura Magazzini and Massimo Riccaboni, ‘The Productivity Crisis in Pharmaceutical R&D’ (2011) 10 Drug Discovery 428
5 Fabio Pammolli, Laura Magazzini and Massimo Riccaboni, ‘The Productivity Crisis in Pharmaceutical R&D’ (2011) 10 Drug Discovery 428
11 Fabio Pammolli, Laura Magazzini and Massimo Riccaboni, ‘The Productivity Crisis in Pharmaceutical R&D’ (2011) 10 Drug Discovery 428
pharma industry continues to be one of the most research intensive and profit making industry in the world. In 2014 with FDA’s approval of 41 new drugs in United States, the biopharmaceutical industry achieved the highest number of approvals in over a decade\textsuperscript{12}. The global pharmaceutical sales crossed the $1 trillion mark by the end of 2014\textsuperscript{13} and it is predicted that the global life science R&D spending would increase by 1.8% in 2016\textsuperscript{14}. According to Pharmaceutical Research and Manufacturers of America, around 7000 medicines are currently being developed around the world and their members had invested $51.2 billion for R&D in 2014 alone\textsuperscript{15}.

Writers like Light and Lexchin had countered the R&D crisis theory and criticized it as a strategy to influence politicians and press for attracting a range of government protections from free market and generic competitions\textsuperscript{16}. They say that the real innovation crisis is that the pharmaceutical research and development turns out mostly minor variations on existing drugs and most new drugs are not superior on clinical measures. Some studies point to the fact that about 85-90\% of all new drugs provide few or no clinical advantages for patients and even result in considerable harm\textsuperscript{17}. Moreover heavy promotion of these drugs has resulted in over use and accounts for as much as 80\% increase in medical expenditure\textsuperscript{18}. Many industry

\begin{itemize}
\item \textsuperscript{12} Thomson Reuters, ‘2015 CMR International Pharmaceutical R&D Factbook’ (Reuters 2015).
\item \textsuperscript{13} Thomson Reuters, ‘2015 CMR International Pharmaceutical R&D Factbook’ (Reuters 2015).
\item \textsuperscript{15} Pharmaceutical Research and Manufacturers of America, ‘2015 Biopharmaceutical Research Industry Profile’ (PhRMA 2015).
\item \textsuperscript{18} D. W. Light and J. R. Lexchin, ‘Pharmaceutical Research and Development : What do we get for all that money’ (2012) 345 BMJ <http://www.bmj.com/content/345/bmj.e4348.long> (accessed 3 March 2016).
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observers had cited the lack of quality internal innovations as the main reason for this decline in productivity. In 2015, Deloitte even published a report on executing open innovation model to increase productivity in pharmaceutical industry. Now there exists a wide perception that success cannot be grounded solely on internal innovations and external innovations also need to be relied for long term success. Empirical studies have already exposed that about 54% of late stage pipeline of big pharma has been acquired from external sources. Pharma industries have now understood the importance of implementing the right R&D model that can accommodate external innovations as well. Open source as a business model, will offer the pharmaceutical industry the possibility of using external innovations to generate value. But the complexities of implementing such a model are many. It includes challenges in building a workable architecture, handling virtually dispersed R&D, modeling incentives for contributors, establishing a governance system and managing of intellectual property. Particularly, the most difficult challenge would be to identify a research focus which will interest the pharma industry and the potential contributors alike. The R&D crisis in drug discovery for neglected diseases would be the best opportunity to break away the shackles of closed innovation model and experiment with the potentials of an open source development methodology in pharma.

4.1 The R&D Crisis in Pharma for Neglected Diseases.

Empirical studies have pointed out that five diverse groups of medical conditions accounts for about 70% of the global disease burden. Infectious diseases at 31.01%, Mental conditions at 12.85%, Injuries at 12.24%, Cardiovascular disease at 9.25% and obstetric conditions at 8.64% contributes to this significant

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19 Deloitte Center for Health Solutions, ‘Executing an Open Innovation Model: Cooperation is Key to Competition for Biopharmaceutical Companies’ (Deloitte 2015).

Some of these medical conditions afflict the developed countries and the developing countries alike. Diseases that are prevalent in developed countries had triggered medical innovation as the affected population or their governments have the capacity to pay. Infectious diseases like HIV-AIDS, TB and Malaria are prevalent in both developed countries and developing countries. Thus at-least, limited R&D activities happen for these diseases, even though it is often insufficient considering the disease burden. But even in case of such diseases there exist a bigger problem of access, as the drug pricing and lack of local availability makes them inaccessible for patients of the developing world. There are certain other diseases which are prevalent mainly in the developing world. Some of these diseases cause social, economic and cultural distress for the developing world. These neglected diseases affecting mostly the poorer sections of developing countries generate little financial interest for pharmaceutical industry. Neglected diseases are medically diverse group of communicable diseases that prevail mostly in developing countries and affect more than one billion people living in poverty, without adequate sanitation and in close contact with infectious vectors.

