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TRIPS, ACCESS TO MEDICINES ANDDEVELOPING NATIONS:

Towards An Open Source Solution

by

Prof. Krishna Ravi Srinivas

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Please address all your correspondence to:

Krishna Ravi Srinivas PhD
Visiting Faculty (ESS Area)
Indian Institute of Management Bangalore
Bannerghatta Road
Bangalore 560 076, India
Email : ravisrinivas@iimb.ernet.in
Phone : + 91 80-26993116
Fax : + 91 80-26581602

TRIPS, ACCESS TO MEDICINES AND DEVELOPING NATIONS: Towards An Open Source Solution [1]

Krishna Ravi Srinivas Visiting Faculty, ESS Area

Executive Summary

The access to drugs and development of new drugs to what are called as neglected diseases in developing nations is a major issue. To what extent intellectual property rights (IPRS) facilitate or hinder this is a controversial issue. The harmonization of global IP regime under TRIPS norms has eliminated many of the options including using process patents without limits, which were earlier available to developing nations. A report of the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) has pointed out the problems and has suggested some solutions to the vexing question of IPRS and access to drugs in developing nations. In this paper one particular solution, using Open Source model as a potential model for drug discovery is taken up for analysis. The potentials and pitfalls are examined. It is pointed out that Open Source model is relevant for developing nations in developing new drugs. It is suggested that developing nations should give this model a serious consideration and try to use this model in the best possible manner considering their capacity for innovation and as a solution to find cures for neglected and most neglected diseases. It is also pointed out that while Open Source model is not a panacea it is certainly a model worth examining and encouraging.

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[1] This is the revised version of an earlier paper prepared for and circulated at AD HOC EXPERT MEETING: INTERNATIONAL ARRANGEMENTS ON INTELLECTUAL PROPERTY AND MEASURES TO IMPROVE DEVELOPING COUNTRY PRODUCTIVE CAPABILITIES IN THE SUPPLY OF ESSENTIAL MEDICINES organized by UNCTAD in Geneva 19-20, October 2006. The author thanks Christoph Spennemann for his interest and for the opportunity. This is not a UN document. The usual disclaimers apply.

I

The first decade of TRIPS has seen upward harmonization of the global intellectual property rights regime.[2] As a result the question of access to medicines in developing nations is more problematic now, perhaps than ever before. While the access to medicines for HIV/AIDS in developing nations highlighted the problems with the patent system, the solutions that were offered were far from adequate. The much-touted solution of Paragraph 6 of Doha Declaration has proved to be more a cosmetic solution than a real solution. It neither gave new flexibility to developing nations in implementing TRIPS nor had resulted in better cheaper and better access to drugs. Over the years much has been said about the flexibilities in TRIPS and how developing nations could use them to their advantage. But in reality due to many reasons, ranging from lack of technical capability to implement them, to lack of a viable national pharmaceutical industry, developing nations are unable to use them fully or derive the best advantage out of them. Although TRIPS does provide for compulsory licenses, many developing nations have rarely used them.

On the other hand developing nations are facing increasing pressure to provide for TRIPS PLUS provisions in their national laws through bilateral trade agreements. These agreements not only make the developing nations to abdicate some of the rights under TRIPS but also impose unnecessary higher standards of protection. The agreements cover test data protection also by making data exclusivity a mandatory condition. Thus the generic industries in those countries are deprived of opportunities to compete. The technology transfer under TRIPS has not been effective, from the viewpoint of the developing nations. The recent amendments to the Patent Act of India have raised questions about the continued supply of generics from India to other developing nations as before and the changing priorities of the pharmaceutical industry in India. Thus the picture after a decade of TRIPS is not heartening. Although developing nations continue to use TRIPS Council and other fora to advocate and seek support to their positions that does not seem to be resulting in any concrete benefits to developing nations.

At this juncture developing nations can continue to use flexibilities in TRIPS and continue to pursue traditional solutions like compulsory licensing but these will not be adequate to increase the access to medicines and more importantly to promote innovation is developing nations as a solution to problems created or made worse by strengthening of intellectual property rights through TRIPS and bilateral agreements. The problems with the patent system, globally and nationally, particularly in the USA have been the subject of many a report and studies. There is an urgent need to think beyond the traditional patent system and conventional solutions. A complex problem would require many solutions and there is no panacea for this problem. Global R&D treaty, patent buyouts are some of the solutions that have been suggested. Solutions like compulsory licensing, implementation of the solution under Para 6 are relevant in helping developing

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[2] The impacts of this harmonization have been the subject of many articles and volumes. For example see articles in Keith E. Maskus, Jerome H.Reichman (Eds) *International Public Goods and Transfer of Technology Under a Globalized Intellectual Property Regime* Cambridge: Cambridge University Press (2005)

nations. But these solutions have many limitations. For example while TRIPS does permit compulsory licensing the balance in the agreement is tilted in favor of the patent holder than the government. The boundaries within which the governments can act have been set by the TRIPS Agreement. The solution under Para 6 is yet to become a significant solution. Thus while due to pressure on MNCs and activism on a global scale there has been some respite in access to drugs in AIDS/HIV, in many other cases the problem persists. Developing nations are in an unenviable position, as they have to balance among multiple demands, pressures and expectations.

The CIPIH report points out that there are three types of diseases.[3] Type I diseases (e.g. diabetes, measles, cardiovascular diseases, tobacco related illness) occur in developed as well as developing nations. In case of type II diseases (e.g. HIV/AIDS, tuberculosis) more than 90% of the cases are in developing nations and developed nations are not fully free of them. Type III diseases (e.g. African sleeping sickness, African river blindness) are almost exclusive to developing nations They are also called very neglected diseases as there is very little R&D is done on them to develop cures and effective drugs. It is also well known that the 10/90 gap i.e. less than 10% of the resources for health research are applied to solve health problems in developing countries where 90% of the avoidable burden of ill-health is found is yet to be bridged. [4].

