

CIPIH STUDY SUMMARIES

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"Pharmaceutical innovation and the burden of disease in developing and developed countries"

Frank R. Lichtenberg

Introduction. The author performed three different analyses of the relationship across diseases between pharmaceutical innovation and the burden of disease in developed and developing countries.

Analysis. First, the author examines the relationship between the number of disability-adjusted life-years (DALYs) attributable to a disease in 2001, by region, and the number of drugs that have been developed to treat the disease and that are sold in the U.S. Second, he examines the relationship between the number of DALYs attributable to a disease in 2001, and the number of drugs launched to treat the disease in approximately 50 countries during the period 1982-2002. Third, he examines the relationship between cancer incidence (the number of people diagnosed with a particular form of cancer), and the number of articles published in scientific journals pertaining to drug therapy for that form of cancer.

Findings. All three analyses indicate that the amount of pharmaceutical innovation is positively related to the burden of disease in developed countries but not to the burden of disease in developing countries. The amount of other medical innovation also appears to be positively related to the burden of disease in developed countries but not to the burden of disease in developing countries, although the developed-vs.-developing difference is smaller than in the case of pharmaceutical innovation.

Discussion. The most plausible explanation for the lack of a relationship between the burden of disease in developing countries and the amount of pharmaceutical innovation is that incentives for firms to develop medicines for diseases primarily afflicting people in developing countries have been weak or nonexistent. Economic research has demonstrated that investment in R&D is greatly affected by incentives that are offered for R&D. To increase the rate of development of drugs for diseases primarily afflicting people in developing countries, incentives for developing these drugs must be strengthened. The establishment of purchase commitment funds may be the most efficient way to stimulate the development and production of these drugs.

"What has been achieved, what has been the constraints and what are the future priorities for pharmaceutical-product related R&D relevant to the reproductive needs of developing countries?"

Peter Hall

Introduction. This paper addresses the role and achievements of the public and private sectors in the development of contraception, as well as other specific pharmaceutical products for reproductive health, such as microbicides and drugs used for medical abortion. Additionally, it looks at some of the obstacles to availability in developing countries and research needs.

Availability of products worldwide.

Contraception. Despite the growing private sector, the public sector remains the principal supplier of contraception in most developing countries. However the use of contraception is dependent on affordability. Donors and/or governments must be able to purchase products for the public sector or social marketing programmes at the lowest possible price.

Medical Abortion. Outside the USA and three western European countries, where costs are paid by the healthcare system or through health insurance, the cost of the product has been prohibitive to most women wanting access to this drug and no alternative anti-progestogens are available.

Microbicides. There are currently no microbicides on the market; however, they represent one of the drugs and vaccines areas for which R&D is being funded through and organized around public-private partnerships. There are currently some 17 products at various stages of clinical trials, five of which are in, or close to, Phase III clinical trials.

Impact of the public sector R&D programmes. Funding from bilateral aid agencies or foundations to public sector R&D programmes has resulted in the development of products which have expanded contraceptive choice for many people in the world. The impact of clinical and epidemiological studies undertaken to investigate the safety and efficacy of products developed by others, by these public and philanthropic-funded programmes is extremely high. Data from these studies have helped make products affordable in developing countries, allowed guidelines for optimal use to be developed, and informed both providers and users of relative safety and use characteristics of these products.

Pharmaceutical industry. Since the 1950s, R&D in the private sector has been responsible for many of the significant advances in both the field of contraception and medical abortion. Oral contraceptives have been the major contraceptive products for these companies in terms of sales; however, in the west this market is changing because of the market penetration of generic manufacturers, thus making them reinvest in R&D, which will give them replacement revenue flows.

With regard to products for the less developed world, there is little incentive for western pharmaceutical companies to participate in "difficult" developing world markets, when the "accessible" developed world is purchasing products with a total sales value that is more than

50 times greater! However, where companies have benefited from products having been developed with public funding, mechanisms should be instituted to ensure that this is reflected in availability and affordability in developing countries.

No major pharmaceutical company is currently involved in the development of drugs for medical abortion and opposition from the pro-life movement is likely to keep them out of research on medical abortion. With regards to microbicides, most of the advanced products are being developed by small biopharmaceutical companies with public sector and some venture capital funding.

Role of developing countries. Except for Brazil, China and India, there has been little R&D of products for reproductive health in developing countries, other than participation in international, multi.-centre clinical trials.

Public sector funding to improve access. The international donors should establish a Global RH Commodity Access Facility (GRHCAF) to act as an International Financing Facility for reproductive health commodities to develop, maintain and survey a network of qualified manufacturers able to meet developing country and international donor needs. The GRHCAF should address all essential reproductive health drugs, such as mifepristone and misoprostol, and work with microbicide development groups in identifying and supporting the development of manufacturing sites for microbicides in certain countries, as they become available and more widely used.

There is a role for the public funded R&D groups in product development to develop agreements to ensure protection of the cost of the product to the public sector of developing countries. The expertise that public sector R&D groups have developed to conduct clinical trials and on the existence of clinical trial networks they have created must be built on.

Opportunities for additional R&D. There remains a significant need for basic research, product R&D, and operational and health systems research in the field of reproductive health. Although there has been some resurgence of interest by the couple of R&D based companies remaining in the field, the overall funding for R&D in reproductive health looks bleak. The report gives specific product-related recommendations.

"Current Interventions and the Global Research Agenda for Diseases Disproportionately Affecting the Poor: The Cases of Malaria, Diabetes and Rotavirus"

Alyna C. Smith

Introduction. In this paper, we consider three diseases -- malaria, diabetes, and rotavirus -- selected because of their contrasts. Parasitic, viral and noncommunicable diseases all have a major impact on health in developing countries, though the nature of the challenge they present, and consequently of the tools needed to address them, vary considerably. These contrasts can illuminate key issues that should be considered in making proposals that are meaningful across a range of conditions, which potentially fall under the umbrella of diseases relevant to the Commission.

Malaria, diabetes and rotavirus have, it can be argued, more contrasts than comparisons. They represent a small sample of diseases with a considerable burden in developing countries, and suggest the very different nature of the problems -- and viable solutions -- at issue with regard to their management and control.

Discussion. Malaria, diabetes and rotavirus have a significant impact on the poor for diverse reasons that relate to the very different causes, manifestations, impact and available treatment options for each condition. Here, a framework is proposed to examine the features of key interventions for each of these conditions within a framework. It borrows from a human rights approach, and focuses in on four dimensions of the issue: availability, accessibility, acceptability, and quality. 'Availability' requires that health products and services be on hand in *sufficient quantities* within a country, including the question of whether the needed intervention exists in the first place. 'Accessibility' requires that all sections of the population, without discrimination, be within physical reach and able to afford them. For simplicity, we focus here on the affordability component of this dimension. 'Acceptability' relates to the degree to which interventions are ethically and culturally appropriate, and 'quality' refers to their scientific and medical appropriateness. Such a framework can be useful for analysis by helping to differentiate in a systematic way the various reasons an intervention may fail to adequately benefit the poor. It can also help in identifying and categorizing potential solutions appropriate for the problems that predominate for a given intervention. Finally, the schema suggests how to frame problems and to identify appropriate solutions *given existing social and economic inequalities*. The inequalities themselves remain outside of the schema and outside of the scope of what this Commission can address, but through such a framework they nevertheless inform proposals that take sufficient account of these realities to be meaningful and even practical.

Conclusions

- **Most diseases disproportionately affect developing countries.** There are several reasons for accepting an expansive view of the diseases that fall under the remit of the Commission. First, the Commission does not give up anything if it accepts an expanded view; it is still addressing neglected (and very neglected) diseases if it addresses the much larger set of conditions that contribute to mortality and morbidity among the poor.

Moreover, a broader understanding of what is captured by "disproportionate" takes a more forward-looking view, and acknowledges the social, economic and demographic trends that are profoundly affecting the disease burden in developing countries. Finally, a human rights and equity (as well as standard public health) arguments insist on giving consideration to the underlying determinants of health in the allocation of scarce resources -- including resources for health-related research -- and thus considering the inter-related factors, both social and scientific, that contribute to unequal health.