It is estimated that more than 1 billion people around the world, which amounts to one-sixth of the world’s population are affected by one or more neglected tropical diseases. At least 2 billion people living in the tropics and sub-tropics are at risk of infection. They are caused mainly by infectious pathogens such as viruses, bacteria, protozoa and helminthes. These infections remain largely untreated due to lack of effective and affordable treatments. As most of the affected population lives in poor countries of developing world, even their governments are incapacitated to

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develop or fund development of adequate therapeutic interventions. Various international organizations have classified neglected diseases differently. World Health Organization has prioritized 17 neglected tropical diseases for developing combat measures. Buruli Ulcers is a chronic skin disease occurring most commonly in rural sub-Saharan Africa. But some reported cases exist in Asia, Western Pacific and Americas. About 5000 new cases are being reported annually from about 15 countries with tropical and subtropical climates. The incidence is high in countries like Ghana where it has been estimated at 150 cases per 100000 populations. There exists an immense necessity to develop an ideal diagnostic kit for direct detection of mycolactone in human tissues\textsuperscript{24}. This may offer a simpler and faster way to confirm suspected cases of Buruli Ulcer and begin treatment\textsuperscript{25}. It is estimated that about $4.3 million per year will be required during 2015-30 for active case finding, diagnosis, treatment and care including medicines. Chagas disease which is caused by infection from a protozoan parasite Trypanosoma Cruzi affects mostly people living in continental Latin American countries. It is estimated that 7 to 8 million people, mostly in Mexico, Central America and South America have Chagas disease as on 2013\textsuperscript{26}. This disease remains as one of the biggest public health problems in Latin America, where it causes more than 7000 deaths per year as well as lifelong morbidity and disability. As of now two medicines, Benznidazole and Nifurtimox are available to treat T. Cruzi infection. But unfortunately there exist no vaccine for Chagas disease. Along with this WHO has identified development of diagnostic

\textsuperscript{24} World Health Organisation, Investing to Overcome the Global Impact of Neglected Tropical Diseases: Third WHO Report on Neglected Tropical Diseases (WHO 2015) 74.


\textsuperscript{26} See for more information on Chagas disease and WHO response measures \textless http://www.who.int/mediacentre/factsheets/fs340/en/ \textgreater (accessed 16 January 2016).
tools, their assessment and optimization of drug dosages as research priorities\textsuperscript{27}. Dengue is a mosquito borne viral disease which results in 3000 deaths every year. Economic burden of this disease is estimated in billions of dollars. A recent study indicated that 390 million new dengue infections are reported per year\textsuperscript{28}. Development of high quality diagnostic kits and preventive medicines are research priorities. Endemic Treponematoses, comprising Yaws, endemic syphilis and pinta result from infection with a bacteria of the genus 'Treponema'\textsuperscript{29}. Children between the age 4-12 years are the worst affected by this disease. It can result in permanent disfigurement, crippling disabilities and deformities. Development of adequate therapeutic measures is a research priority for this disease.

Human African Trypanosomiasis or Sleeping Sickness which is caused by infection with protozoan parasites of the genus trypanosoma affects mostly people living in impoverished rural areas of sub-Saharan Africa. This disease may become fatal if not correctly diagnosed and treated. It is expected that active case finding and treatment may require investment of about US $ 13.5 million per year during 2015-2030. The research priorities are development of a new generation diagnostics test and oral medicines that are easy to use and active against all forms of the disease\textsuperscript{30}. Visceral Leishmaniases caused by protozoan parasites are fatal within two years if left untreated. It is prevalent in about 98 countries spread across five continents. Approximately 1.3 million cases are being reported annually. It affects mostly people belonging to the lowest socio economic groups. An effective vaccine to prevent infection and transmission of this disease is an urgent requirement. Other


research priorities include development of rapid diagnostic kits, new therapeutics and easy to apply treatments. Lymphatic filariasis is caused by infection of filarial nematodes. It is estimated that about 120 million people around the world are infected with filarial parasites\textsuperscript{31}. Development of new medicines and new combinations of existing medicines effective at killing or sterilizing adult worms are a vital necessity\textsuperscript{32}. Onchocerciasis or River blindness is caused by infection with filarial nematode. It is estimated that around 37 million people are infected with this disease. About 99\% of these victims live in Sub-Saharan African countries. The research priorities include development of new diagnostic tools and more effective therapeutic interventions\textsuperscript{33}. Rabies is an infectious viral disease which is almost always fatal following the onset of clinical signs. Rabies causes tens of thousands of deaths annually. About 90\% of this happens in Africa and Asia. WHO has identified the development of thermostable vaccine and antiviral drugs as research priority\textsuperscript{34}. Schistosomiasis is a parasitic disease caused by blood flukes of genus schistosoma\textsuperscript{35}. Development of sensitive and specific diagnostic tests and discovery of new medicines are research priorities. Soil transmitted helminthiases are a group of diseases caused by intestinal parasites. WHO estimates that about 875 million children require annual treatment with preventive chemotherapy\textsuperscript{36}. There exists an immense necessity to develop adequate medicines. Trachoma caused by infection Chlamyda trachomatis, accounts for about 3\% of all cases of blindness worldwide. It


\textsuperscript{34} World Health Organisation, *Investing to Overcome the Global Impact of Neglected Tropical Diseases: Third WHO Report on Neglected Tropical Diseases* (WHO 2015) 149.


is estimated that more than 21 million have active Trachoma and about 7.2 million require surgery. Development of alternative diagnostic strategies and medicines are the immediate research priority.