II

It is contended that for neglected and very neglected diseases developing nations should harness the potential of Open Source model. The Open Source model offers much flexibility. It is compatible with Public-Private Partnerships and since it avoids some of the pitfalls of the patent system, patents need not be a stumbling block in production, access and distribution.[5] While Open Source is not a panacea for all the ills that afflict the health care system it can provide viable working solutions to some of the vexing problems.

Conventional wisdom holds that grant of monopoly power provides an effective incentive for investing in research and development and to avoid the issue of free riding.[6] It is

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[3] Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) *Public Health, Innovation and Intellectual Property Rights* Geneva: World Health Organization (2006)

[4] For a recent survey of this see, Mary Ann Burke , Andres de Francisco (Eds) *Monitoring Financial Flows for Health Research 2005* Global Forum For Health Research Geneva (2005) For a philosophical and moral perspective and solution see Thomas Pogge Human Rights and Global Health *Metaphilosophy* 36: 182-209 (2005)

[5] Public-Private Partnerships have been established to find cures for neglected diseases. International donor community including international aid agencies, private foundations and UN organizations supports them

[6]See Bruce Abramson, Promoting Innovation in the Software Industry: A First Principles Approach to Intellectual Property Reform, *8 B.U. J. Sci. & Tech. L. 75, 76 (2002).* On patent laws the U.S. Supreme Court has observed, "The authority of Congress is

argued that patent protection is essential to recover the hundreds millions of dollars invested in the development of new drugs.[7] . However whether patents are the best means to promote innovation is a controversial question. According to Bently and Sherman

"The role that the patent system played in inducing invention and the implementation of new industrial practices has been widely but inconclusively debated" [8]

One of the controversies about patents and property rights acting as a disincentive for further research and inventions is about the impact of the anti-commons. Proliferation of owners and fragmented property rights can result in what is known as anti-commons.[9] Typically a researcher applies principles of biochemistry to develop new drugs. In other words upstream knowledge is applied to develop downstream products. Although the anti-commons problem is often cited as a major issue there is no consensus on this issue. For example Keiff argues that patent rights provide an incentive for investment. In his view neither multiple inputs nor overlapping patent rights are sufficient to prevent an industry, from operating successfully.[10]. A much-cited study on this issue concluded that patenting of upstream research has increased but this has not become a major factor in denial of access. Rather 'working solutions' like licensing, designing around patents, using public databases etc were adopted.[11] .

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exercised in the hope that "the productive effort thereby fostered will have a positive effect on society through the introduction of new products and processes of manufacture into the economy, and the emanations by way of increased employment and better lives for our citizens.'" *Diamond v. Chakrabarty, 447 U.S. 303, 307 (1980)* (quoting *Kewanee Oil Co. v. Bicron Corp., 416 U.S. 470, 480 (1974))*

[7] A controversial 2001 study from Tufts University estimates that the average cost to develop a new drug is $ 802 million. Joseph A. DiMasi et al., The Price of Innovation: New Estimates of Drug Development Costs, 22 J. Health Econ. 151, 166 (2003); But for a critique of this study and another estimate about the cost of developing a new drug see Public Citizen, Rx R&D Myths: The Case Against the Drug Industry's R&D "Scare Card" 6 tbl.2 (2001), available at http://www.citizen.org/documents/acfdc.pdf

[8] L. Bently and B.Sherman *Intellectual Property Law* Cambridge: Cambridge University Press (2001) at P 315

[9] "The tragedy of the anticommons refers to the more complex obstacles that arise when a user needs access to multiple patented inputs to create a single useful product. Each upstream patent allows its owner to set up another tollbooth on the road to product development, adding to the cost and slowing the pace of downstream biomedical innovation " Michael A. Heller & Rebecca S. Eisenberg, Can Patents Deter Innovation? The Anticommons in Biomedical Research, 280 *Science* 698 (1998).

[10] See F. Scott Kieff, Facilitating Scientific Research: Intellectual Property Rights and the Norms of Science - A Response to Rai and Eisenberg, *95 Nw. U. L. Rev. 691 (2001)*

[11] John P. Walsh, Ashish Arora, and Wesley M. Cohen, Working Through the Patent Problem, *Science*, 14 Feb. 2003, at 1021.

While the industry argues that there would be no research based drugs without patent protection and hence there should be universal patent protection, it is also argued by the critics of the current patent system that

"... Patents are irrelevant for the development of the products needed to address the diseases prevailing in developing nations.... The extension of pharmaceutical patent protection to developing nations, mandated by TRIPS Agreement, can do very little to prompt the development of such products, while it generates costs in terms of reduced access to the outputs of innovation " [12].

While patent pools are common in other industries they are not so common in pharmaceutical industry. Pharmaceutical companies are not keen to participate in patent pools, as that would undermine their exclusivity. According to an OECD Report

"However the pharmaceutical industry may be fundamentally different from the electronics sector. It is not an industry in which defining standards is important and assuring interoperability of technologies is not very important, especially not in the development of therapeutics. A company's worth is tightly ties to its intellectual property and fosters a 'bunker mentality'. There are likely to be disagreements among partners over the value of different pools in a pool, and dominant players may not have a strong incentive to join the pool. If limited field of application and essential patents can be defined, the patent pool model is worthy of consideration in biotechnology. " [13]

This 'bunker mentality' is the result of the exclusive rights granted by patents. A patentee who gets extensive rights through patents for an invention in the early stages is able to block further work by others and thereby hinders diffusion.[14] .