- **Improving "access" is not enough.** "Access" alone is an inadequate determiner of the extent to which interventions reach the desired groups. Very often, the term "access" is employed in a manner that can easily confound problems that are of fundamentally different kinds, and impede the application of appropriate remedies. A model which considers the four dimensions of *accessibility*, *availability*, *acceptability* and *quality* provides a useful framework for systematically analyzing the nature of the challenges that exist, as well as their possible solutions.
- **Research is a critical part of nearly every phase of the 'discovery to delivery' chain.** Diseases can have a disproportionate impact on developing countries because no effective treatment exists, or because effective treatment exists but is clinically sub-optimal; inadequate supply to implement on a large-scale; too costly to be afforded by low-income groups; less effective, ineffective or of unknown effectiveness in vulnerable groups; inadequate on its own; or impractical for use in low-income settings. Research of various kinds is therefore essential to addressing the impact of these diseases, including to understand better the basic etiology of the disease, to identify possible targets for improved diagnosis / treatment, to create all-new interventions, and to modify existing treatments so that they are effective in sub-optimal settings.
- **'Delivery' concerns should be part of decision-making early in the R&D process.** Malaria, diabetes and rotavirus provide good examples of the role of research across the 'discovery to delivery' chain. Thinking about the challenges of distribution and delivery needs to start as early in the research chain as possible. It cannot be taken for granted that, once created, a product that shows efficacy under trial conditions will prove effective in the more rugged conditions that characterize many developing countries. Effectiveness is a more relevant measure, and takes into account both intervention's efficacy and its acceptance to those for whom it is intended, under routine conditions.

"Intellectual Property Rights and Technology Transfer: Enabling Access for Developing Countries"

Anthony D. So, Arti K. Rai, & Robert M. Cook-Deegan

Introduction. This study addresses how intellectual property and technology transfer practices—particularly at academic research centers, in non-profit institutions and in government (the “public sector”)—influence the availability and affordability of biomedical technologies relevant to developing country concerns.

Analysis. A comprehensive discussion of this subject would require data on the number and type of public sector patents that cover either essential medicines needed in developing countries or tools relevant to research on neglected diseases. In the absence of large-scale empirical research directly on point, the authors make some inferences from available data on the large role that the public sector plays in biomedical innovation as a whole, at least within the U.S.

Findings. The public sector in the U.S. conducts a significant proportion of biomedical research, both basic and applied. Studies indicate that between 60 and 75% of innovative new drugs developed in the last few decades would not have been developed, or would have been delayed significantly, absent public sector research.¹ In the last 25 years, an increasing percentage of this public sector research has become the subject of patent rights. According to one rough estimate, research universities owned almost 15% of all biotechnology-related patents granted in the U.S. in 2000; moreover, about half of university patents granted during that year were in the biotechnology arena. And patents represent only part of the story: proprietary rights controlled by the public sector can arise not only through patenting but also through assertions of contractual rights to future royalty streams when tangible physical materials are transferred.

How the general rush towards proprietary rights in public sector biomedical research affects the availability and pricing of health technology most relevant to developing countries is not yet fully known today. However, it stands to reason that a significant percentage of these rights do cover technology relevant to developing countries, particularly because diseases relevant to developing countries include not only infectious disease but also ailments such as cancer, heart disease, and diabetes. To be sure, some of these patents may not be filed in developing countries. But there have been some important cases of drug patent filings, particularly in countries such as South Africa and India that have the manufacturing capacity to produce generic drugs. Patents on research inputs may be problematic even if not filed in developing countries: to the extent that research is often conducted in the developed world, such patents may pose problems for researchers.

Recommendations. The authors make the following recommendations:

- *Humanitarian Licensing.* For a number of reasons, including efficacy in solving the problem but perhaps most of all realistic near-term likelihood of implementation, we strongly endorse efforts at humanitarian licensing.
- *The Need for Norm Entrepreneurs.* In the area of intellectual property and technology transfer, collective action by universities has a mixed history. PIPRA, a more recent effort at collective action, appears to have achieved some initial success. Arguably, PIPRA represents a reasonable analogy for collective action in biomedical humanitarian licensing.
- *Collective Action Through Pools.* Collective action on humanitarian licensing will be most useful in averting future problems, but will not necessarily address existing thickets. Collective action through pooling may tackle both problems. In areas outside of health, patent thickets—and particularly the possibility of stacking royalties that either overwhelm the value of the project or lead to pricing at inefficiently high levels—have given relevant players sufficient motivation to form a patent pool.
- *Collective Action by the Scientific Community.* Closely related to NIH's role as a norm entrepreneur is the role of scientists as norm entrepreneurs. To the extent NIH has been successful in bolstering open science, its success has been closely linked to support from prominent scientific leaders. In the specific case of global health, collective action by scientists could be useful.

"The Use of Flexibilities in TRIPS by Developing Countries: Can they Promote Access to Medicines?"

Sisule F. Musungu & Cecilia Oh

Introduction. This study was commissioned to: (1) examine the extent to which the flexibilities contained in the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property (TRIPS) have been incorporated into the legislation of developing countries and the extent of the actual use for public health purposes; (2) review the stated trade policies of major industrialized countries, particularly the United States (U.S.) and the European Union (E.U), vis-à-vis developing countries to determine whether these take adequate account of the public health priorities of developing countries; and (3) examine the practical effect and implications of recently concluded bilateral and regional free trade agreements (FTAs) for public health protection in developing countries. The study has been compiled based on existing literature and other available evidence.

Findings. Overall, the study finds that the use of TRIPS flexibilities can promote access to medicines in developing countries. Most developing countries whose laws and practices we reviewed had incorporated one or more of the TRIPS flexibilities and there has been increasing usage of these flexibilities such as compulsory licensing for public health purposes. There remain, however, important gaps both in terms of incorporation and usage of flexibilities, which will need to be addressed if the TRIPS flexibilities are to be used effectively across the developing world. With respect to the stated trade policies of the U.S. and the E.U relating to the protection of intellectual property in third countries, especially developing countries, we find that although some concern for the public health needs of developing countries is reflected, in general, the policies fail to adequately take into account the public health priorities of developing country trading partners. Finally, with respect to FTAs, we find that a number of provisions in recently concluded FTAs between developed countries (essentially the U.S.) and developing countries, pose a real risk of undermining the effective use of TRIPS flexibilities in developing countries for public health purposes.

Recommendations. The analysis and conclusions about the use of TRIPS flexibilities by developing countries, the intellectual property-related trade policies of the U.S. and the E.U, and the implications of FTAs for public health protection in developing countries, are underpinned by a number of public health principles for the implementation of intellectual property in the area of pharmaceuticals. It is in this context that the authors make a range of recommendations for the consideration of the Commission on how intellectual property regimes could be better implemented, used and/or reformed, nationally and internationally, to facilitate the development and access to medicines in developing countries.

The achievement of public health objectives must be the guiding principle for the implementation of intellectual property rules and policies. Thus it is recommended that the implementation of intellectual property rules and policies should ensure the following:

- a rapid and effective response to public health needs;
- sustainability of supply of quality medicines at affordable prices;
- competition, through the facilitation of multiplicity of potential suppliers, both from developed and developing countries; and

- the provision for a wide range of pharmaceuticals to meet an array of health needs, as well as, the need to ensure equality of opportunities for countries in need, irrespective of their level of technological capacity including countries with insufficient or lack of manufacturing capacity, and irrespective of their membership in the WTO.