These diseases represent an enduring medical need as they face a lack of effective, affordable and easy to use treatments. Neglected diseases affect one in six of the world’s poorest and marginalized people including 500 million children. These infectious diseases account for about ten million deaths each year, of which more than 90% occur in developing countries. According to the WHO health report 2000, most of these infectious and parasitic diseases are preventable or treatable. Even though these diseases create large burden in developing countries there exist insufficient therapeutic products to treat them. Some of these diseases have preventive measures and medical treatments available only in the developed world and which are unaffordable and unavailable in poorer regions. Unavailability of appropriate drugs, high cost of existing drugs and lack of on-going R&D into these diseases are major challenges in combating them. Out of the 850 new therapeutic products registered in the period 2000 to 2011, only 37 i.e., 4% were indicated for neglected diseases. Currently there are about 40 active researches working to identify or develop new drugs to combat neglected diseases. The total combined global R&D investments by the public, philanthropic and private sectors in neglected disease research in 2010 was approximately $ 2.4 billion. This accounted for only 1% of overall health R&D investments. The level of funding for neglected diseases is the biggest challenge in the way of combating neglected diseases. See <https://www.msfaccess.org/our-work/neglected-diseases/article/956 > (accessed 21 January 2016).


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diseases R&D has remained constant without any significant increase since 2010. Despite the increasing demand from the developing world for new therapeutic products, the neglected diseases R&D has not achieved any significant progress. There is an immense necessity for disease specific research plans with more focus on drug discovery. Considering the health burden of neglected diseases, there exists a clear imbalance in the R&D investment available for neglected diseases compared to the overall global R&D investment in pharmaceuticals.

4.2 Failure of Formal IP Model in Incentivizing R&D for Neglected Diseases.

The pharmaceutical industry is one particular sector where significant investment and effort is required to innovate successfully. Among the 5000 to 10000 experimental compounds considered during the R&D stage, only one may gain the drug regulator's approval, that too after spending an average of more than ten years and costing around US $ 2.6 million \(^{40}\). Indeed, the pharmaceutical research happens under a very challenging business model. The role of formal intellectual property model in pharmaceutical industry is to fuel innovation by providing financial incentives. It protects the economic interest of pharma companies by ensuring market exclusivity that will facilitate recouping of investment and generation of profit. Without intellectual property protection, competitors can simply copy the innovations as soon as they are proven safe and effective thereby generating profit without investing time and money \(^{41}\). It also enables the pharmaceutical companies to secure funding for future research. PhRMA argues that strong intellectual property right protection and fair and transparent market access provide powerful

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\(^{40}\) PhRMA uses these figures to show that biopharmaceutical companies operate under a challenging business model. See for more details <http://www.phrma.org/innovation/intellectual-property> (accessed 30 January 2016).

incentive that drives and sustain investment into pharmaceutical R&D\textsuperscript{42}\textsuperscript{43}. They justify this by pointing out that only two out of ten medicines will recoup the investment made on R&D and the intellectual property law facilitates this by ensuring market exclusivity. Thus the patent law guarantees profit at least in cases where research and development hits a target successfully. Pharmaceutical industry is of the view that patents promotes competition and thus provides greater treatment options. It is also argued that patents promote faster access to new medicines. An interesting study points out that pharmaceutical companies are launching their products sooner in countries where there is effective patent protection and enforcement\textsuperscript{44}. The industry has always lobbied for stronger intellectual property protection and promotes the view that strong intellectual property protection provides essential incentives to invest in biopharmaceutical sector\textsuperscript{45}. But an implied assumption behind this theorem is that intellectual property system is going to work in an economic and technological context where they can induce innovation\textsuperscript{46}. Such a system may incentivize innovations in developed countries where there exist industries with sufficient economic and technological capabilities and also a market rich enough for recoupment of investment. But the same may miserably fail in low income countries with no technological capability and lacking a profitable market.


\textsuperscript{43} Pharmaceutical Research and Manufacturers of America, ‘Special 301 Submission’ (PhRMA 2016) 5.


The problem with formal intellectual property model is that it subordinates the global public health necessities to commercial interests of pharmaceutical industry. It fails in encouraging development of new medicines for neglected diseases, as it focuses more on market demands and not on societal needs. Thus the development of 'me-too' drugs that produce incremental health improvement in a large number of people living in developed world, offers better financial rewards than developing innovative medicines that produce major improvements in patients of neglected world\textsuperscript{47}. The neglected diseases which heavily burdens the developing world is seen as a resource limited market which is less lucrative from an economic perspective. The cardinal problem with intellectual property model is that innovation incentive is directly linked to market exclusivity and drug pricing. The entire model is based on granting of market exclusivity for a limited period of time which allows the industry to price heavily and make profit. The incentive to innovate is directly linked to the returns based on number of units sold in the market. This actually provides companies with enormous incentive for aggressive marketing rather than innovating in new areas. There exist statistical evidence as to pharma companies spend only 1.3% of their revenues to discover new molecules\textsuperscript{48} where as they spent as high as 25% on promotion and marketing\textsuperscript{49}. The current patenting system fosters the development of expensive medicines that are marketable in a crowd having the capacity to pay and completely discourages pharmaceutical companies from venturing into neglected diseases research. This is because neglected diseases are not perceived as a commercially viable market as the developing world is impaired of the purchasing power to afford such treatments.