As Janet Hope points out
" that over the years the pharmaceutical industry (which has its roots in the chemical industry) has successfully pushed for patent grants that are broad enough to effectively cover not just a particular molecule that happens to have value as a drug, but all the variations of that molecule that might be effective, with the result that pharmaceutical patents are actually almost impossible to invent around." [15]

See also, John P. Walsh, Ashish Arora, and Wesley M. Cohen, Research Tool Patenting and Licensing and Biomedical Innovation, (in W.M. Cohen and S. Merrill, eds. *Patents in the Knowledge Based Economy*. Wash. D.C.: National Academies Press) (2004)

[12] Carlos Correa and Pakdee Pothisiri , CIPIH Report P 224 WHO (www.who.int) (2006)

[13] *Genetic Inventions, Intellectual Property Rights and Licensing Practices – Evidence and Policies* – OECD, 2002 www.oecd.org/pac/dataoecd/42/21/2491084.pdf

[14] Robert P. Merges, Richard R. Nelson, "On the Complex Economics of Patent Scope," *Columbia Law Review*, 90(4): 839-916 (1990)

[15] Open Source Biotechnology – Janet Hope- http://rsss.anu.edu.au/~janeth/home.html

A researcher working on follow on or cumulative research is constrained as (s)he has to seek licenses etc and these impose transaction costs. Thus the blocking of diffusion hinders further innovation. The 'bunker mentality' is linked to the power of the proprietary rights in maximizing the appropriation. One solution to this problem is to turn this logic on its head and promote diffusion by a different set of rights.[16]

Open source approach does precisely this. Open source is not anti- intellectual property rights. It does not grant an exclusive right to appropriate at the cost of diffusion or further cumulative research. Thus Open source models are more conducive to diffusion and follow on / cumulative innovations than the patent system. For example to add a new functionality to a browser developed through open source, the developer(s) need not seek the permission of the original developers. In case of Netscape, an add-on to enable secure Internet transactions was attached by Australian programmers, within hours of release of the source code.[17] Although source code is made available Open Source is not based on that idea that everything is free for everyone. If at all anything, open source software development and the software are governed by some norms and regulations.[18] Although it has been suggested that open source can be a potential alternative to current paradigms in fields as diverse as in drug discovery, biological sciences bioinformatics etc , skeptical views have been expressed about the suitability of Open Source in domains other than software. [19]

It is obvious that many features, which are unique to software development, testing and application, may not be extendable or applicable in other areas. For example development of software codes does not involve the physical handling of materials but most sciences demand not only handling of materials but also manipulation of materials and data using sophisticated instruments. Internet makes decentralization possible in software development as developers need not meet in meat space but can exchange codes and communicate through the web. Moreover the decentralized development and co-ordination is made possible by the use of Internet by all participants. This 'mode of production' is hardly applicable in other technologies that involve not only physical transfer of materials but also verification by repeating experiments and by transformation

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[16] This need not necessarily result in rights that are opposite to intellectual property rights. Rather the rights are enforceable in such a way that no body is able to prevent further innovation through exclusive rights. In that open source provides an alternative intellectual property rights regime.

[17] Feldman R, The Open Source biotechnology movement: Is it patent misuse *Minn J.L. Sci. Tech* 6, 1(2004)

[18] Yochai Benkler Coase's Penguin, or Linux and the Nature of the Firm, 112 *Yale L.J* (2002)

[19] For example See Wesley M.Cohen Does Open Source Have Legs in *Intellectual Property Rights in Frontier Industries* (Ed) Robert W.Hahn Washington D.C: AEI-Brookings Joint Center (2005) www.aei-brookings.org

of materials.[20] In other words code and data alone are not sufficient in many technologies for groups or researchers to work together. The collaborative invention/production model and collaborative ownership has received much attention in the recent years. [21]. This model has interesting implications for science, production of public goods, sharing of information and data, and, copyright in the digital environment.

What factors motivate persons and groups to contribute to a common project or objective, even in the absence of economic benefits and claims to ownership has been the focus of many studies on open source software development. [22]. The very fact that 'gift economies' are possible and there are factors other than altruism in open source software development indicate that there are many other incentives and motives for people to work together, contribute and develop a product, although there are no rights to ownership. This has lot of implications for production of goods and services. Since open source software is often superior to commercial software and such software has a dominant share in some Internet applications open source software model is not a freak model.

For example according to research conducted by Optaros, Inc., and InformationWeek magazine, of the 512 companies surveyed, 87 percent are using open source software, and, with companies earning over $ 1 billion in annual revenue saving an average of $ 3.3 million by using open source software in 2004.[23] Apache HTTP Web Server, open source software, is used on three times as many Internet servers as its next closest competitor, Microsoft Windows.[24] The ever-increasing numbers of open source projects and its success in diverse applications, ranging from e-governance to development of software to meet needs of various users and in various regional languages, prove its workability and viability. [25]

Under Open Source principles, one is free to use a part of the commons; but one should not use intellectual property rights to fully privatize or enclose the commons. The licenses that specify the rights and obligations of the parties can be crafted to meet this essential principle. Licenses for example can place restrictions on the modification of the software provided unless some other condition is adhered to, and licenses can limit or restrict, if not prohibit outright commercialization of the software.