Additionally, for countries to make effective use of the paragraph 6 Decision (Doha Declaration) to achieve public health objectives, however, it will be important for domestic laws or regulations to reflect the following aspects:

- Provide for a broad range of grounds for the grant of compulsory licenses and specific provisions for government use of patents, as already stated above. In this case, grounds for compulsory license should also specifically include importation.
- There should be a time limitation for negotiations for voluntary license so that where prior negotiations for a voluntary license with the patent holder is required, a definite time limit should be set for such negotiations, after which the requirement shall be deemed satisfied, so that the grant of a compulsory license can proceed without unnecessary delay.
- Provisions in domestic law should not limit the implementation of the Decision to a restricted list of products or diseases, as it is clear that the Decision is applicable without any restrictions on products or diseases. There could also be a clear definition of "pharmaceutical products" for which the Decision can be used. Countries should consider explicitly including diagnostics, vaccines and medical devices used for treatment. Provisions in national legislation should also allow for the compulsory licenses or the government use authorisation to refer to the product, instead of the patent(s) on that product, as this will facilitate the decision making, and reduce the time required to conduct patent searches on all patents in force.
- The Decision also included a waiver for Article 31(h) so the requirement that adequate remuneration be paid to patent holders should be waived in the importing country. A specific provision should be made in domestic law on this waiver.
- Any litigation or appeal by the patent holder should not suspend the implementation of a compulsory license.

"R&D for Development of New Drugs for Neglected Diseases: How Can India Contribute?"

Sudip Chaudhuri

Introduction. Despite the inadequate stress on R&D for new drug development, some new drugs did emerge in India primarily from the public sector laboratory, Central Drug Research Institute (CDRI). India has one of the few public sector organizations in the world, which have their own drug development infrastructure. However, the basic limitation of the CDRI drug development programme has been the lack of commercial orientation.

On the other hand, the model that Indian companies have adopted is to develop new molecules and license these out to the MNCs in the early phase of clinical development. As a result, Indian companies are not targeting the neglected diseases of the developing countries but the global diseases which interest the MNCs.

New drug development. Indian companies have proved their competence as innovators of new processes. But they are yet to demonstrate their capability in new drug development. While some of the molecules developed are at clinical trials stages, no new drug has yet been approved for marketing.

The most important issue in Indian is how to develop the infrastructure for new drug R&D and how to fund it. Since the private sector in Indian is not yet prepared to undertake R&D investments on their own, the options are to collaborate with MNCs, governments, and international agencies. Indian has initiated two Public-Private Partnerships (PPPs) -- one coordinated by the Department of Science and Technology and the other by CSIR.

Funding. First and foremost, funding must improve. One way of improving funding is to accept the recommendation of the Mashelkar Committee (1999) to impose a 1 per cent tax on pharmaceutical sales. Additionally, governments should earn profits from PPPs for which market incentives exist. This return would then be used to cross subsidize those neglected diseases in which market incentives are absent, public support is needed, and no projects have been initiated.

Differential pricing. For the domestic market, a system of voluntary licensing may be introduced on payment of royalty at pre-determined rates. For the international market, particularly for the large and lucrative market in developed countries the IPR rights may be exercised. If product patent rights are exercised, thereby resulting in high prices, then it should be the responsibility of the governments of the developed countries to subsidize the expenditure for the consumers in their countries.

India's global contribution. International initiatives can take advantage of Indian's cost advantage and reduce the cost of new drug development. Indian companies can be more involved in molecule development for neglected diseases. Their world class skills in chemical synthesis and process engineering can be used for such purposes.

Furthermore, 40 percent of the new drug development cost goes towards clinical trials. India's advantages include - huge patient population, speed of recruiting patients and conducting trials, large number of hospitals including specialty hospitals with state of the art facilities, skilled English speaking investigators including doctors trained in western countries and low costs. The regulatory environment has improved - guidelines have been issued and laws have been changed for making it mandatory to conduct clinical trials as per GCP norms.

"Patents, Price Controls and Access to New Drugs: How Policy Affects Global Market Entry"

Jean O. Lanjouw

Introduction. The choices made by each country about its patent system and price regulation will have many ramifications – influencing the size of future investment in medical research, the availability of the resulting therapies, how the financial burdens are distributed across countries, and finally the health of consumers. The author focuses on how patent rights and price regulation affect whether new drugs are marketed in a country, and how quickly.

Effect of IP, launch decision on product entry. Because there are fixed costs associated with launching new products, it would seem intuitive that both weaker price regulation and stronger intellectual property would facilitate entry by virtue of increasing firm profit. However, what makes this an interesting economic problem is that intellectual property can have a second important effect. While patents indeed make local markets more attractive, they also convey control over launch decisions to multinational firms with global interests. Multinationals may delay or even avoid launching drugs in lower-priced countries because they are concerned about the implications for pricing in *other* markets. If they hesitate, and patent rights block otherwise willing local entrants, then strong patent rights may actually reduce product entry.

Process versus Product Patent. Although relatively weak, process patents may nevertheless encourage product entry by slowing down the arrival of competitors, allowing firms to cover fixed entry costs. If innovator firms could be assured of a local monopoly through product patents, it was suggested, they would find it attractive to launch more products. In the presence of externalities, however, this argument is no longer obvious.

International Pricing Externalities. Several mechanisms can generate international pricing externalities. Physical arbitrage across country borders can erode prices in higher-priced markets. Additionally, the behavior of political interest groups can push prices towards uniformity. The author examines whether product patents can reduce access to new drugs by making firms that care about externalities – whatever the source – more important players. Whether access is, in fact, limited is also a key question for interpreting the welfare implication of firms' inability to fully price discriminate across countries.

Analysis. The analysis covers a large sample of 68 countries at all income levels and includes all drug launches over the period 1982-2002. It uses newly compiled information on legal and regulatory policy, and is the first systematic analysis of the determinants of drug launch in poor countries.

Findings. Price control tends to discourage rapid product entry, while the results for patents are mixed. There is evidence that local capacity to innovate matters and that international pricing externalities may play a role.

Short-term patent protection that includes products, or long protection only of manufacturing processes, are both patent regimes that tend to encourage more or faster launches in the developing world. Increasing the strength of a patent system to include long-term protection on pharmaceutical products appears to spur market entry – among the high-income countries. For the low- and middle-income countries, the evidence that extending protection enhances access to new pharmaceuticals is mixed.

There is some evidence that high levels of protection might encourage more frequent entry of innovative products in the short term, particularly in countries where multinationals might otherwise hesitate because local technical capacity might create competitive pressures. On the other hand, in the longer term that same domestic capacity could be an alternative source of entry, and we find that a country offering extensive patent protection may lose the benefits of that activity and have fewer new products in the market overall as a result.

Like intellectual property, the standard argument regarding price regulation – that it will dissuade market entry – appears to have more relevance among the high-income countries. For these countries, extensive price control is always found to lower the probability of market entry, and moderate regulation appears to do likewise, even in the long run. Not so for the poorer countries. There we find that while price regulation makes it less likely that new drugs will be available quickly, it does not appear to prevent new products from being launched eventually.

"Statistical Trends in Pharmaceutical Research for Poor Countries"

Jean O. Lanjouw & Margaret MacLeod

Introduction. It was argued that introducing patent rights in developing country markets might stimulate greater R&D investment targeting their specific health needs – areas long neglected. This paper examines this argument using statistical data and survey evidence.

Analysis. We identify a set of diseases where 99% of the burden is estimated to fall in lower income countries. Because science gaps and market potential will influence R&D priorities, we break this group into a subset that already have low-cost and effect treatments, and those that to not. We then examine trends in indicators of R&D activity. These include grants dispersed by the NIAID as an indirect measure of the direction of pharmaceutical researchers' interests; trends in citations to the biomedical literature, which should be a relatively early indicator of R&D activity; and patenting in the United States – the most direct signal of commercial interest in an area of research.

Findings. Based on these statistics, the level of innovative activity related to diseases specific to poor countries remains extremely low relative to pharmaceutical research overall. The subset already having good treatments available has continued to see a persistent downward trend in its share of U.S. pharmaceutical patenting and biomedical citation over the past twenty years. By contrast, the set of diseases still in need of better low-cost treatments has seen a trend increase in its share of patenting and bibliometric citation, normalized by the relevant (growing) population totals.