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World Bank had reported that eliminating communicable diseases would almost completely level the mortality gap between the richest 20% of the world population and the poorest 20%\(^50\). But the current model of pharmaceutical R&D based on intellectual property rights had failed to advance research to these neglected areas. Available statistics points out that 90% of global investment on health research is spent on health problems of less than 10% of world's population\(^51\). The developing world which accounts for 80% of the world population represents barely 20% of drug sales\(^52\). The landscape of pharmaceutical research, that is expected to cater the needs of 7 billion populations around the world, is spread across universities, research institutes, clinical research in hospitals and the drug discovery and development in pharmaceutical industry. But the economic arguments for the sustenance of a patent based innovation incentive are often centered on the statistics limited to pharmaceutical industry. This is partly because of the heavy reliance placed on multinational drug industry to deliver new medicines. Contrary to industry propaganda, the most creative part of drug discovery research which is the in depth study on disease conditions, is always carried out at universities and government research labs\(^53\). At the same time it is interesting to note that more than four fifths of all funds for basic research to discover new drugs and vaccines come from public sources\(^54\). In some cases, universities and research institutes become part of even advanced drug development research. To harness profitable innovations


\(^53\) Marcia Angell, MD, The Truth about the Drug Companies – How They Deceive Us and What to Do about it (Random House 2004) 23.

from public funded research, law had adapted in certain jurisdictions and started to encourage patenting\textsuperscript{55}. In United States, pharmaceutical companies actively collaborate with public funded research institutes and view them as the main source for in-licensing of innovations. Certain studies points to the fact that, highly innovative drug discovery research happens mainly in public funded research institutes and pharmaceutical companies only acquires them, secures the regulatory approval and develop them into a marketable product\textsuperscript{56}. This new landscape of pharmaceutical research provides new thoughts as to the development of possible alternatives in a situation where formal intellectual property right model had failed to deliver result. Even WHO had raised the issue of failure of contemporary intellectual property incentives in facilitating drug discovery for neglected diseases and the need to look for alternatives\textsuperscript{57}. Around the world several models have been proposed as an alternative to trigger drug discovery into neglected diseases. Some of the models completely denounce intellectual property rights while some others innovate on its newer uses to effectively engage and collaborate with different stakeholders. However, the success of an alternative model of drug discovery depends on becoming a viable alternative by incentivizing innovations into neglected areas and at the same time resolving the access issues caused by intellectual property model.

4.3 Alternative Models for R&D in Neglected Diseases.

Traditionally there has been a huge reliance on the pharmaceutical industry to develop new drugs and make them available to the patients. This has been so even while the universities, research institutes, hospitals and government labs which

\textsuperscript{55} For example the Bayh-Dole Act of United States introduced to regulate the ownership of inventions made with federal funding allowed private industry to acquire and own inventions developed by Universities and research institutions.

\textsuperscript{56} Marcia Angell, MD, \textit{The Truth about the Drug Companies – How They Deceive Us and What to Do about it} (Random House 2004) 25.

receive substantial public funding played a significant role in the early stage drug discovery research. Pharmaceutical industry has always more concentrated on the product development part leaving the basic scientific research to public funded institutions. Intellectual property law allowed the pharmaceutical industry to claim exclusive monopoly rights for their products and thus control the market. It also facilitated the industry to acquire by in-licensing and own potential researches from public funded institutions. The market exclusivity enabled the industry to amass huge profit and thus establish substantial control over the global public health landscape. But in the post-TRIPS era, world began to increasingly realize the public health crisis that the intellectual property led pharmaceutical research model has created. It had completely failed to address the public health needs of developing world while concentrating drug discovery research to areas having market potential. This resulted in the emergence of new organizations and movements which attempted to develop alternative models for pharma research with an objective to cater the needs of developing world. By 2005, Medicines for Malaria Venture (MMV), Global Alliance for TB Drug Development (TB Alliance), Drugs for Neglected Diseases Initiative (DNDi), Institute for One World Health (iOWH) and the World Health Organization’s Special Programme for Research and Training in Tropical Diseases (WHO/TDR) together accounted for about 75% of all neglected diseases drug discovery research projects\textsuperscript{58}. Different organizations had divergent research priorities based on which they developed and proposed different alternative models. CEWG had evaluated many of these proposals and emphasized their importance in accelerating research on neglected diseases\textsuperscript{59}.

\textsuperscript{58} Rebecca Goulding and Amrita Palriwala, ‘Patent Pools: Assessing Their Value-Added for Global Health Innovation and Access’ (Results for Development Institute 2012) 40.

Orphan drug schemes is one such alternative model which aims at promoting development of drugs to treat diseases that affect relatively few people.\textsuperscript{60} This scheme provides for extended market exclusivity to drugs developed for orphan diseases. This allows pharmaceutical companies to recoup investment from drug pricing even if the target population is less. The experience from implementation of The United States Orphan Drugs Act of 1983 shows that there has been a tenfold increase in the rate of development of orphan drugs.\textsuperscript{61} The pharmaceutical industry perceives this model as a highly successful one and even advocates its expansion into neglected diseases. Even though this model may increase availability of drugs for some neglected diseases, its equity and distributive impact is difficult to be assessed.\textsuperscript{62} The fundamental problem with this model is that the incentives for drug discovery are directly linked to extended market exclusivity and drug pricing. This will lead to increased drug prices making it unaffordable for the less privileged. It may even result in large increases over previous prices of the same product. Orphan drug schemes work with the assumption that the targeted population have the capacity to pay. But the case of neglected diseases is totally different and consideration of recouping investment from drug pricing is out of question. Transferable Intellectual property rights (TIPR) is another proposed alternative which incentivizes innovation in neglected areas by extending market exclusivity for an unrelated product in a developed country market.\textsuperscript{63} This is severely criticized for blocking of generic entry and for resulting in huge increase of drug prices which will detrimentally affect the interest of under privileged patients in developed country markets. This model also fails in evolving as a workable alternative.