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[20] See Steve Webber *The Success Of Open Source* Cambridge: Harvard University Press (2004) for analysis of open source 'mode of production' and its features

[21] See Rishab Aiyer Ghosh (Ed) *CODE : Collaborative Ownership and the Digital Economy* Cambridge: The MIT Press (2005) for perspectives from various disciplines

[22] For an overview see Stephen M. Maurer, Suzanne Scotchmer *Open Source Software: The New Intellectual Property Paradigm* NBER Working Paper 12148 (2006)

[23] Stephen Walli, Dave Gynn & Bruno von Rotz, *The Growth of Open Source Software in Organizations* http://www.optaros.com/publications_wpapers.shtml

[24] see Netcraft:Web Server Survey Archives, http://news.netcraft.com/archives/web_server_survey.html

[25] See DiBona, Chris , et al (eds) *Open Sources 2.0* . Sebastopol: O'Reilly and Associates(2005)

This is ensured through the licenses that establish the rights and obligations of the parties. For example some licenses place restrictions on the modification of the software provided, while some prohibit or restrict the commercialization of the software [26]. Licenses can specify that while licensees are free to modify or improve the software, they should make available the improved version or modifications also to other users and any additional property rights that arise out of the changes or improvement are subject to the terms and conditions of the original license. This is generally known as copy left principle.

How 'open' are the licenses claimed to be Open Source licenses is a matter of debate as not all licenses give the same rights or demand the same obligations. Licenses are developed and agreed to, depending upon the objectives and aims. For example a developer who wants very minimal rights and wants dissemination without restrictions may opt for a license that facilitates. A developer who wants to be cautious about misappropriation or privatization of the source code can opt for a license that places restrictions on this, even as it grants the rights to modify, distribute and develop to any future user. Some licenses may be 'closed' or partially open and some can be open but with restrictions. Some licenses take in to account the needs of the users to acquire intellectual property rights but they also have clauses to safe guard the interests of the developers of original source code and those who contributed to the improvements. For example Apache License is more like the standard BSD license. The version 2.0 of the Apache license takes in to account the issue of patent license. The patent license under this version provide an irrevocable, royalty free license to that extent that patent rights are necessary for using the original work and contributions there to. Hence it has a specific clause that states

"If you institute patent litigation against any entity (including a cross-claim or counterclaim in a law suit) alleging that the Work or a Contribution incorporated within the Work constitutes direct or contributory patent infringement, then any patent licenses granted to You under this License for that Work shall terminate as of the date such litigation is filed"[27]

Thus the Rights to Work under this license can prevent the party getting the benefits, from suing against the contributor or licensor.

Open Source software can be incorporated in commercial software/products but this does not prevent the availability of the software or the code in Open Source mode. For example, Sendmail is available in commercial versions as a part of proprietary software

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[26] *see* http://www.opensource.org/licences/ See also Andrew M.St.Laurent *Understanding Open Source and Free Software Licensing* Sebastopol: O'Reilly and Associates(2004)

[27] http://www/opensource.org/licences/apache2.0.php

and it is also available in Open Source mode/version. The mixed i.e. open source and proprietary software strategy helps the vendors to incorporate Open Source software with clearly defined rights and obligations. Thus Open Source model can create some rights that will not be translated in to exclusive rights to prevent others from making improvements or blocking any further work by others. The availability of various licenses and the possibility of crafting licenses to meet specific needs while still adhering to Open Source principles makes Open Source model and licenses well suited for different purposes.

Open Source provides freedom to users by not binding them to a particular product or technology. It also facilitates further development and licenses play an important role in this. Unlike the End Users License Agreements, which generally restricts or prevents the customer/user from modifying or customizing the software, the license under Open Source provides rights to do so. In other words the developer or vendor of Open Source software does not get exclusive rights to prevent others from modifying it. Any right of the developer does not over ride the rights and freedom of the user to tinker with the software. If a research tool is distributed under Open Source license, the need for specific research exemption does not arise at all as the Open Source license will take care of that exemption. Organizations using shared resources can work together with specific licenses that does not prohibit one party from developing different products based on the shared resource.

Commercial business models using Open Source are common now. For example IBM, SUN and many other industry bigwigs support Open Source in a big way and often employ experts in Open Source to develop software. For example IBM encourages Open Source software development in a big way[28]. It helps IBM in increasing the demand for its hardware.

Although Open Source principles and applications may sound familiar in the context of software, they have been used or used with modifications in other fields also. For example there can be systems of collective property, mode(l)s of production based on collective property. Cassier discusses some such systems and models and suggests that they can be used to create a better balance among various property rights regimes. [29] . It is not claimed that such systems and models will resolve all the problems associated with

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[28]" IBM now reportedly contributes $100 million a year to the development of Linux and other open source software projects. IBM donated some components of its proprietary AIX software, the IBM flavor of Unix, to Linux to strengthen the latter's ability to provide enterprise-level capabilities and scalability. IBM also released the Eclipse software tools suite and framework on an open source basis and contributed resources to start an open source consortium to support and extend it"
Pamela Samuelson IBM's pragmatic embrace of open source *Communications of the ACM* Volume 49, Number 10,21-25 (2006)

[29] Maurice Cassier Private property, collective property, and public property in the age of genomics *International Social Sciences Journal* 83-97 (2002)

or arising out of the patent system. Rather it is claimed that they provide workable solutions based on alternative perspectives on exclusive rights and collective rights and obligations.

The major objective of The Hapmap Project is to compare the genetic sequences of individuals to identify halotypes.[30] The information is made available to researchers freely, but subject to a data access policy. The 'click-warp' agreement forbids the users from reducing the access to data and shares the data with only those who had made the same agreement. By this data availability to researchers is ensured. At the same time the agreement acts as a barrier from filing patents on the halotypes. A similar initiative is the SNP consortium.[31] Here also the objective is to ensure that intellectual property rights do not result in blocking access to data to other researchers and companies. To avoid the anti-commons situation there is need for an agreement that intellectual property rights will not hinder data access. The success of Hapmap Project and SNP Consortium indicate that open source principles can be applied in contexts where there are many stakeholders and there is a common objective. Neither the Project nor the Consortium is against patents per se. But what they want to avoid is the use of patents to deny access to data or proliferation of patents with fragmented proprietary rights.