In the case of patenting, we observe in the data what may be the beginning of a speeding up of this trend increase in the early 2000's, but it is too early to be confident that it will persist.

R&D in the developing world. We also pay particular attention to R&D occurring in India – as indicated both by U.S. patenting by India-based scientists and the results of a pair of R&D surveys in 1998 and 2003. One might expect scientists working in India to have a comparative advantage in developing drugs targeting developing country markets and that new R&D activity would be most apparent there. Pharmaceutical patenting by India-based inventors has grown rapidly as a share of all patenting in the U.S. – to over 2% - with a similar trend in Europe. Total R&D expenditure in this sector within India also surged.

The survey results suggest, however, that in 2003 at most 10% of that expenditure was directed towards creating new products specifically suited for developing country markets. This is a significant drop from the 16% share found in the baseline survey of 1998 and may indicate a further concentration of R&D efforts on global products.

"Intellectual Property and Product Development Public/Private Partnerships"

Jon F. Merz

Introduction. This is the final report of an interview study of US-based product development public/private partnerships (PDPPPs) focused on the development of new drugs, vaccines, and other products for diseases that disproportionately affect developing countries. PDPPPs are nonprofit entities that sponsor others to perform or directly perform themselves at least one of the following R&D activities: basic research (such as target identification, validation and proof of concept), animal, preclinical and clinical testing, licensing, and manufacturing. The successful PDPPP may also be responsible for distribution. PDPPPs are distinguished from Access PPPs, which are nonprofit entities concerned primarily with expanding access by pulling together manufacturers, funding agencies (such as GAVI, USAID) and developing countries to enable the purchase and distribution of existing drugs, vaccines, and other medical products.

Study. The aim of this study is to describe: 1) the range of models used to organize and fund each effort; 2) the nature and comprehensiveness of intellectual property (IP) faced in an area, and the strategies and experiences of PDPPPs in addressing IP issues; 3) the number and nature of collaborative and licensing arrangements used to gain access to necessary IP and technological know-how; and 4) any problems faced and solutions developed to ensure freedom to use. One aim of this study is to place intellectual property issues into the larger context of development and distribution of products in an environment that is technologically and fiscally challenging, highly regulated, and subject to international trade conditions.

Analysis. The method used in this study was to: 1) develop a census of US-based PDPPPs; 2) examine publicly available information (e.g., websites, news accounts, and published case studies) about the founding, goals, funding, and strategic planning of the organizations; and 3) use semi-structured interviews of top managers, attorneys, and consultants to examine experiences with the use of and problems raised by intellectual property.

Findings. Overall, most survey Respondents did not perceive IP issues to be insurmountable, but they clearly are requiring substantial efforts in time and money to manage. Several Respondents mentioned the high costs of patents, maintenance fees, freedom to operate studies, and legal services related to contract negotiations, the costs of which they would prefer to spend on their science.

Discussion. The results reported here suggest that the environment in which these PDPPPs are operating is changing rapidly. Several Respondents noted that universities and others are more open now to innovative licensing strategies than they had been in the past. It was also noted that the NIH has been moving from basic science funding towards sponsoring development. Indeed, numerous Respondents noted that what they are doing really is a no-brainer. There are substantial potential benefits of facilitating product development for use everywhere, with a focus on ensuring access in developing countries.

There are also few downsides, and the approaches being pursued should appeal to everyone, including industry. Several Respondents noted that they have the “moral high ground” that can be used, if necessary, to publicly pressure corporations, universities, and governments to license on reasonable terms. It was acknowledged, however, that this card should not be played often, or lightly.

From a critical perspective, a health policy colleague, Don Light, suggested that, because of the primacy of corporate interests served in PPP arrangements, PPPs should be called private/public partnerships. We find that in most partnerships, corporate partners retain substantial rights for manufacturing, subject to meeting developing country demand. Pricing would be set to provide some profit. By externalizing for the firm at least some R&D costs and otherwise helping to facilitate the overall process, PDPPPs aim to bring value to their corporate partners while retaining rights to markets that cannot afford patent rents. Interestingly, the best price in these (as a matter of fact, all) markets would arguably be achieved by pure competition for manufacturing and distribution, as this would drive prices toward their marginal costs of production. Nonetheless, only one Respondent explicitly mentioned pursuing this model. Instead, only if the corporate partner fails to meet demand or otherwise breaches production targets would the PDPPP be free to look for alternative manufacturers. It does seem that IP ownership or exclusive rights in developing country markets unburdened by contingent manufacturing rights of partners would be a dominant strategy for a PDPPP to pursue. Nonetheless, that PDPPPs have not secured broader rights may reflect their lack of market power or perceived value added for firms.

"Economic Aspects of Access to Medicines after 2005: Product Patent Protection and Emerging Firm Strategies in the Indian Pharmaceutical Industry"

Padmashree Gehl Sampath

Introduction. The main purpose of this study is to investigate what the effect of introduction of product protection for pharmaceuticals in India is likely to have on the pricing of new medicines in the Indian domestic and third country markets, the importance of this change, and to what extent compulsory licensing can be an economically feasible alternative for generic producers.

Analysis. The study employs a multi-method field study approach. A variety of data sources, including primary sources, secondary sources and case studies that rely considerably on scientific expertise perception of scientists were used at various stages of the analysis. A firm-level survey of 103 firms (within in the top 135, when Indian pharmaceutical firms are ranked according to export data, R&D investments and net sales) is the central focus of the study, conducted to derive results on the impact of product patent protection on emerging R&D and business strategies in the Indian pharmaceutical industry. The focus of the survey has been mainly on learning and innovation processes and how these will be affected by stronger intellectual property protection and less so on innovation inputs and outputs, which have been addressed in previous literature.

Findings. Product patent protection in India is in fact emerging as a very important decisive factor in determining access to medicines, both in India and other countries in Africa. The survey shows that Indian firms will face severe challenges to adapt to the emerging patent regime while (a) operating in an industrial and regulatory climate that still is not fully aimed at providing a conducive environment for the industry and (b) coping with the losses induced by the restrictions placed on them. This is in keeping with earlier studies on the topic such as Chaudhuri, Goldberg and Jia (2003), which show that the losses to the Indian industry in certain segments following India's full scale TRIPS compliance are very high. Therefore, emerging strategies of Indian firms are shaped mostly by survival needs and not by issues related to access to medicines of the general public, whether in India or other least developed countries.

Recommendations. The main policy recommendations that follow from the analysis are as follows:

- The Indian government has to invest more extensively in building local competition enforcement agencies, patent examiners, informed judiciary which is more attuned to the public health and local industry needs in a country like India, and price control mechanisms in order to promote access to medicines in the local market and other LDCs.
- The present Act still contains several provisions that are open to interpretation and therefore whether all the flexibilities that are permissible under the TRIPS Agreement will be used by India or not, is still much in the open.

- Other rules affecting the industry, such as those on data protection should be enacted only after taking into consideration the interests of the generics industry and the scope of its production. If the generic industry in India is curbed further, a large amount of cheap supply of medicines at very competitive prices will be seriously affected.
- The government should apart from providing an expedient administrative procedure for the implementation of Section 92(A) of the Act, create a higher level of awareness on the option of compulsory licensing to supply to other least developed countries amongst the local industry. This may create a more conducive attitude amongst the firms to deal with requests from other least developed countries in future.
- The government should, in a concerted effort with the industry, plan ways in which to reduce bottlenecks to pharmaceutical R&D in the local Indian context. These will be very helpful to aid the industry to devise and implement strategies for survival.
- Promotion of R&D into diseases of the developing world, as the survey goes on to show, will remain a public good problem, irrespective of the capacities in the pharmaceutical sectors in developing countries. The government of India (either singularly or in collaboration with other governments in developing countries) should initiate public R&D programmes that utilize the strengths of the Indian industry to find cures for neglected diseases.