Prize fund model aims at replacing market exclusivity of new innovations with monetary rewards called as prizes. The quantum of monetary rewards is calculated based on the therapeutic value of the innovation. Since the governments already pay the cost of much drug discovery research directly or indirectly, it is expected that they can finance the prize fund which award big prizes for developers of drugs for neglected diseases\textsuperscript{64}. This can be complemented with foreign assistance budgets and private donations. The prize fund model can be of two types. Milestone prizes are rewards for reaching specified milestones in R&D process while end prizes are rewards for reaching specified end targets. This model can resolve some of the problems of intellectual property model as drug pricing is completely de-linked from R&D expenditure. It also offers the possibility of redirecting the R&D activities towards public health priorities by incentivizing them with rewards. The rewards schemes under this model can even specifically target priority research areas and attract contributions. Thus the prize fund implementing agency can set a high value on products that would have correspondingly high public health impact.

The principal purpose of this model is to de-link the cost of R&D from product prices so as to promote accessibility\textsuperscript{65}. To achieve this objective, the prize fund implementing agency must be able to put certain obligations on the prize holders to promote availability and affordable access. These obligations may include renouncing of intellectual property rights, permitting of open access, technology transfer and price control. A major drawback of this model is that it is always dependent on external funding. It is also based on the assumption that substantial governmental and non-governmental resources are available to fund research.


Innocentive is one working model that facilitates prize fund scheme. Its platform allows commercial organizations and government agencies to propose challenges that can be crowd sourced. The Bill and Melinda Gates foundation and DNDi have also successfully attempted this model. Prize funds if implemented with adequate financial back up and in right direction, have the potential to redirect our scarce research resources towards more efficient uses and ensuring that benefits of that research reach people who are currently deprived of them.

Green Intellectual Property is another proposed alternative to patent system. It is suggested as a reformed patent system which would divert a part of the patent related monetary flow towards a monetary pool for financial aid in developing countries. Its peculiarity is in finding financial resources from within the current intellectual property model. It proposes to create a GIP trust fund by diverting a part of the patent related monetary flow in the form of budgetary reserves, taxes and premiums. This monetary fund will be used to support R&D activities for neglected diseases. This proposal relies heavily on the current intellectual property based pharmaceutical model to generate funds. A major demerit of this model is incidental increase in prices for patented medicines. This will result in new medicines becoming inaccessible and unaffordable. Patent pools is another highly

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advocated alternative model to facilitate drug discovery research for neglected diseases. The primary assumption behind this model is that the exclusivity element of intellectual property rights is blocking downstream innovations and makes drugs unaffordable. Patent pools are created by intellectual property holders like companies, universities, researchers and government institutes who voluntarily offer to license their patent to a pool under certain conditions. The participants may include distinct groups of patent holders and users interested in accelerating drug discovery and delivery for neglected diseases. The objective of patent pools is to facilitate the availability of new technologies by making patents and other forms of intellectual property rights more readily available to entities other than patent holders. Any drug manufacturer interested in using a patent can obtain the license by either paying a royalty fee to the consortium or by agreeing to the price control obligation imposed by the donors. Patents pools are expected to create adequate incentives for the drug manufacturers to access the pool and develop new drugs. This model has nothing to directly incentivize drug discovery research. But the patent pool platforms may enable increased access to research data which may serve as base materials for further research. Patent pools also offers the universities and individual researchers the advantage to more effectively engage with the pharmaceutical industry and take newer products to market. Pharmaceutical industry, universities and public health groups have shown interest in this model. Medicines Patent Pool (MPP) created by UNITAID and Pool for Open Innovation floated by GlaxoSmithKline are working examples. MPP has signed agreements with AbbVie, Bristol-Myers Squibb, F. Hoffmann-La Roche, Gilead Sciences, MSD, the NIH, and ViiV Healthcare for transferring their patents to the pool. These


patents have been sub-licensed\textsuperscript{75} to 12 generic manufacturers who manufacture the drug and make it available to patients. The Pool for Open Innovation has also attracted patent donations from GlaxoSmithKline, Massachusetts Institute of Technology, UC Berkely, Medicines for Malaria Venture (MMV) etc.

A comprehensive international framework under the auspices of World Health Organization for supporting priority medical R&D for developing countries is also being proposed\textsuperscript{76}. The underlying idea is that national governments would commit themselves to spending a certain proportion of their national income on medical R&D. CEWG report even concluded that all national governments shall commit to spent at least 0.01\% of GDP on government sponsored R&D efforts for neglected diseases\textsuperscript{77}. It is also suggested that this can be raised to 0.15 - 0.2\% in case of developed countries\textsuperscript{78}. It is expected that the treaty would setup a transparent, participative and effective governance structure for assessment of R&D gaps, priority setting and allocation of funds for enhanced R&D efforts. Such a mechanism for international governance will provide a comprehensive solution to the problem of underfunding and lack of global coordination of pharmaceutical research\textsuperscript{79}. The main focus of proposed framework is to involve all governments in setting priorities and coordinating and funding of R&D efforts with the objective to

\textsuperscript{75} See for more information <http://www.medicinespatentpool.org/ourwork/current-sub-licenses/ > (accessed 8 February 2016).


completely de-link the prices of medicines from cost of R&D\textsuperscript{80}.

It is interesting to note that the focus of most of these models is on alternative financing for drug discovery. The proposed incentive structures in most cases either rely on formal intellectual property or on some other economic incentives awarded or derivable from market. These models fail at making any substantial changes in the pattern of drug discovery research. They also continue to rely more on the pharmaceutical industry and fails in addressing the significant role which can be played by the enormous research potential that lies outside the constraints of market. This necessitates the development of new models, that can capitalize on the innovation capabilities that lies outside the industry. One such possibility is to reorganize the drug discovery research by organizing an open collaborative network. Such a model can rely on the principles of open source production methodology and can significantly change the current pattern of pharmaceutical research. But it all depends on how the collaborative network is organized by involving the individual scientists, research institutions and pharmaceutical industry.