It is not contended that these are ideal models that can be repeated elsewhere. There are some problems with the data access policy of the above examples. In both examples the stakeholders have come together and have commercial interests also. But they want to use data access policy in such a way that the 'commons' are available to all subject to some conditions. The conditions that bind all ensure that private interest is balanced with collective interest. To what extent such a balance can be achieved depends on so many factors including the value of the data (or commons) and what are the alternatives. In cases where it is better to opt for intellectual property rights as a defensive strategy and building a patent thicket gives a strategic advantage not all the stakeholders will be interested in such a data access policy unless that acts as a disadvantage or collaborative action benefits the self-interest [32].

The major objective of CAMBIA is biotechnological invention should be available to researchers with least restrictions.[33] For that CAMBIA has launched many projects including BIOS (Biological Innovation for Open Society).[34] The BIOS has been promoting BiOS Licenses as an alternative. The BiOS Licenses under the BIOS initiative constitute another potential model. To a great extent the BiOS License is based on the GPL philosophy. Under the BiOS licensee is permitted to use all intellectual property for

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[30] See www.**hapmap**.org
http://en.wikipedia.org/wiki/International_**HapMap_Project**

[31] http://**snp**.cshl.org

[32] For a discussion see ' Data Bases, Access and Open Source Models: A Review (Work in Progress)

[33] www.cambia.org

[34] www.bios.net

development and commercialization but the licensee should license all the improvements lest further research and development should suffer. It is too early to evaluate the BIOS Initiative. The BIOS initiative may seem more appropriate for bio/life sciences but such a license can be used elsewhere with modifications.

III

It is becoming clear that increase in pharmaceutical Research and Development (R&D) is not resulting in commensurate increase in new drugs or real breakthroughs. The R&D spending by pharmaceutical industry doubled in seven years i.e. between 1995 and 2002 but this has not resulted in significant increase in the number of new molecular entities approved FDA.[35] Many suggestions have been put forth to overcome this problem. NIH has launched the Roadmap Initiative with the objective of bringing major changes in basic research and clinical research.

Over the years the pharmaceutical industry has undergone changes and the advances in life sciences had their impact on major aspects of drug research, including organizational and managerial aspects. [36]. According to Franco Malerba and Luigi Orsenigo

"Collaboration with universities, NBFs and internal research were indeed strongly complementary. Thus, a dense network of collaborative relations emerged, with the start-up firms positioned as upstream suppliers of technology and R&D services and established firms positioned as downstream buyers who could provide capital as well as access to complementary assets. Networking was facilitated by the partly "scientific", i.e. abstract and codified nature of the knowledge generated by NBFs, which made it possible, in principle, to separate the innovative process in different vertical stages: the production of new scientific knowledge, the development of this knowledge in applied knowledge, the use of the latter for the production and marketing of new products. In this context, different types of institutions specialized in the stage of the innovative process in which they were relatively more efficient: university in the first stage, the NBFs in the

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[35] "In 2002 the U.S. Food and Drug Administration approved only seventeen new molecular entities (NMEs) for sale in the United States – a disappointing fraction of fifteen year high of fifty six NMEs approved in 1996 and the lowest since 1983....The same pattern is apparent in worldwide statistics where the annual number of new active substances approved in major markets fell by 50 percent during the 1990s, while private sector pharmaceutical R&D spending tripled"
Cockburn, Iain M., (2004), "The Changing Structure of the Pharmaceutical Industry," *Health Affairs*, 23(1): 10-22.
See also CDER NDAs approval in calendar years 1990-2004 Rockville: FDA www.fda.gov/rdmt/pstable.htm

[36] Cockburn op.cit notes that "as 'rational drug design " took center stage, changes in the nature of research activity were accompanied by complementary changes in the internal structure of commercial R&D organizations. Drug companies began to look and behave more like universities, with increasing emphasis on collaboration, publication and exchange of (precompetitive) information.

second stage and large firms in the third. A network of collaboration between these actors provided then the necessary coordination of the innovative process. The new firms acted as "middlemen" in the transfer of technology between universities -- which lacked the capability to develop or market the new technology -- and established pharmaceutical firms that lacked technical expertise in the new realm of genetic engineering but that had the downstream capabilities needed for commercialization." (Citations omitted) [37]

However what are important is the changes in the shift to guided research, more use of molecular biology and genetic engineering in pharmaceutical sector. It has been pointed out that as knowledge- base has become more 'divisible', the discovery and application can be broken into modules that could be handled by different groups of researchers. After reviewing the trends in changes in the structure of pharmaceutical R&D Niman and Kinch point out

"Finally, pharmaceutical research has become less "context-specific" as the scientific knowledge embodied in pharmaceuticals has become more generic in nature. This has given rise to the development of a market for research ideas and the development of networks of pharmaceutical companies where the research function has become modularized and decoupled from the manufacture, testing and marketing of new drugs"[38] (citations omitted)

Contract Research Organizations are well suited to make the best advantage of this modularization and divisibility of knowledge base. They need not be located in a single country or in a time zone. This division of labor in the pharmaceutical industry gives a unique advantage to developing nations like China, India and countries that have a strong indigenous drug industry producing generics. Companies can also outsource some of the specialized research or some part of the discovery process to small companies in developing nations with expertise. The partnering of pharmaceutical companies with biotechnology companies in USA and Europe is too well known. The proliferation of Contract Research Organizations (CROs), particularly in developing nations indicates that a good portion of the research and development and trials is being outsourced. The pharmaceutical CRO industry in India was valued at $100 m – 120m , with an annual growth rate of 25%.[39]