"The Right Tool(s): Designing Cost-Effective Strategies for Neglected Disease Research"

Stephen M. Maurer

Introduction. This paper stylizes existing proposals for how to fund research as “end-to-end” and “pay-as-you-go”. “End-to-end” models create a single reward to elicit discovery throughout the drug development pipeline. The leading end-to-end model, “AdvancedMarkets,” would use subsidies to boost the prices that LDCs pay for new drugs, thus reinvigorating incentives for private sector investment while leaving R&D decisions firmly in the private sector.

The leading “pay-as-you-go” model, “Virtual Pharma,” would create the non-profit equivalent of private drugmakers. In this scenario, the public sector would retain control of R&D but outsource most of the work to private vendors. This paper seeks to advance the discussion beyond theory by identifying – and in some cases starting to assess – the empirical evidence on which any rational decision must be based.

AdvancedMarkets or Virtual Pharma? Funding agencies and governments (hereinafter “sponsors”) urgently need to know which solution can deliver new drugs at the lowest possible price. Success will require, in the gray language of business, cost containment. Because drug development entails roughly one dozen separate and distinct research tasks, cost-containment will require sponsors to accomplish two separate goals. First, a successful strategy must ensure that each research task is performed at the lowest possible cost. This will often mean outsourcing work to low cost providers. Second, it is not enough for R&D to be performed by the lowest cost providers. A successful strategy must also pass these savings on to sponsors.

Challenges.

There are at least three reasons to think that an AdvancedMarkets strategy would overpay for research:

- *Setting the Reward.* Sponsors know very little about commercial sector R&D costs, thus tend to overpay by twenty to thirty percent on average.
- *Inefficiency in Outsourcing.* Commercial drugmakers face significant restrictions on their ability to outsource due to “piracy” and open source concerns.
- *Mistrust of Sponsors.* Commercial firms may worry that sponsors will renege on their promises, thereby demanding compensation to cover this risk.

Virtual Pharma strategies also face significant challenges:

- *Inadequate Buying Power.* Publicly-funded Virtual Pharmas are unlikely to have the same purchasing power as large drugmakers, unless they budget for spending levels found in private industry.

- *Picking Winners.* Pay-as-you-go models like Virtual Pharma assume that non-profit organizations can pick winners at least as well as their commercial counterparts, which requires de-funding of inefficient ventures.

Recommendations. This paper argues that the foregoing drawbacks are generic and inescapable. Neither AdvancedMarkets nor Virtual Pharma is ever likely to be perfect. Instead, sponsors should choose whichever strategy is least imperfect. In principle, this decision is no different than the dollar-and-cents judgments that commercial businesses make every day. Cost – not ideology and sentiment – should be the determining factor.

Designing Incentives: Beyond Patents. Virtual Pharma strategies usually cost more when drug candidates are patented. This suggests that successful strategies should choose appropriate non-patent incentives for each step of the R&D process.

- *Basic Research.* Basic science requires intense individual creativity and the ability to combine and elicit knowledge from around the world. Grants are an appropriate incentive for meeting these social challenges.
- *Early Phase Drug Discovery.* Early phase discovery translates basic research into ideas for curing disease and, eventually, specific chemical compounds (*i.e.*, “drug candidates”). Here, the dominant social challenges include persuading researchers to exercise creativity and eliciting knowledge that may be widely scattered around the world. Open source, prizes and (perhaps) grants are effective mechanisms for meeting these challenges.
- *Pre-Clinical and Clinical Testing.* Given that testing is extremely expensive, the dominant social challenge is cost containment. Contract R&D is particularly valuable in this environment because competition forces companies to offer the low prices.
- *Manufacturing.* Contracts are also a powerful way to encourage price competition among manufacturers.

"A Review of IP and Non-IP Incentives for R&D for Diseases of Poverty. What Type of Innovation is Required and How Can We Incentivise the Private Sector to Deliver It?"

Adrian Towse

Introduction. OHE Consulting has been commissioned to provide a review of market and intellectual property (IP) related proposals, in addition to a study of the importance of incremental versus breakthrough innovation.

Characterising innovation in general. Innovation has a number of characteristics or dimensions; advances along any one dimension or a combination of dimensions can be of value. Therefore, the distinction sometimes made between incremental and breakthrough innovation is not a particularly meaningful one. What matters is to identify the attributes of innovation that are important and seek to find products that will provide them.

Characterising innovation in pharmaceuticals. For pharmaceuticals, however, there is a need to make a distinction between the final user (i.e. the patient) and the payer, as these usually do not coincide, because of the use of third party payers, private and social insurance, and tax-based systems in many parts of the world. In many parts of the world there is medical need but no ability to pay and no third party insurance system. The purpose of this paper is to explore how the private sector can be incentivised to deliver innovation in these circumstances. In this context, the ability to alter the institutional environment by providing incentives will be crucial.

Innovation for neglected diseases. To illustrate the types of innovations required to better treat, and in some cases prevent, neglected disease the author has selected three disease case studies, one from each of the Commission on Macroeconomics and Health categories: acute respiratory infections, Malaria, and Leishmaniases.

PPP and R&D. Most of the research in neglected diseases is now conducted by a range of players through the vehicle of public private partnerships (PPPs), which, on the basis of funding from philanthropic sources, are able to harness the skills of different organisations at different stages of the R&D process. Large companies play an important role, albeit in a semi-commercial basis; small companies require a commercial return.

R&D incentive mechanisms for the private sector. To generate the innovations needed, commercially-based incentive mechanisms, if carefully designed, have the potential to complement the activities of PPPs.

Drawing on the experience of two existing incentive mechanisms – orphan drug legislation and the paediatric initiative, we conclude that the following “pull” incentives have the greatest potential to generate the innovation needed:

- transferable/roaming intellectual property rights (TIPR), whereby a company is awarded additional IP on a product of its choice in exchange for developing a given neglected disease product;

- transferable fast track/priority review/accelerated approval (TFT) whereby a company receives more rapid regulatory review for a product of its choice in exchange for developing a neglected disease product (effectively lengthening the period of patent protection for the chosen product);
- advance purchase commitments (APCs) provided through a guaranteed purchase fund.

The ability to trade these rights will be important so that in all three cases it should be possible, for example, for a small biotech company involved in early stage development to sell its product to a larger company after (say) completion of Phase I or Phase II trials.

Each of the three has strengths and weaknesses. For example: APCs can most easily be fine tuned and hence may be most cost-effective; TPR has most credibility with the industry; TFT delivers efficiency gains to developed countries. All can be made complementary to existing “push” approaches such as PPP funding. They are not mutually exclusive measures and could be designed to address different innovation needs.

"Public-Private Partnerships for Product-Development: Financial, scientific and managerial issues as challenges to future success"

Elizabeth Ziemba

Introduction. The purpose of this paper is to examine certain aspects of public-private partnerships for product development (PPP-PDs); to measure their progress as well as challenges in certain key areas. The report identifies for the World Health Organization additional steps to increase the likelihood of product development and distribution for medicines, vaccines and devices for neglected diseases by PPP-PDs.

Analysis. Twenty-four PPP-PDs were selected for in-depth study based on their primary missions being devoted to the development of a drug, vaccine or product to treat and/or cure a neglected disease.

Recommendations. Recommendations to the WHO based on the studies key findings include:

- (1) Scale of past, current, and future funding, and the question of financial sustainability
 - Assist with the development and implementation of product roll-out plans working with disease-based alliances,
 - Work to improve coordination among disease-based alliances, PPP-PDs, and other entities to reduce duplication of efforts and maximize resources.
 - Assist PPP-PDs to secure funding by opening or continuing dialogue with new potential funding sources.
 - Assist PPP-PDs to work with the World Bank and other funders to expand the pool of investors and expand the types of investments.
- (2) Portfolio Management and the scientific challenges facing PPP-PDs
 - Develop new and support existing mechanisms to support basic and translational research to assist the work being done by PPP-PDs.
- (3) Governance, Representation, and Accountability for PPP-PDs
 - Work with PPP-PDs to ensure that the fruits of these entities benefit societies equitably in that very poor countries with large populations, unpopular governments or poor infrastructure may be excluded from these partnerships,
 - Facilitate with PPP-PDs to ensure that they are working in harmony and integrated with national health priorities,
 - Lead the development of transparent policy and procedural frameworks to protect the public interest,
 - Promote and support research aimed at identifying good partnership practice,

- Lead the discussion to ensure that developing country governments are given an adequate voice in PPP-PDs,
- Assist with capacity development in low income countries through coordination with PPP-PDs.