4.4 The Open Source Model for Pharma R&D

Beyond just sharing of source code, open source implies a set of cultural practices, collaborative production methodology with continuous peer-review and a licensing model which relies on a distinctive use of property\textsuperscript{81}. Its efficiency in coordinating collaborative creativity and providing concrete results is a proven fact in software industry. In scientific sectors also open source model has successfully demonstrated its ability to efficiently organize peer production, focusing on specific


research priorities\textsuperscript{82}. The non-proprietary initiatives like HapMap Project and SNP consortium\textsuperscript{83} evidences that open collaborative models are workable even in life science\textsuperscript{84}. Implementation of open source models in life science has resulted in development of genomic databases and many bioinformatics software, that can be freely used by follow-on innovators\textsuperscript{85}. Some writers have even opined that open collaborative models align closely with academic research as they embrace the notion that science is a communal enterprise\textsuperscript{86}. However, the replication of this model in drug discovery research will be a real challenge.

Even though open source has been adopted as a development model in many sectors, its real success as a viable business model was in software. Mozilla, Android and Linux are all examples of how successfully the model has grown. Interestingly there exist some similarities and many fundamental differences between the software development methodology and drug discovery research. But the advancement in computational chemistry and the use of computer-aided drug design in modern day pharmaceutical research create new relations between the two sectors. And certain aspects of pharmaceutical research like genome sequencing are easily amenable to open source development model\textsuperscript{87}. Just like software, drug discovery research also happens in a highly decentralized format. It happens in a

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phase by phase manner, separable into tasks which can be done by researchers organized in groups. At the same time there exist many significant differences in partitioning and distribution of tasks. It is interesting to note that the pharmaceutical industry is increasingly considering adopting the agile software development methodology into drug development. It is expected that the adoption of agile methodology can be effective by increasing efficiency and delivering quality output. All this evidences the underlying similarity between the sectors, despite several differences. The drug discovery research flows through different phases which are highly time taking and requires multiple domains of expertise. Software development gives quick results, while drug discovery research takes years to provide any material result. The advanced scientific knowledge required for drug discovery research is incomparable to the computing time of hobbyists required for software development. While the open source software development relies heavily on hobbyists, it would be a real challenge for open source drug development to attract contributors with adequate expertise. The real success of open source was in facilitating collaborative production and attracting volunteers to contribute without any economic incentives. The non-monetary motivational factors like ideology, personal satisfaction, chance to learn new skills, peer-recognition and possibility of impressing potential employers were sufficient in open source software development to attract contributors. How far these factors will succeed in attracting contributors for open source drug development is yet to be seen. Even though the intrinsic


motivational factors will still be effective, the additional incentives may have to be restructured to adapt to the context.

Open source software had the possibility of attracting user-programmers as the main contributors. This minimized the gap between developers and users thereby instilling a sense of community. But this won't be possible in case for drug development. A major advantage with open source software was the possibility of circulating pre-release versions with ordinary users. This allowed the developers to examine the user reception and make changes. Users also played a significant role in reporting bugs and defects of pre-release versions. This continuous engagement with users had contributed much for improving the quality of open source products. Open source model has also facilitated a distributed and transparent peer-review process. It ensured that new inputs are immediately reviewed, improved and accommodated into the main creation. Such an efficient peer-review system ensures quality of the final output. Drug discovery framework won't offer the possibility of this kind of continuous engagement and testing. The success of open source drug development is highly dependent on the incorporation of a distributed and transparent peer-review process into its model. Moreover, it is a highly lab intensive research. Unlike software, pharmaceutical research would require certain key infrastructures like lab equipment and advanced databases to facilitate computational drug discovery. They will be highly expensive equipment and facilities which only business enterprises and public funded research institutes can possess. On the other side the hobbyist programmer of open source software movement wasn't required to have access to any costly equipment for his participation. But there was a time when computational resources were highly expensive and only big corporates and universities possessed them. The open source

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movement had its origin in those days and it emerged as a successful model. Moreover, the costs of drug discovery are expected to reduce significantly due to the introduction of computational methods. This challenge can also be resolved by attracting participation of more academics and scientists who work in universities and research institutions and having access to expensive laboratory equipment.

Unlike software industry, legal regulations require that the products of pharmaceutical research can be taken to market only after extensive clinical trials and securing regulatory approval\(^93\). The safety and efficacy of new drugs has to be proved to the satisfaction of the regulator through clinical trials. Clinical trials are time taking process that requires enormous expenditure\(^94\). Even though open source development model is adaptable for drug discovery research, taking the drugs to clinical trial and securing of regulatory approval will be major hurdles. Current models of open source drug development expect to rely on pharmaceutical companies for taking the drug through clinical trial and securing regulatory approval. In that case, sufficient incentives must have to be developed to encourage participation in product development and commercialization. The open source licensing of drug discovery is also going to be challenging. Open source software developers relied on copyright to develop workable legal relations. Copyright based licensing was much effective as it didn't require registration and offered enough flexibility. But drug discovery results in 'inventions' which are protectable under patent law. Patents have to be secured through registration which is an expensive and time taking process. More over patent law presupposes that the invention is not made publicly available at least till the application for patent is made. But this conflicts with the fundamentals of open source model. Decisions on what to patent