The CROs are able to take advantage of availability of highly qualified technical expertise at low cost in developing nations. The availability of telecommunication facilities and reduction in the costs of computing has been another factor for growth of

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[37] Franco Malerba, Luigi Orsenigo *Innnovation and Market Structure in the Dynamics of the Pharmaceutical Industry and Biotechnology : Towards a History Friendly Model* (Presented at the DRUID Nelson and Winter Conference, Aalborg, June 12-15, 2001)

[38] Neil B.Niman, Brian T. Kench *Open Source and Future of the Pharmaceutical Industry* 2005 (mimeo)

[39] http://www.drugresearcher.com/news/ng.asp?n=69977-india-china-contract-research

CROs. CROs should be viewed also as opportunities for developing nations to learn and upgrade their capabilities. Since some companies are involved in basic research and development as well as doing Contract Research either through subsidiaries or through a division of the company they are able to make significant contributions.

One can compare the modular nature of this R&D and other functions with the modularity in software development. In Open source approach many teams work on many aspects, often in parallel and share their results. While one group may be working on improvements in kernel, some other group may be working in debugging the code and making it more perfect, and yet another group may be working on developing libraries and interfaces. This division of labor is possible because of the modular nature of software development. In case of pharmaceutical industry it is pointed out that in every stage (i.e. in Pre-Clinical, clinical and production stages) it is possible to cooperate and share.

An Open-Source network that can also function as a clearinghouse for information, hold intellectual property rights, can facilitate such collaboration. William R. Brody The President of Johns Hopkins University has put forth idea of developing an open-source network to develop as well as to test drugs. The license for the new compound developed through these interactions would be assigned to the network. The network will hold the license for the associated intellectual property and create database for sharing information. The consortium will grant a royalty-free license to firms that agree to make and distribute the drug at a cost that is much less than that of the new proprietary drug.[40] (Since only a bare sketch is available, we will not go into the pros and cons of this idea)

One reason for the success of Open source is the modularity nature of software testing and development. There is a co-ordination process and ultimately the software that is developed in the Open source mode is made available as a 'finished' product. But this does not stop others from working on it further and come out with a better or more useful product. Since code is made available for sharing and for improving follow on innovation and diffusion is made possible in a coherent manner. The licenses specify the rights and obligations of the developer as well as the user. Since there are no exclusive proprietary rights, and as licenses specify the limits of 'appropriation', competition is possible.

To what extent these are applicable in pharmaceutical research and particularly in development of drugs and vaccines for neglected diseases. There is no consensus in this issue. For example according to Janet Hope

"As with any other strategy, there are costs as well as benefits associated with an open source approach. Opportunity costs are the gains that an innovator could have made by adopting an exclusive proprietary approach according to the traditional model in biotech and elsewhere. Actual costs include the costs of producing and then diffusing an innovation (if you choose to actively build a user community around your open source

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[40] The Uncensored Idea – William H. Brody http://www.hopkinsmedicine.org/mediaII/enews/uncensored.html

product, obviously maintaining and supporting that community will entail extra costs).

Whether the balance of costs and benefits of an open source approach make it more attractive to an IP owner than the traditional proprietary approach will depend on the circumstances. From what I've seen, the likelihood of pharmaceutical companies "open sourcing" their drugs - the actual therapeutic molecules - seems very low" [41]

On the other hand proponents of this idea i.e. application of Open Source in pharmaceutical R &D for development of drugs point out the feasibility of using Open Source. But there is one area where Open Source can play a major role, particularly in developing nations, is using Open Source software for drug discovery and development.

Open source software can play a crucial role in drug discovery and pharmaceutical research and development. Open source software coupled with Open Standards, open application programming interfaces, open and modular components can result in many approaches with open features. Open source Language Python is used software for physics, chemistry and biology. One major advantage of developing a full spectrum of open source applications is that the flexibility in them can be fully utilized by the user communities. The user communities need not get bound to proprietary software. As source code is available it is easy to customize the software and modify it according to the needs of the user. The Open Components, Open APIs and Open Data standards can be used to develop Open source applications in bioinformatics also. Since this needs human resources and access to net and computers only, developing nations that are rich in human resources (e.g. India, China) and developing nations that have a well developed R&D system to undertake research in pharmaceutical sector should explore the possibility of using Open source to meet their needs. Obviously due to the modular nature of Open source software countries can make the best use of their relative strengths in software development, testing, customization and implementation.

According to DeLano

"Chief among these reasons is the fact that unlike in other mature sectors of the economy, such as banking or insurance, software needs in drug discovery are neither static nor well defined. Therapeutic discovery is a dynamic activity that will continue to evolve, exploiting new technologies and scientific discoveries as it does so. Indeed the recent emergence of information – intensive activities such as high-throughput screening, genomics, combinational chemistry, rapid structure determination, and informatics, has made drug-discovery software more of a moving target than ever".[42]

Hence it makes sense for developing nations to foster open source software and open source informatics products in drug discovery. If the governments, universities and the

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[41] http://rsss.anu.edu.au/~janeth/OSBiotech.html#93

[42] Warren L. DeLano The Case for open-source software in drug discovery, *Drug Discovery Today*, Vol 10 No 3 2005

private sector come together in this much can be achieved in developing nations. The modular nature of Open source software development can be taken advantage of. Depending upon the relative strengths and capabilities various actors and groups can focus on different aspects like developing, testing/debugging, customization and other aspects. This will also help the Open source software sector in developing new products specific to the needs of pharmaceutical industry and related research and development.