(4) Role of PPP-PDs in developing capacity in low income countries.

- Advocate for developing capacity and to establish basic, achievable goals including: regionally harmonized clinical trial guidelines, ICH compliant Institutional Review Boards (IRBs) for ethical and safe clinical research, health research requirements, and local capacity.

(5) Product delivery to developing countries

- Integrate PPP-PDs into the blueprint for introduction of HIV vaccines and other new medicines,
- Utilize its authority to engage national governments in the planning for the introduction of new medicines.

(6) Collective activities in support of PPP-PDs

- Act as a facilitator for PPP-PDs to collaborate and provide a forum for research and discussion,
- Evaluate and direct collection of epidemiological data tailored to each country to ensure that decisions about the introduction of new medical products matches the disease burden of individual countries.

No title

Warren Kaplan

Introduction. The fact that partnerships between the for-profit and non-profit sectors (e.g., public private partnerships - PPPs) exist at all is testament to two conditions: millions of people globally die or become disabled from diseases for which there are no or inadequate medicines and the free market has no incentive to develop such medicines. Although PPPs formed in response to this market failure must view contractual IP agreements as a way of 'managing risk', they have another agenda, i.e., to make sure that the new product emanating from the PPP will be as affordable as possible for citizens in developing countries.

Price setting. The concept of "affordability" means that a licensee must provide the product at prices that patients can afford, or retain the right to limit the price of the products when sold. However, it is likely extremely difficult to get parties in a negotiated agreement to agree to conditions regarding prices, even if applied only to developing countries. This is particularly true for "early stage" technology that carries a risk of never being a product. Additionally, for-profit entities do not want to commit to any price structure too early.

Contract language often implies the price i.e., a stipulation that the cost of the final product could be the cost of production (assuming one or both parties knows this), plus some reasonable mark up that is negotiated in advance. For drugs only supplied to low-income markets, products could be priced at average cost, in contrast, for drugs sold in both high- and low-income markets, products for the poorer countries could be priced at marginal cost, since profits from higher income markets could cover fixed costs. Prices could include income-adjusted margins for countries with greater ability to pay, such as lower- and upper-middle income countries.

Access as proxy for price. The more common proxy for "price" is "access".

- A PPP can help determine "access" by posing requirements for further development by others depending on various circumstances, such that for instance, a license is granted in "Developing Countries" [either a pre-set list or defined by national economic indicators ...] under the IP for treating [condition X] ..."
- A PPP can help determine "access" by attempting to segment markets within countries (into public and private).
- A PPP can request various "white knight" stipulations, which require the licensee to provide for the establishment of a benefit flowing from the technology supplier or user to the local community.
- A PPP can create a "non-suit" agreement which, in effect, bars the holder of intellectual property, from enforcing the IP within a certain set of countries and under a certain set of conditions. In essence, a typical IP license agreement is an implied "non-suit" makes this "permission to exploit" explicit.

The fact remains that current contractual language cannot ensure affordability or equitability access to a product. Even the lowest prices charged may not be affordable. A well-thought out contract is necessary, but insufficient, to make sure that all stakeholders respect human rights norms and ethical standards.

"Traditional Medicine: Modern Approach For Affordable Global Health"

Bhushan Patwardhan

Introduction. This paper explores the place and utility of Traditional Medicine (TM) as a vehicle to affordable health to large un-served or underserved populations in developing countries. Most developing countries have relied and will continue to rely on traditional natural medicines due to the deterrence of high costs and availability of modern allopathic medicines.

Policy concerns. Prime issues of concern for attention of local government and/or policy makers are: endorsement of TM, validation of efficacy, regulation of safety, standardization of materials and harmonization of practices, professionals' training, construction of delivery infrastructure, protection of intellectual property, enforcement of equitable distribution of TM, guarantee of sustainability of supply of resources, supervision of price structure, IPR inequities and back pressure from pharmaceutical industries (lack of innovations and productive outcomes).

A major problem with traditional indigenous medicine is discovering a reliable 'living tradition' rather than relying upon second hand accounts of their value and use. In many parts of the world the indigenous systems of medicine have almost completely broken down and disappeared.

Opportunities. Lag phase for botanical medicine is now rapidly changing for a number of reasons. Problems with drug resistant microorganisms, side effects of modern drugs, and emerging diseases where no medicines are available, have stimulated renewed interest in plants as a significant source of new medicines.

TM knowledge and experiential database can provide new functional leads to reduce time, money and toxicity-- the three main hurdles in the drug development. These records are particularly valuable since effectively these medicines have been tested for thousands years on people. Thus the TM knowledge database allows drug researchers to start from a well-tested and safe botanical material. With Ayurveda, the normal drug discovery course of 'Laboratory to Clinics' actually becomes from 'Clinics to Laboratories'— a true Reverse Pharmacology Approach.

Developing countries could exploit traditional medicine to kick-start biotech, only if their products measure up to the demands of Western regulators. For example, the traditional Chinese medicine - Kanglaite Injection is ready to enter Phase II clinical trials in the United States for the treatment of several cancers, including breast and prostate cancer. Efforts are underway to establish pharmacoepidemiological evidence-base to TM, safety and practice.

Recommendations. The author provides a list of global (presented below) and regional (in paper) recommendations.

- WHO should invite a collaborative mega project, consisting of numerous medium to small sized projects to collect primary data regarding TM in developing countries, first singly and then collectively, from an exclusive perspective of public health, albeit not overlooking relevant purely scientific data.
- Parallel but optimally following, WHO collaborative centers, fashioned somewhat similar to NCCAM at NIH of the USA, should be developed (to begin with in countries where TM has major presence) to conduct rigorous fundamental and applied research (incorporating novel quantitative and systems approaches) in TM using appropriate methodologies.
- WHO led global social marketing campaign should be developed and undertaken to disseminate current holistic data on TM (that would educate about not only practices of TM but about philosophies and basic principles underlying respective TM practices) to health care sector- particularly in developed countries and among modern medicine service providers at all levels.
- WHO should develop with help from respective expertise, workable protocols and regimens to treat diseases afflicting developing world population based on TM after weighing in benefit-cost and efficacy-ignorance ratios- in cases where inadequate data tilt towards integral value, and then distribute and disseminate those literature among practitioners in developing countries- traditional or modern.
- WHO should fast track, through various world bodies, the issues around IPR protection around TM, to ensure that, while knowledge does not get lost in secrecy and is available to modern medical science to further cause of human health, the major portion of profits from knowledge and technology arising out of TM should be channeled to needs of those populations that historically played custodian to that body of knowledge.

"Innovation in Developing Countries to Meet Health Needs: Experiences of Brazil, China, India, and South Africa"

The Centre for Management of IP in Health R&D (MIHR)

Introduction. The studies undertaken for this Report throw light on how various organisations can, through the efforts of biomedical research, innovation and production systems, help poor people in the developing world gain improved access to the drugs and vaccines they need. The report examines the experiences of four developing countries, Brazil, China, India, and South Africa, with regard to the status and determinants of biomedical innovation in those countries and make recommendations that may assist policy development in those and other developing countries in relation to meeting their health needs.