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and when to patent will also create challenges as the entire drug discovery research is happening collaboratively. As patenting incurs significant expenses, it will result in additional burden for the community. Pharmaceutical industry relied heavily on patenting as it was important for their business model\textsuperscript{95}. They used the exclusive market monopoly to recoup investment and generate profit. But unlike proprietary model, open source drug development will have limited use with patents. Traditionally opens source communities used intellectual property based licenses to prevent enclosures of downstream innovations\textsuperscript{96}. Grant back clauses ensured that downstream innovations also have to be distributed in accordance with the open source license terms. But the use of grant back clause in drug discovery may face issues as it won’t be legally valid under patent law of some countries\textsuperscript{97}. Without grant back clause the chances for forking are high and the add-on innovations will not be available as open source. Thus the licensing choices of open source drug development have to be made very carefully. Even though the underlying idea behind open source is to generate value without substantial investment by relying on peer production, drug discovery is a very costly affair. Thus open source drug development will have to generate funding to sustain itself. Open source may face challenges as a viable economic model if it fails to generate funding and sustain itself. Despite these challenges open source methodology has already been adopted into drug discovery research. OSDD\textsuperscript{98} and Open Source Malaria (OSM)\textsuperscript{99} are

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\textsuperscript{95} For information on PhRMA’s approach to IP see <http://phrma.org/innovation/intellectual-property> (accessed 8 February 2016).

\textsuperscript{96} Most open source softwares have copyright-based licences which grant freedom to use, adapt and distribute the software. However, some open source licences will have a clause that requires that all the improvements and additions made to the source code by the user shall also be circulated under same license terms.

\textsuperscript{97} See, for example, The Patent Acts, 1970 (India), s 140(1)(d).

\textsuperscript{98} Open Source Drug Discovery (OSDD) promoted by India’s Council for Scientific Research operates an online collaborative platform available at <http://www.osdd.net> (accessed 12 February 2016) CSIR is premier R&D organization under the Government of India. It is one among the world’s largest publicly funded R&D organizations.

\textsuperscript{99} Open Source Malaria (OSM) is an open collaborative platform available at <http://opensourcemalaria.org> (accessed 12 February 2016).
working examples for open source development model in pharma.

Open Source Malaria (OSM) started with funding from Medicines for Malaria Venture (MMV) and Australian Research Council. Open Source Drug Discovery (OSDD) is promoted by India’s Council for Scientific and Industrial Research (CSIR). Both of them aim to pursue open source model of pharmaceutical research by operating a drug discovery platform and attracting participation of volunteers. OSM project operates on pure open source principles and follows a Creative Commons Attribution 3.0 Unported license. It is basically a copyright license that grants permission to share and adapt the work for any purpose including commercial use. Thus the research results developed by OSM can be academically and commercially exploited provided the project is cited. Majority of the work undertaken by OSM involves synthesis of compounds and developing them till Phase I trials. OSM mainly works on compounds which are put into public domain by pharmaceutical companies. The drug discovery research happens through crowd sourcing which is constantly updated into the portal. Experimental data is recorded online in a openly readable Lab Notebook. OSM completely denounces patenting and vows that ‘open project is bigger than, and is not owned by, any given lab’. On the other hand OSDD has developed its own licensing model. They intend to hold all information submitted by users and

100 More information on CSIR’s OSDD initiative is available at <http://www.osdd.net/about-us/funding> (accessed 17 February 2016).


102 Creative Commons Attribution 3.0 unported License can be accessed at <https://creativecommons.org/licenses/by/3.0/> (accessed 17 February 2016).

103 Open Source Malaria had worked on compounds put into the public domain by pharmaceutical companies like GlaxoSmithKline and Pfizer.

104 Open Source Malaria’s Lab Notebook can be accessed at <http://malaria.ourexperiment.org/> (accessed 17 February 2016)


results of collaborative research as 'protected collective information'. As per the license, the ownership of 'protected collective information' will belong to CSIR\textsuperscript{107}. The license also obligates user of 'protected collective information' to grant back any additions or improvements made to it. But there is no restriction on using it commercially or non-commercially by providing sufficient credits to the contributor. OSDD follows a micro-attribution system where by contributors will get rewards in form of credit points based on peer-review of their contributions\textsuperscript{108}. The OSM's open source model ends by putting the compound ready for clinical trial in public domain\textsuperscript{109}. It expects generic industry to secure regulatory approval and take the drug to market. But OSDD proposes to conduct public funded clinical trials involving public institutions. It intends to follow open source approach in clinical trials as well\textsuperscript{110}. Even though both these models have attained only limited success, they demonstrate the different possibilities of implementing open source methodology in drug discovery research.


Nobody would have imagined that it was possible in Capitalist economy to have a mode of production based on voluntary labor, without private control and ownership. Moreover open source emerged successful in software industry which is seen as one of the most complex research intensive sector of our times\textsuperscript{111}. Open source has the ability to efficiently organize peer-production and thereby direct

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\item[110] See for further information on OSDD’s policy on clinical trials <http://www.osdd.net/about-us/osdd-policies/approach-to-clinical-trials> (accessed 17 February 2016).
\item[111] Stephen M. Maurer, ‘Open Source Drug Discovery: Finding a Niche (or Maybe Several)’, (2007) 76 UMKC Law Rev 405
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creativity even into areas where market has failed. It is a proven fact that open source can facilitate effective utilization of available resources. If introduced into drug discovery for neglected diseases, open source can certainly make a difference with its alternative model of product development. It can facilitate collaborative research which suits well with the methodology of pharmaceutical research. As the scientific community in universities and public funded research institutes has traditionally contributed to drug discovery research, open source model should be able to attract them as voluntary participants. The crisis in R&D for neglected diseases and the incidental public health challenge are sufficient ideological motivations to attract contributors. As open source research happens through an open collaborative platform, it increases the ability of researchers to access critical research data and creativity of others. Thus open source ensures technology dissemination and increases the capacity of developing countries to engage in pharmaceutical research. Working in open source reduces drug development cost and accelerates research. This collaborative drug discovery model truly has the potential to change the current pattern of pharmaceutical research.