Developing nations can use the Open source software and databases based on Open source principles. There can be a sui generis system for data sharing and access to databases. Such a system should be flexible enough to meet the genuine needs of users without making data available to all at no cost. What is not proprietary need not necessarily be free for all and available without obligations. Hybrid models that regulate access and that confer quasi-proprietary rights can be developed. In such models data will be made accessible subject to some conditions like no user can appropriate data per se through patents.

It is possible to combine Open source principles with the idea of Limited Common Property (LCP).[43] LCP is a hybrid property form that is neither totally private nor totally public. A community of researchers and institutions can hold some part of the data as LCP and some part in public domain. Based on this common understanding protocols and licenses for access and use of data can be developed. LCP will be relevant where there is a vibrant community or a community can be developed based on a common objective or there is a vital and common interest (e.g. conservation of a resource, finding a vaccine for a disease) among stakeholders. The community can deliberate and develop common norms, guidelines and good practices for treating LCP and for using various rights. For example the community can decide that no member will claim or enforce patent rights in such a manner that it restricts or limits the rights of other members to engage in research or develop follow on innovation. The community can create a patent pool, provide cross-licenses and enforce Material Transfer Agreements.

Now the question that arises is will this be relevant to drug discovery and research and development. The answer is a yes, a qualified yes. Such a model will be relevant in development of drugs that can be used for follow on innovation or cumulative innovation.

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[43]This category is what I call the "limited common property" or LCP — property held as a commons among the members of a group, but exclusively vis-à-vis the outside world. I will argue that the new developments in cyberspace and environmentalism particularly demonstrate how much we need to develop our concepts of the LCP, a property type that is neither entirely individualistic nor entirely public. Our legal system has hitherto been oddly oblivious to many forms of limited common property — even though common property itself is actually ubiquitous, if unremarked. The reasons for that obliviousness are in some measure economic, but they are also in part cultural — a culture now quite dramatically challenged by the questions of property in intellectual creativity and environmental protection
Carol Rose The several futures of property: of cyberspace and folk tales, emission trades and ecosystems. *Minn. L. Rev.* 129 (1998)

For example a potential drug (in a pre-clinical stage) can be treated, as a LCP and only the members of the community will have access to it. All members are free to work on the potential candidate and take it to next stages for clinical trials. Each member is free to seek funding from financial investors and others. While the successful member has every right to take it to the production stage (s) he should not opt for patent rights that are too broad to deny follow on innovation or cumulative innovation. Other members are free to develop various products based on that potential drug and compete in the market.

For example there can be a community dedicated to development of vaccine for a particular disease. The community will work on various potential drugs and share the information among the community. Groups that are competent can take up the work done by others further and go to next stage. The basic research and development can be split in to various modules and done by different members or groups in the community. A dedicated group that develops or customizes Open source software can support the community. The community can outsource some of the work, work that cannot be handled by members of the community. The community need not abhor patents. It can use patents for defensive purposes when it is relevant. The model of production based on collective property can be tested in drug discovery and development. There are some examples of models of production using the collective property paradigm. It is neither necessary nor desirable that the same should be replicated here. A model of production involving public-private partnerships is possible.

It has been suggested that pharmaceutical companies can co-opt Open source model but it may not be a substitute for traditional drug R&D.[44]. On the other hand Stephen Maurer etal have put forth a model based on Open source approach as a potential solution for finding cures for tropical diseases. [45]Neil B.Niman and Brian T.Kench have suggested a different approach using the Open source model. Munos finds lots of advantages in using an Open source approach. According to him

"If Open source drug R&D takes hold, what will probably emerge is not replacement of one model by another, but an ecology in which big pharma, biotech and collaborative research compete and collaborate at the same time, feeding off each other synergistically while moving towards therapies along their own distinctive paths".

It should be pointed out that software developed through Open source approach is not always available as a non-proprietary software. But what sort of synergy is possible between initiatives that aim at providing access at affordable prices and R&D of pharma Companies. Synergy may not always be possible as there are potential conflicts of interests. For example pharmaceutical industry prefers patenting at the early stages of drug discovery, partially as a defensive strategy. In Open source approach that is not all desirable. The model suggested by Niman and Kench envisages that there is both co-

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[44] Munos B Can open-source R&D reinvigorate drug research *Nature Reviews Drug Discovery* Sep 2006

[45] Maurer S. Rai.A, Sali. A Finding Cures for Tropical Diseases : Is Open Source an Answer *PLoS Medicine* Vol 1 No 3 Dec 2004

operation and competition at all stages of drug discovery. Their model tries to solve the co-ordination problem and they also discuss about the possibility of new types of co-coordinating structures that can merge or supplant or synchronize with traditional pharmaceutical companies. They also suggest a two part tariff and membership fees based on usage or some other criteria. According to Niman and Kench

"By eliminating patents on basic research, open source could level the knowledge playing field, create market place not only for ideas but also promote a bootstrapping approach where one idea built upon another in a cumulative process. ... This alternative process could also lead to an expansion of the rate of technological diffusion, there by increasing the likelihood that a piece of basic research would lead to superior new drugs ".[46]

Their whole model is based on some assumptions about the changes in the drug discovery model and the difference between knowledge production under patent model and open source model. In their decentralized R&D process access barrier is practically non-existent. To what extent these models can be put to practice and proved to be viable is an open question. The three models have some common features but they lay importance on very different aspects. The model suggested by Munos tries to combine best of both open source and traditional pharmaceutical R&D. The Tropical Diseases Initiative model envisages collaboration at both armchair and wet laboratory modes.

What sort of institutional mechanisms are needed for this type of drug development? Niman and Kench suggest that a social partnership similar to HapMap project or a model similar to Open Source Development Lab (ODSL). As indicated earlier HapMap model will work in some circumstances where the members have a shared vision and a common objective and are willing to share through the public domain. HapMap project, SNP consortium structures can be used for some stages of drug discovery but may not be suitable for all stages. We should realize that each stage the actors may have different priorities and hence this structure may not work at all times. On the other hand some features of the HapMap model, SNP consortium can be adopted for open source drug discovery. The OSDL model is a much more structured model and is efficient in many aspects. It can be used as a model for some stages of drug discovery.