Six determinants of innovation. The developing countries discussed in this paper also have national systems of innovation (NSIs) but not necessarily directed to health and with little concern for diseases of the poor. There is a need to develop such NSIs that will help to redress health inequities. The development and implementation of an effective NSI requires an understanding of the determinants of innovation. We propose six determinants:

- Creating capacity for and undertaking R&D
- Creating and sustaining capabilities to manufacture products to appropriate standards
- Promoting and sustaining domestic markets including government health systems
- Promoting and sustaining export markets including sales to international organisation such as UNICEF
- Creating and implementing systems of IP management appropriate to the needs of the country
- Creating and implementing systems for drug, vaccine, diagnostic and device regulation to help ensure safety, efficacy and to take into account issues of cost benefit.
- The six determinants are assumed to be dynamically linked such that progress in one is facilitated by and dependent upon progress in the others.

Findings. Despite promising developments in their innovative capabilities as measured by patents, publications, and manufacture of health technologies, the private sector in Brazil, China, India, and South Africa has not been oriented towards diseases of the poor. They seem to have similar decision making criteria as their developed country counterparts. This reality calls for the development and implementation of government policies to provide incentives to the private sector to address diseases of the poor.

Each of the four countries recognizes the value of good IP systems and effective IP management although there is a lack of trained personnel, institutions, and systems in each country. Efforts are underway to address this need but the challenges are immense. A promising development is the rapidly growing level of international collaboration that helps the private sector to increase rapidly its IP expertise.

It is still too early to determine the impact of TRIPS in these four countries. Each country has embraced TRIPS and there are strong government policies to use TRIPS as a means to enhance R&D capabilities, and to increase trade and investment. There are some early indications of increased foreign investment, particularly in India. However, the question of the impact of TRIPS on access to health technologies by the poor remains unanswered.

Recommendations. These findings lead to a number of possible implications for how these and other developing countries can increase their success in innovation.

- There may be opportunities to increase trade between developing countries and to seek to establish price controls on a regional basis
- As each country develops economically, it should look particularly at the need and opportunity to expand domestic markets to the underserved in rural areas.
- Governments should provide tax incentives for small and medium enterprise (SME) in biotechnology. The government could also promote innovation by supporting the establishment and expansion of R&D centres in both the public and private sectors.
- Governments should encourage the continued growth of the generic drug (and vaccine) production industries. TRIPS has no impact on the production of products for which the patents have expired.
- Governments need to continue their efforts to expand capabilities in IP management and policy formulation and to explore the ways in which they can most effectively work within the TRIPS framework.
- The private sector in these countries should look for niche products (e.g. diagnostics) that may take advantage of particular strengths and needs in the country.
- At all levels governments should seek to promote dynamic linkage among the key institutions for innovation – R&D centres, producers, buyers and users (both domestically and foreign), IP centres and regulators.
- Perhaps the most highly impactful action that governments can take is to promote the formation of public private partnerships (PPPs) focused on the development of health technologies to meet the needs of the poor.

"Implications of Product Patents – Lessons from Japan"

Reiko Aoki & Tomoko Saiki

Introduction. The authors identify possible consequences of the introduction of the product patents in Japan in 1976. They look at changes that occurred in the domestic pharmaceutical market, as well as innovation and changes in the context of the international pharmaceutical market. At the time it was envisaged that stronger patent protection, such as product (material) patents, would make some substitutes unavailable to the market and result in higher price of products that are protected by patents. In case of Japan, prescription drug prices are set by the Ministry of Health, Labor and Welfare for the purpose of insurance reimbursement and are not determined by the market.

Findings. The availability of products was not adversely affected by the stronger patents. This was the case for over the counter (OTC) products as well, of which prices have been falling. We actually observe a steady increase in number of drug products after the introduction. We suspect there was a mild reorganization of the pharmaceutical market. Changes in concentrations ratios suggest that the very largest firms became more dominant while some large firms either left the market or lost shares. Since the total number of pharmaceutical firms did not decline, the most dominant products seem to have increased market share. Additionally, stronger protection increased foreign investment in production and research facilities in Japan.

Both the absolute number of R&D expenditure and as a proportion of sales increased around 1976 and continued to increase. Firms also increased the proportion of research employees. Foreign firms also became innovative by building research facilities in Japan after the law change.

Although we do not observe significant increase in number of patents, there was significant reduction in use of process patents, meaning firms did in deed take advantage of product patents. At the same time there was a significant increase in original drugs developed in Japan and a change in trading pattern of pharmaceutical technologies. These facts lead us to conclude that quality of Japanese pharmaceutical innovation shifted (such as from modification to application (Hara, 2002), or from process modification to product modification) after the introduction. The quality became more in line with the imported technologies suggesting Japan “caught up”.

Recommendations. In considering product patents, public health policy and industrial policy should be separated. In case of Japan, product patents were introduced from industrial policy point of view. Governments control price of drugs and delivery of health services to counter patent protection. The long run benefits from introduction of patents take longer to materialize, but such benefits may increase the national resources available for public health eventually.

"Traditional Chinese Medicine Could Make “Health for One” True"

Qian Jia

Introduction. Traditional Chinese Medicine (TCM) has been systematized and theorized in practice and has developed many methods to improve health over thousands of years. TCM has become academic rather than experiential medicine. TCM has developed a systematic health care system, which is practical and advanced, universal and thorough, and notably characterized by simplicity, convenience, affordability, safety, efficacy, and effectiveness.

Evaluation of TMC. The value of TCM is judged by its potentialities, as well as its present applications. Evaluation of TMC should be based more on the TCM theory-based method than merely on scientific-based standard. After the general introduction of TCM theory and therapies, we find out that mastering its knowledge and using it actively in practical work is the most convenient and valuable way to preserve and develop TCM. Without the usage being directed by TCM theory, its character such as being simple, convenient, cheap and effective will disappear because of the misuse of TCM therapies and products.

Use of TMC. Now in China, TCM accounts for around 40% of all health care delivered. Many other developing countries have learned from China the experiences of harmonizing traditional medicine and modern medicine in achieving the goal of primary health care. Apart from the infectious diseases, certain chronic diseases, senile diseases and psychosomatic disorders can also be cured by TCM. The most encouraging fact is that many new therapies can be invented according to TCM theory.

Challenges and recommendations for innovation of TCM. To develop new drugs by innovating on TCM now draws plenty of attention and interests all over the world. It is considered a convenient way to develop low-cost, more available and affordable new drugs. The key problem is that TCM theory has not been studied and understood systematically.

- Incorrect policies and rules are made by the government in administering TCM due to making little of the theory and value of TCM. TCM is gradually losing its characteristics and clinic advantages mainly from the misdirection of national policy due to a lack of practical standards to evaluate the safety, efficacy of TCM, it isn't fit for Chinese medicines to examine and ensure their quality by analyzing quantities of one or a few measurable components, and research on TCM theories are increasingly divorced from clinic practice. Additionally, indigenous practitioners of TCM are not qualified to treat patients. Authorities should qualify excellent indigenous TCM holders to treat patients with traditional knowledge with required continuation of training.
- Need to ensure the sustainable supply of wild animals and plants used in TCM. To guarantee TCM to have enough materials resources to use, the government, local community and the medical enterprises should strengthen the endangered wild species to be farmed and cultivated and tamed, for the complement alternation of herbal materials and artificial synthetic are not effective.
- No good methods have been developed to protect traditional knowledge including TCM from being used without consent. Individuals and countries that have created

and kept such knowledge could not benefit from it while the “biopiracy” frequently occurred in the developing areas. Governments should attach importance to the experts of both TCM and intellectual property, and establish specific policy and regulatory issues for traditional medicines all over the world as well. It is also a practical measure to establish “Database of TCM knowledge”, service agencies of intellectual property of TCM and self-discipline organizations.

- The existing evidence revealed a serious flaw in the educational system of TCM including textbooks, curriculum and faculty and so on because many graduates from TCM academies couldn't master the essentials of TCM and employ TCM to treat patients. Authorities should emphasize the insistent use of TCM and improve the efficacy of TCM by reforming the current TCM educational system.
- Some serious side effects and toxicity of Chinese medications occurred because many people including most doctors who don't understood TCM enough haven't used TCM following the theory of TCM. The important way to avoid toxicity of Chinese medication is to understand TCM theory as well as characteristics of Chinese herbs. The government should encourage mastering appropriate use of TCM by training and additional education.
- TMC is not understood within the existing framework of science and technology studies. TCM has characteristics and advantages to be used by modern society and will be better understood and accepted only after the modern science and technology develop further.