The key factor that deterred pharmaceutical companies from venturing into neglected diseases research was their intellectual property based business model. In this model, pharmaceutical companies rely upon market sale to recoup investment and generate profit. Here the drug pricing is directly linked to the business model of pharma. This often results in the drug becoming inaccessible to the patients of the developing countries. This also results in limiting drug discovery research to diseases which affect the population having the capacity to pay. Thus in sectors like neglected diseases where market exclusivity has no purpose, pharmaceutical companies will have to look for alternatives. In this context it is interesting to note that pharmaceutical companies are increasingly considering open innovation models
as an essential element of their R&D strategy\textsuperscript{112}. Involving in open source, allows pharmaceutical companies to source external innovations without significant R&D expenditure. This allows them the possibility of entering neglected diseases market without making significant R&D investment. In that case pharmaceutical companies would have to develop newer business models that allow them to rely on open source and at the same time make their business viable. The economics of peer-production that de-links the cost of production from the price of final output offers newer possibilities in this regard. The possibility of de-linking the cost of drug from the R&D expenditure is usually looked upon from a user perspective. The de-linking economics that alternative drug discovery models propound is expected to make the drug accessible to patients. In such models R&D investment will never be dependent on market potential.

The biggest advantage of open source is the possibility of utilizing social labor. Socially organized labor without any direct financial incentives is the foundation of open source model. Drug discovery requires researchers with advanced scientific knowledge. Pharmaceutical companies usually invest heavily for procuring adequate human resource for research. Even after this, pharmaceutical industry is facing the crisis of lack of internal innovations. Pharmaceutical companies can rely on open source model to resolve this challenge. Open source has the ability to organize social labor for achieving desired results. Just like open source in software, if the drug discovery model also succeeds in attracting volunteers there would be significant reduction in R&D expenditure. Thus the investment required for open source research would be limited to providing essential infrastructures like the portal for collaborative research and organizing of open source research. But the final research output will be completely de-linked form the R&D expenditure involved. Most of the current models of open source drug

\textsuperscript{112} Deloitte Center for Health Solutions, ‘Executing an Open Innovation Model: Cooperation is Key to Competition for Biopharmaceutical Companies’ (Deloitte 2015) 2.
development have designed their licenses to enable commercialization of results without any limitations. In fact OSM has vowed to put the results in public domain while OSDD has permitted commercial utilization of results with limitation on patenting. This signifies the role that the open source drug development models expect the pharmaceutical industry to play. The de-linking economics enables the pharmaceutical industry to mass produce drugs developed through open source research just like generic drugs. As the R&D expenditure incurred is insignificant, the drug can be made available in the market at a price covering the production cost plus profit. The open source drug development model indeed has the ability to alter current model of pharmaceutical research and development. Open source in software has already demonstrated the ability of social labor to organize and create without any easily perceivable incentives. If this model is successfully replicated into drug discovery, it can definitely bring significant changes in the present model of pharmaceutical production.

4.6 Conclusion

The emergence of open source as a highly successful innovation model in software industry has evidenced its capacity to organize peer-production and deliver socially desired innovations. Many theorists had articulated for its introduction into newer areas like pharmaceutical research in order to resolves the many challenges posed by intellectual property model. Open source drug development is one such initiative which attempts to alter the current model of pharmaceutical research. It is interesting to note that open source model is emerging at a time when pharmaceutical industry is facing the crisis of lack of internal innovations. Collaborative research is an easier option to combat the challenge of innovation crisis. Adoption of open source methodology will make the collaborative research

113 Open Source Malaria and Open Source Drug Discovery licenses permit commercial utilization of research results without any significant restrictions.
easier. It offers the possibility of bringing together expertise from diverse backgrounds and to resolve the challenges through collaborative effort. Open source research will become attractive for the industry as it offers an opportunity to access the talent pool that exist outside the company and thus a way forward in the era of innovation crisis. The R&D crisis in pharmaceuticals thus offers a real possibility to experiment with the viability of open source model in pharma research. But this does not signify that open source research is not adoptable in areas outside neglected diseases sector. In fact, there exist many open collaborative models promoted by the pharmaceutical industry itself that focuses on a wide variety of areas other than neglected diseases. But the significance of neglected diseases is that it is one sector where the intellectual property led pharmaceutical model has failed in delivering its social objective. Thus the adoption of open source drug development has to be seen as an attempt to make the pharmaceutical production model more social centric. The efficient utilization of social labor can lead to socially relevant innovations in pharma sector. This will indeed be a boon to the third world population who is in need of immediate medical attention. The success of this model is dependent on how well the implementation challenges are addressed. If implemented efficiently, open source drug development can significantly alter the contemporary model of pharmaceutical production in a way more suitable to the global public health requirements. The implementation of open source drug development model by OSDD is examined through an empirical study in the next chapter to assess its success and limitations.