A crucial question is why should pharmaceutical companies collaborate or use Open Source model when the existing patent system has been very effective in protecting their interests. It is a difficult question to answer. In Information Technology industry companies like IBM who also own and protect many patents have promoted Open Source. Yet they have found that sharing IP and pledging support to Open Source helps the interests of all. Patent Commons project exemplifies such an initiative, wherein the companies have come together to innovate, collaborate and create a commons for the developers and users of software, particularly Linux.[47]They are willing to make

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[46] Niman and Kench supra

[47] http://www.patent-commons.org

commitment not to sue or enforce patents against third parties, in certain circumstances. [48]

In case of drug discovery and research such a commitment may not be forthcoming easily for obvious reasons. But this does not mean that patent holders cannot come together to find solutions. At present there may not be a community among companies involved in drug development and research to make similar commitment. But it may evolve as a result of initiatives and incentives for using Open Source models in drug discovery. If non-profit institutions and universities come together and form a community to test this and organize themselves on lines similar to SNP consortium or Patent Commons it will be a good starting point.

The question of appropriate licenses is very important. There are many Open source Licenses. Depending upon the restrictions and rights granted a suitable license can be designed for drug discovery. A sui generis model for data access combined with an appropriate license(s) can be developed so that each actor or party is clear about his or her rights and obligations.

Another approach to this question of using Open source is to study initiatives in some sectors where Open source principles are applied to solve real life problems. [49]Although all these initiatives may not be 100% open source one can develop some hybrid models that combine different ways of putting open source approach to work. In that sense Open source may be used as a term to denote a wide variety of approaches and perhaps as a metaphor. [50]

In short there are many key issues to be resolved in applying the Open source approach in drug discovery and development. Although the models suggested have some flaws it is possible to make them better or develop new models based on them. One way to tackle this issue is to use Open source as a metaphor than as a model and develop new ways of combining private and public, proprietary and non-proprietary and create models that envisage collaborations that mediate in the in between spaces and domains.

However there is also an urgent need to develop conceptual models and theoretical principles to take this further. Existing proprietary models may not be adequate for this. Similarly the idea of Open source as an alternative intellectual property paradigm has to be developed further. Some sort of restricted rights with obligations can be developed. For example while a company can be free to obtain patents, there can be obligations that it does not block further innovation through follow on innovation can be imposed. Licenses specific to drug/pharmaceutical industry can be developed. A weaker form of patent rights can be granted and regulated through such licenses. However it is too early to say what exactly those rights can be.

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[48] http://www.patent-commons.org/commons/

[49] http://www.merid.org/showproject.php?ProjectID=9318.0

[50] See Krishna Ravi Srinivas Intellectual property rights and bio commons: open source and beyond *International Social Science Journal* (forthcoming)

Developing nations should try to support Open source approaches as it helps them to overcome some of the limitations of the present model and patent system. Since Open source model provides ample scope for harnessing the creative potential of experts and amateurs alike developing nations that are rich in human resources should take a lead in testing such approaches. It is suggested that institutions in developing nations can work with not for profit institutions in developed nations, seek and enlist the capabilities and talents of scientists and others all over the world in this. Developing nations can come together to form a body to oversee and co-ordinate this. This body can adopt the models used by Public-Partnerships in drug development/ vaccine research and co-ordinate the Open source drug discovery process. Generic industry in developing nations can join hands with this body and assist it in various stages. It is envisaged that developing nations will arrive at a mutually beneficial mechanism to share the results of this process and develop appropriate licenses and policies regarding intellectual property rights.

Although in terms of persons affected with neglected diseases and avoidable mortalities on account of such diseases the picture in developing nations may look gloomy and hopeless, the innovation capacity in developing nations need not be underestimated. [51]

What is needed is an out of the box thinking to find solutions. Today neither public sector nor private sector can tackle these problems solely by themselves. To begin with this body can take up work on specific diseases for which some preliminary work has been done and information is available in public domain. This could be in the form of Public-Private Partnerships. There should be sufficient incentives for private sector to join such partnerships.

Open source alone may not be able to provide all the necessary solutions. Open source drug discovery can be combined with patent pools, cross-licensing and other measures.[52] Incentives in the form of tax concessions, guaranteed purchase contracts can also be offered to companies that are developing and testing drugs developed under this approach.

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[51] China is the leading producer of penicillin in the world. Four developing nations (India, Cuba, Brazil, and Indonesia meet 60% of the vaccine requirements of the UNICEF's Expanded Program on Immunization. 67% of India's drug exports and 74% of Brazil's drug exports (in terms of dollars) are directed towards developing nations.
Carlos Morel et. al. Health Innovation : the neglected capacity of developing countries to address neglected diseases *Science* 309: 401 –404 (2005)

[52] See also Dianne Nicol and Janet Hope, "Cooperative strategies for facilitating use of patented inventions in biotechnology", *Law and Society* (forthcoming 2006) for a discussion on similar cooperative strategies in biotechnology.

Conclusion

Open source provides a unique opportunity to developing nations to overcome some of the problems associated with patents. Although the viability of this model is yet to be proven, the models suggested in the literature, point out the potential benefits of Open source approach and its relevance to meet the needs of developing nations. However a lot of work remains to be done in both developing and testing the models and in creating an institutional mechanism to actualize this potential. Developing nations can take a lead in this and can try some innovative models , particularly in neglected and most neglected diseases.