"Pharmaceutical Tariffs: What is their effect on prices, protection of local industry and revenue generation?"

Müge Olcay and Richard Laing

Study. The objective of this study was to examine tariffs levied on medicines. This paper provides data on the tariff rates levied and revenue generated by over 150 countries around the world on different categories of pharmaceutical products. These categories include active pharmaceutical ingredients, finished products and vaccines for human medicines. Data for selected sub-categories of pharmaceutical products is also provided.

Findings. The analysis has shown that many countries for which data are available do not levy duties on pharmaceutical products. Fifty-nine percent of countries for which data are available levy tariffs on pharmaceutical active ingredients. Sixty-one percent of countries levy tariffs on finished pharmaceutical products. A total of 35% of countries still levy import duties on vaccine imports. Ninety percent of countries apply less than 10% tariff rates on medicines. Pharmaceutical tariffs generate less than 0.1% of Gross Domestic Product (GDP) in 92% of countries for which data is available.

Based on our analysis of the available data, we conclude that tariffs have a very limited impact on pharmaceutical prices in most countries, that tariffs do not appear to be used substantially for industrial policy objectives of protecting local industry and that very little revenue is actually generated from these tariffs. Other measures related to pricing, taxes, mark-ups and financing are likely to have far greater impact on access to medicines.

Discussion. The Uruguay Round demonstrated the international communities' willingness to address the issue of high tariff rates. The Doha negotiations about the public health implications of the TRIPS agreement have shown that medicines have a special status and should be treated differently from other products and services. For the first time, health sector commodities have been brought into the international trade negotiations arena. Tariffs on pharmaceutical products not only constitute an international trade issue but are also a public health issue, especially for the populations of those few countries that continue to levy high tariff rates on both active ingredients and finished products imports. Negotiations during the Sixth WTO Ministerial Conference which will be held in Hong Kong, People's Republic of China in December 2005 should continue efforts to address the issue of tariffs levied on pharmaceutical products.

It must not be forgotten that although high tariff rates can increase the price of medicines, they are a relatively small factor, since even countries with low tariff rates may have excessive manufacturer prices, high add-on costs and additional taxes such VAT or other forms of central or local government taxation which can significantly increase prices of medicines. These markups can have a compounding effect on the prices of medicines. (Levison & Laing, 2003).

Nonetheless, tariffs on medicines may prevent some individuals in some countries having access to affordable medicines. In this context, tariffs may play a role in contributing to the high price of medicines.

Recommendations. While governments may generate some revenue and may protect local industries, the public policy implications of exclusively levying duties on the sick must be considered. It is vital that policymakers, both at a national and international level, address the issue of tariffs on medicines and recognize the regressive nature of these duties, which ultimately tax the sick without regard for their economic status or ability to afford these medicines. From this public policy standpoint, tariffs on medicines should be eliminated during the Doha round of trade negotiations.

"Drug Regulation and Incentives for Innovation: The Case of ASEAN"

Sauwakon Ratanawijitrasin

Introduction. The focus of this paper is to examine the ways in which regulatory frameworks affect the incentives for pharmaceutical innovations in developing countries, using member countries of the Association of South-east Asian Nations (ASEAN) as case study.

Analysis. The paper employs a two-level focus approach: a wide-angle view of drug regulation in the region whose members possess varying levels of research and development capacities, supplemented by a zoomed view using data from Thailand where more detailed data are available to the author. Data collection relied mainly on review of documents from various sources. Interviews and personal communication were carried out for added information and deeper understanding.

Experiences of ASEAN on Issues Related to Drug Regulation and Research. ASEAN member countries share a number of common characteristics with regards to their pharmaceutical sector and regulation. Some of these characteristics can be said to reflect what found in developing countries in general. Key relevant characteristics are:

- Drug regulatory frameworks in ASEAN member countries do not appear to discourage research and development of drugs and vaccines.
- Drug regulatory capacities in the majority of ASEAN members are constrained by limited human and financial resources.
- Gaps exist between written regulation and actual enforcement in a number of ASEAN member countries.
- Among the member countries, only Singapore—which has the most advanced R&D and regulatory capability in the group—adopts a registration system that relies on product assessment and approval of other competent DRAs.
- All ASEAN countries are net importers of pharmaceuticals. All except Singapore do not have capability for new drug development.
- Evidence from some ASEAN members shows that R&D capability is a result of a country's investment and research environment, not a result of a compromised and weak drug regulation system.
- The process of development and implementation of ASEAN harmonized registration standards follows the traditional ASEAN culture of consensus building and flexibility.
- Levels of health insurance coverage among the populations of ASEAN members vary. In many countries, the majority of the population pays out-of-pocket for drugs. Consequently, even when drugs are available, affordability is a significant issue for access to necessary drugs. For countries with health insurance systems, high drug price affects system sustainability and service quality.

Reframing Policy Questions and Recommendations. Societies aim to protect consumers from the harms that unsafe and inefficacious drugs might bring, and to promote R&D for the discovery of new drugs that will help prevent and solve health problems at the

same time. Therefore, public policies must strike balance among competing goals without compromising them.

Since the majority of developing countries lack adequate capabilities in both drug regulation and research and development, key policy questions, then, are 1) how to improve these capabilities? and 2) how to do better given existing limitations? A number of measures can be considered to improve capabilities in developing countries:

- Recommendations for improving drug regulatory capability
 - Risk management
 - Make use of “trusted” DRAs
 - Continuous improvement
 - Human resource development
 - Reduce enforcement gaps
 - Get rid of unnecessary bureaucracy
- Recommendations for improving R&D capability
 - Government commitment and investment
 - International collaborations
- Recommendations for improving knowledge management. A great number of new ideas and new developments have taken place worldwide which will evolve into different policy models. It is important for the international community to be able to learn from these models lessons of success and failure, to identify with what features and under what conditions one model works while another does not.

"Health Innovation Systems in Developing Countries: Towards a Global Strategy for Capacity Building"

John Mugabe

Introduction. This paper examines factors that account for the low levels of scientific and technological capacities for improving public health in developing countries. Author takes the systems approach to define a national system of health innovation as the network of public and private institutions whose interactions and activities generate and/or use scientific knowledge and produce (as well as apply) technologies to solve specific disease problems. It treats innovation as a social process that is determined by institutional arrangements in which it evolves. Emphasis is placed on institutions supporting technical advances for the discovery and production of medicines in developing countries.

Findings. Some of the factors that account for the low levels of scientific and technological capacities for improving public health in developing countries are:

- Many of these countries have not reviewed and revised their health policies to focus on the role of science and technology. Their policies treat science and technology as exogenous variables to the improvement of health.
- The countries have devoted considerably low, and in many cases declining, funding to health research and innovation. Most of them spend less than 0.5 percent of their Gross Domestic Product (GDP) on health R&D. The low and declining expenditure on health R&D is a manifestation of the low priority that countries have given to science and technology. Private sector's contribution to public health R&D is low or non-existent in many of these countries. Most governments have not instituted specific policy and legal measures to attract private investment in public health R&D.
- Generally there are weak links between public health R&D institutions and private industry. Research results of public R&D activities do not often get accessed and used by pharmaceutical and medical industries. In many cases there is mismatch between health R&D activities on one hand and industrial development goals and strategies on the other.

Recommendations. The paper provides an indicative assessment of scientific and technological capacity needs of developing countries to improve public health. It identifies programmatic and institutional measures that are necessary to build scientific and technological capacities. The role regional and international collaboration to establish new institutional arrangements for public health innovation is explored with a focus on networking centres of excellence. The paper recommends that the international community should pull its resources together to assist developing countries, on a regional basis, to create and sustain new forms of health research and innovation institutions. Developing countries will need to do more to improve the science and innovation content of their health policies and programmes.